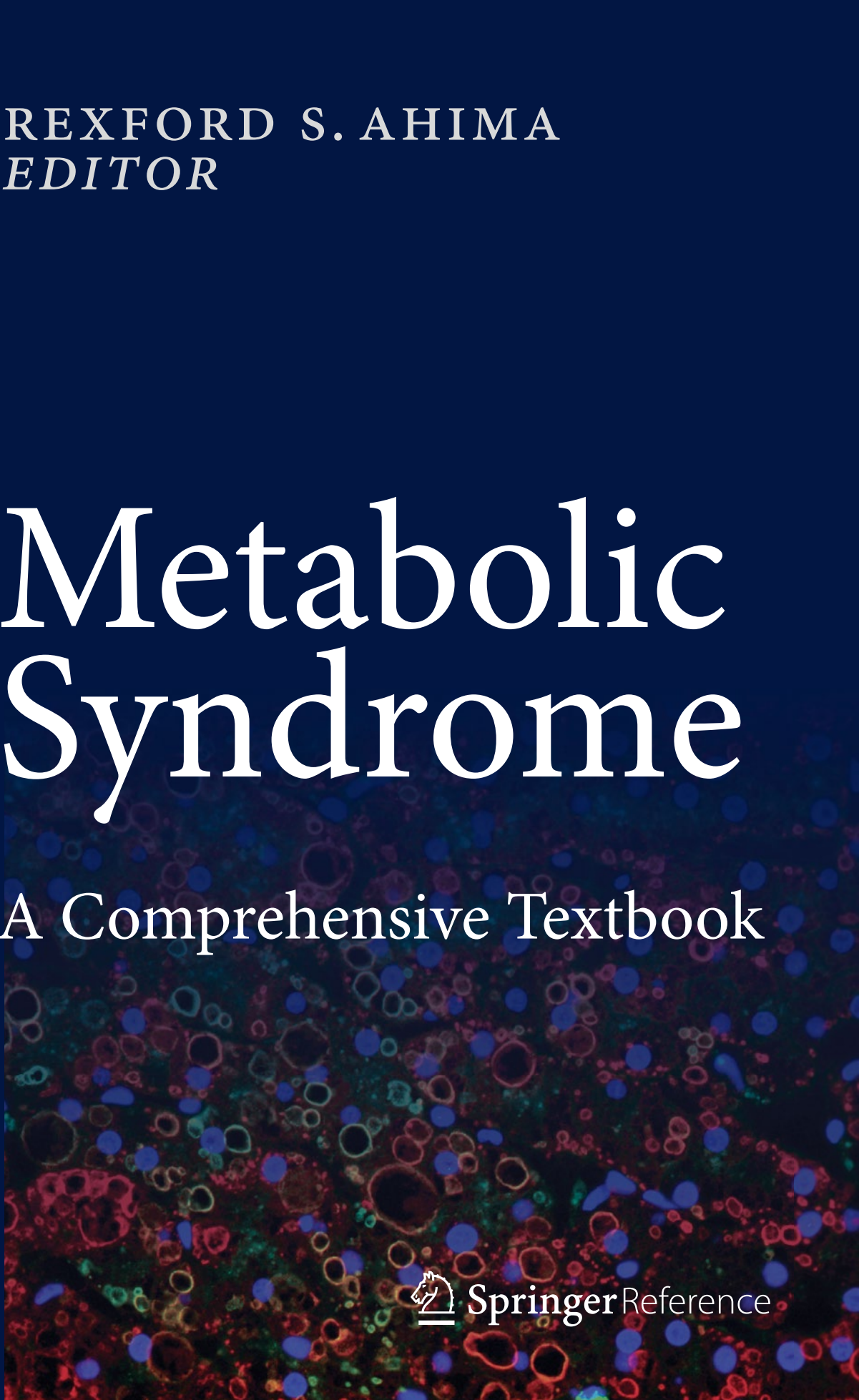
REXFORD S. AHIMA
EDITOR

Metabolic Syndrome

A Comprehensive Textbook



SpringerReference

Metabolic Syndrome

Rexford S. Ahima
Editor

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A Comprehensive Textbook

With 93 Figures and 44 Tables

Springer Reference

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"To know nothing is bad. . .. To learn nothing is worse"
(*African proverb*)

To my family, friends, colleagues, and trainees
who make it worthwhile.

Preface

This comprehensive reference work presents an up-to-date survey of the current scientific understanding of the metabolic syndrome, as well as an overview of the most significant advances in the field. The book provides a thorough reference for obesity and the metabolic syndrome and will prove an indispensable resource for clinicians and researchers at all levels. The obesity epidemic has generated immense interest in recent years due to the wide-ranging and significant adverse health and economic consequences that surround the problem. Much attention has been focused on excessive consumption of energy-dense food, sedentary lifestyle, and other behaviors that contribute to the pathogenesis of obesity. However, obesity is a highly complex condition that is influenced by genetic as well as environmental factors. The metabolic syndrome comprises of central obesity, impaired glucose tolerance or diabetes, hypertension, and dyslipidemia. The incidence of metabolic syndrome is growing worldwide, affecting more than one-third of adults in some countries. The metabolic syndrome increases the risk of developing coronary artery disease and stroke, and it is also closely associated with fatty liver, dementia, cancer, sleep apnea, kidney failure, infertility, and other diseases. This reference work covers the full range of scientific and clinical aspects of obesity and metabolic syndrome: epidemiology, genetics, environmental factors, pathophysiology, diseases associated with obesity, and clinical management.

Contents

About the Editor

Rexford S. Ahima is a Professor of Medicine at the University of Pennsylvania. He received his medical degree from the University of Ghana Medical School and a Ph.D. in Neuroscience from Tulane University in New Orleans, Louisiana. He did his internship and residency training in Internal Medicine at the Albert Einstein College of Medicine in New York and clinical and research fellowship training in Endocrinology, Diabetes, and Metabolism at the Beth Israel Deaconess Medical Center and Harvard Medical School in Boston. Dr. Ahima is a member of the American Society for Clinical Investigation (ASCI) and the Association of American Physicians (AAP) and a fellow of the American College of Physicians (ACP), The Obesity Society (TOS), and the American Association for the Advancement of Science (AAAS). He has served in various committees of the National Institutes of Health and other organizations and as an associate editor of *Gastroenterology* and the *Journal of Clinical Investigation*. He is currently an editor of the *Annals of the New York Academy of Sciences Year in Diabetes and Obesity* and an associate editor of *Molecular Endocrinology*. Dr. Ahima's research is focused on central and peripheral regulation of energy homeostasis and glucose and lipid metabolism. He is an attending endocrinologist at the University of Pennsylvania and the Director of the Obesity Unit of the Institute for Diabetes, Obesity, and Metabolism.

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Part I

Epidemiology

Overview of Metabolic Syndrome

1

Rexford S. Ahima

Abstract

The diagnosis of metabolic syndrome is based on the presence of abdominal obesity, increased blood pressure, elevated glucose and triglycerides, and low high-density lipoprotein cholesterol (HDL-C) levels. The prevalence of metabolic syndrome has increased globally mainly due to excessive intake of energy-dense foods and reduced physical activity. Metabolic syndrome increases the risk of developing type 2 diabetes (T2D), cardiovascular diseases, nonalcoholic fatty liver disease (NAFLD), cancer, infertility, dementia, and other diseases. The purpose of this book is to highlight the epidemiology, pathophysiology, clinical features, and treatment of metabolic syndrome. We are hopeful the chapters will provide valuable current insights as well as critical questions to guide future research.

Keywords

Metabolic syndrome • Obesity • Hypertension • Cholesterol • Glucose • Diabetes • Cardiovascular

The term "metabolic syndrome" was first used in the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) to describe the co-occurrence of obesity, dyslipidemia, hypertension, and abnormal glucose metabolism (Expert Panel on Detection and Treatment of High Blood Cholesterol in 2001). However, the association of metabolic disorders and cardiovascular risk factors had been recognized for many decades (Sarafidis and Nilsson 2006; Albrink et al. 1980). In his American Diabetes Association Banting lecture in 1988, Reaven (1988) used the term "syndrome X" to describe the relationship of insulin resistance, hypertension, type 2 diabetes (T2D), and cardiovascular diseases. Other investigators have

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Table 1 Definitions of metabolic syndrome

	WHO (1998)	AACE (2003)	NCEP ATP III (2005)	IDF (2005)	IDF (2009)
Criteria	IGT, IFG, T2D, or reduced insulin sensitivity plus any two of the following	IGT or IFG plus any of the following	Any three of the following	Increased WC plus any two of the following	Three out of five of the following
Obesity	*Men*: *WHR >0.90*; *Women*: *WHR >0.85 and/or BMI >30 kg/m^2*	*BMI ≥25 kg/m^2*	*WC ≥102 cm in men or ≥88 cm in women*	*Population-specific increased WC cutoffs*	*Population- and country-specific WC cutoffs*
Glucose	*IGT, IFG, or T2D*	*IGT or lFG*	*≥100 mg/dl (including T2D)*	*≥100 mg/dl (including T2D)*	*≥100 mg/dL*
Triglycerides (TG)	*TG ≥150 mg/dl*	*TG ≥150 mg/dl*	*TG ≥150 mg/dl or on therapy lowering TG*	*TG ≥150 mg/dl or on therapy lowering TG*	*TG ≥150 mg/dl*
HDL-cholesterol (HDL-C)	*HDL-C <40 mg/dl in men or HDL-C <50 mg/dl in women*	*HDL-C <40 mg/dl in men or HDL-C <50 mg/dl in women*	*HDL-C <40 mg/dl in men or HDL-C <50 mg/dl in women on therapy increasing HDL-C*	*HDL-C <40 mg/dl in men or HDL-C <50 mg/dl in women on therapy increasing HDL-C*	*HDL-C <40 mg/dl in men or HDL-C <50 mg/dl in women*
Blood pressure	*≥140/90 mmHg*	*≥130/85 mmHg*	*≥130/85 mmHg or on antihypertensive therapy*	*≥130/85 mmHg or on antihypertensive therapy*	*≥130/85 mmHg or on antihypertensive therapy*

Abbreviations: *HDL-C* HDL-cholesterol, *IGT* impaired glucose tolerance, *IFG* impaired fasting glucose, *TG* triglycerides, *T2D* type 2 diabetes, *WC* waist circumference, *WHR* waist/hip ratio

referred to the clustering of metabolic and cardiovascular risk factors as the "insulin resistance syndrome" (DeFronzo and Ferrannini 1991; Haffner et al. 1992).

Various organizations have proposed different criteria to describe the relationship of cardiovascular and metabolic diseases (Table 1). The International Diabetes Federation (IDF) characterized the metabolic syndrome as symptoms and physical or biochemical findings coexisting more often than could be explained by chance alone (Alberti et al. 2006). The American Diabetes Association (ADA) acknowledged the clustering of clinical and laboratory features in metabolic syndrome but questioned the utility of insulin resistance as a biomarker for cardiovascular risk (Kahn et al. 2005). In 1998, the World Health Organization (WHO) proposed a working definition for metabolic syndrome focusing on the presence of insulin resistance, impaired glucose tolerance (IGT), or T2D, as well as two of the following conditions: dyslipidemia (reduced HDL-C and increased triglycerides), hypertension, and microalbuminuria (Alberti and Zimmet 1998). The European Group for the Study of Insulin Resistance (EGIR) criteria for metabolic syndrome were similar to those of the WHO but did not include microalbuminuria (Balkau and Charles 1999). The NCEP ATP III defined metabolic syndrome based on increased waist circumference (WC), lipids, blood pressure, and fasting glucose levels (Grundy et al. 2004; Marchesini et al. 2004). The American Association of Clinical Endocrinologists' (AACE) definition of metabolic syndrome focuses on the presence of insulin resistance and not diabetes. In order to account for population differences, the IDF recently proposed specific racial/ethnic cutoffs (Grundy et al. 2005;

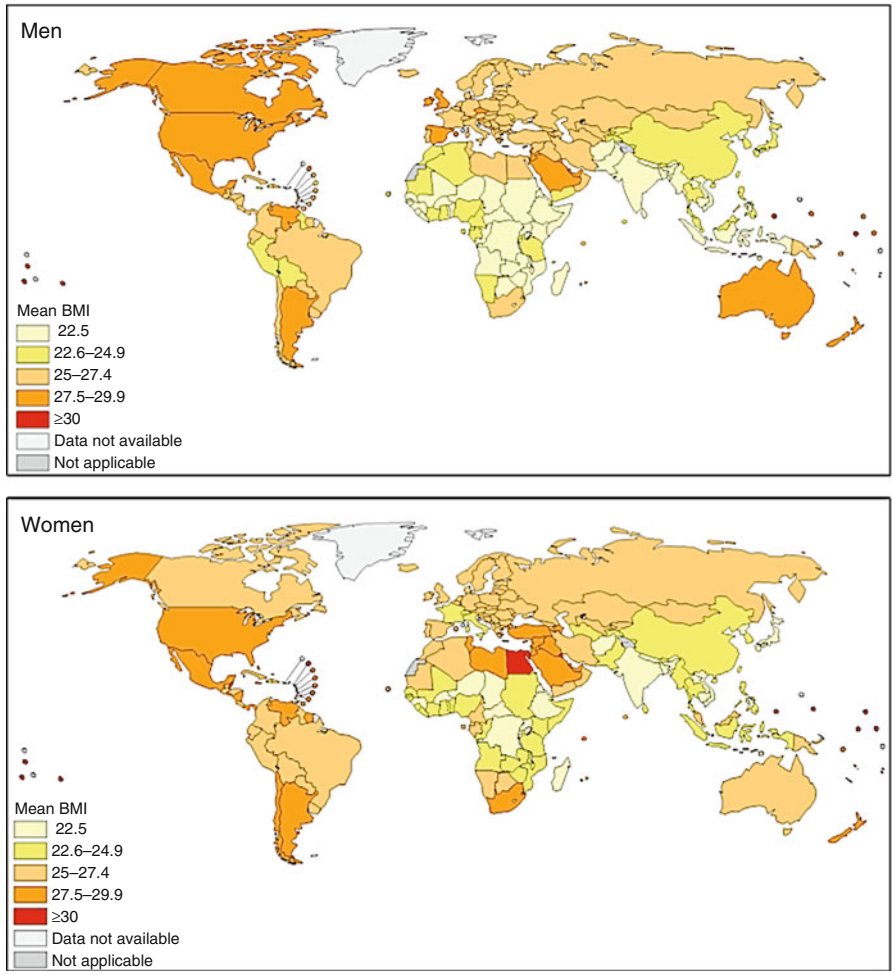

Fig. 1 Mean body mass index (BMI) in adults 20 years or older in 2008 (World Health Organization Global Health Observatory Map Gallery http://gamapserver.who.int/mapLibrary/app/searchResults.aspx)

Bloomgarden 2003). Moreover, the new IDF metabolic syndrome criteria focused on fasting plasma glucose concentration and not insulin resistance (Alberti et al. 2005, 2009). These differences in metabolic syndrome definitions by various organizations are unlikely to be resolved. However, given our current and evolving knowledge of the pathogenesis of obesity, T2D, and related diseases, future criteria for metabolic syndrome may need to consider the contributions of adipokines, pro-inflammatory cytokines, and other humoral factors linked to insulin resistance, diabetes, and cardiovascular diseases.

Figures 1, 2, 3, 4, and 5 illustrate global patterns of body mass index (BMI), elevated glucose, cholesterol and blood pressure, and mortality rates due to diabetes or cardiovascular diseases. Diseases associated with metabolic syndrome have increased worldwide, and these trends are influenced by age, sex, race/ethnicity, low physical activity, and other lifestyle factors (Mozumdar and Liguori 2011; Ford et al. 2002; Nestel et al. 2007; Lim et al. 2011; Jeppesen et al. 2007; Lorenzo et al. 2006; Harzallah et al. 2006; Chien et al. 2008; Zabetian et al. 2007; Mattsson et al. 2007; Ilanne-Parikka et al. 2004; Jorgensen et al. 2004). The prevalence of metabolic syndrome in youth also varies according to the definition, age, and population under study (Berenson et al. 1998; Li et al. 2003; Raitakari et al. 2003; Sun et al. 2008;

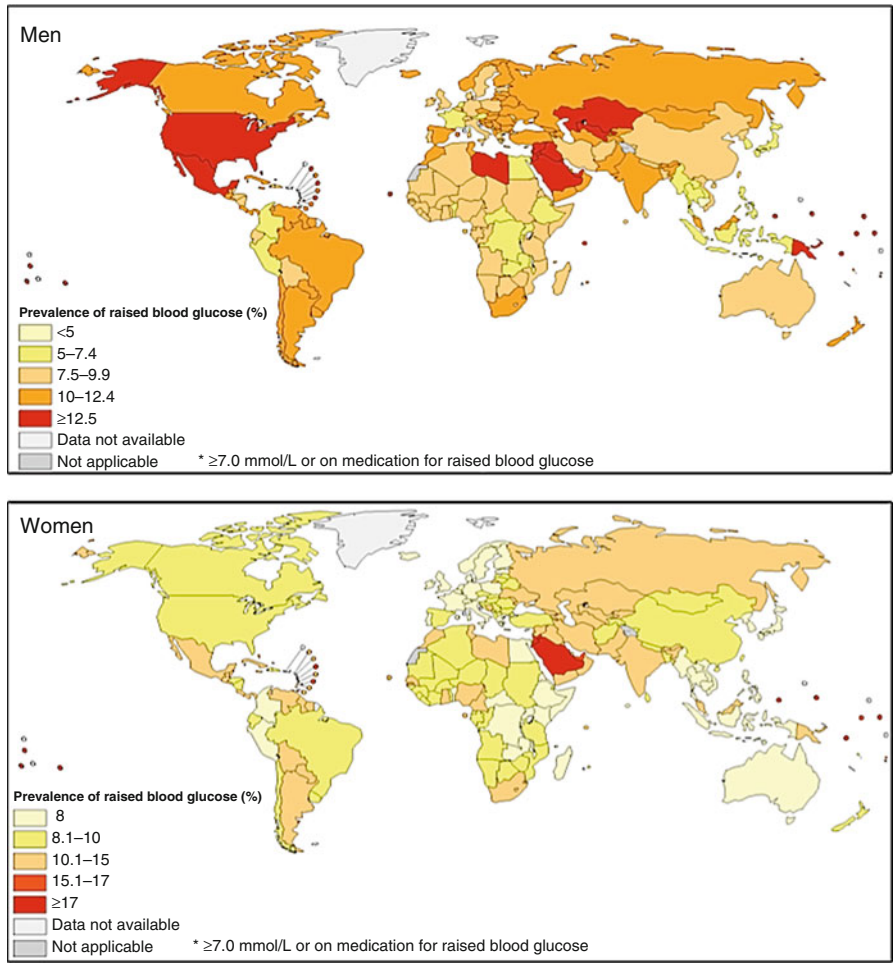

Fig. 2 Prevalence (%) of elevated fasting glucose in adults 25 years or older in 2008 (World Health Organization Global Health Observatory Map Gallery http://gamapserver.who.int/mapLibrary/app/searchResults.aspx)

Cook et al. 2003, 2008; de Ferranti et al. 2004; Cruz et al. 2004; Weiss et al. 2004). Studies suggest that metabolic syndrome in youth is a strong predictor of future risk for diabetes and cardiovascular disease (Berenson et al. 1998; Li et al. 2003; Raitakari et al. 2003). The high global prevalence of metabolic syndrome has been attributed to overconsumption of energy-dense foods, sedentary lifestyle, low socioeconomic status, and rapid urbanization (Alberti and Zimmet 1998; Grundy et al. 2004). An inverse association between the level of education and the risk of metabolic syndrome has been described (Lucove et al. 2007; Wamala et al. 1999; Silventoinen et al. 2005; Brunner et al. 1997; Park et al. 2007). In developing countries, the prevalence of metabolic syndrome is higher in urban compared to rural areas (Jeppesen et al. 2007; Lorenzo et al. 2006; Harzallah et al. 2006; Chien et al. 2008; Zabetian et al. 2007; Weng et al. 2007).

A hallmark of metabolic syndrome is insulin resistance, a pathological condition in which high insulin concentrations fail to produce a normal response in peripheral target tissues. Insulin resistance is commonly associated with abdominal obesity (Petersen and Shulman 2006; Gill et al. 2005), though some insulin-resistant individuals who are not obese may have ectopic fat accumulation in the liver and muscle (Jensen et al. 1989; Lim and Meigs 2014). In adipose

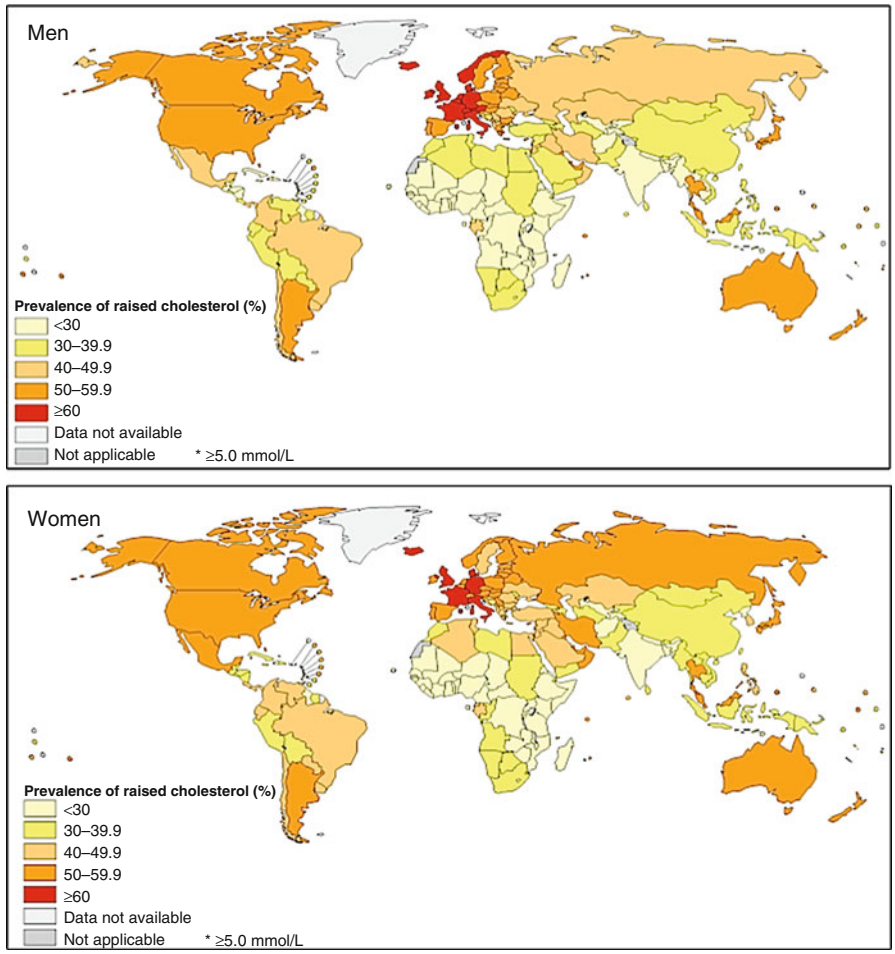

Fig. 3 Prevalence (%) of elevated cholesterol in adults 25 years or older in 2008 (World Health Organization Global Health Observatory Map Gallery http://gamapserver.who.int/mapLibrary/app/searchResults.aspx)

tissue, insulin resistance attenuates the anti-lipolytic effect of insulin which leads to elevated fatty acid levels. Insulin resistance in the muscle disrupts insulin-mediated glucose uptake and decreases glycogen biosynthesis. Insulin resistance in the liver impairs the ability of insulin to suppress glucose production. Insulin resistance is very common in obesity, and this metabolic setting increases the demand for pancreatic β-cells to synthesize and secrete more insulin. Hyperinsulinemia in obesity promotes lipogenesis and steatosis and contributes to salt retention and hypertension. The inability of pancreatic β-cells to produce enough insulin leads to elevated fasting glucose, glucose intolerance, and ultimately T2D (Petersen and Shulman 2006; Gill et al. 2005).

Studies have also shown that metabolic syndrome is associated with low-grade inflammation and oxidative stress, partly mediated by adipokines, nutrients, and other factors (Dandona et al. 2004; Festa et al. 2000). There is a positive correlation between high-sensitivity C-reactive protein (hs-CRP) and metabolic dysfunction (Festa et al. 2000; Han et al. 2002; Laaksonen et al. 2004). Other biomarkers, including fibrinogen, apolipoprotein B, uric acid, and adhesion molecules, are associated with metabolic syndrome (Onat et al. 2006, 2007, 2009; Rubin et al. 2008). Atherogenic dyslipidemia in metabolic syndrome manifested by high triglycerides and low HDL-C levels is associated with inflammation and oxidative stress (Ruotolo and Howard

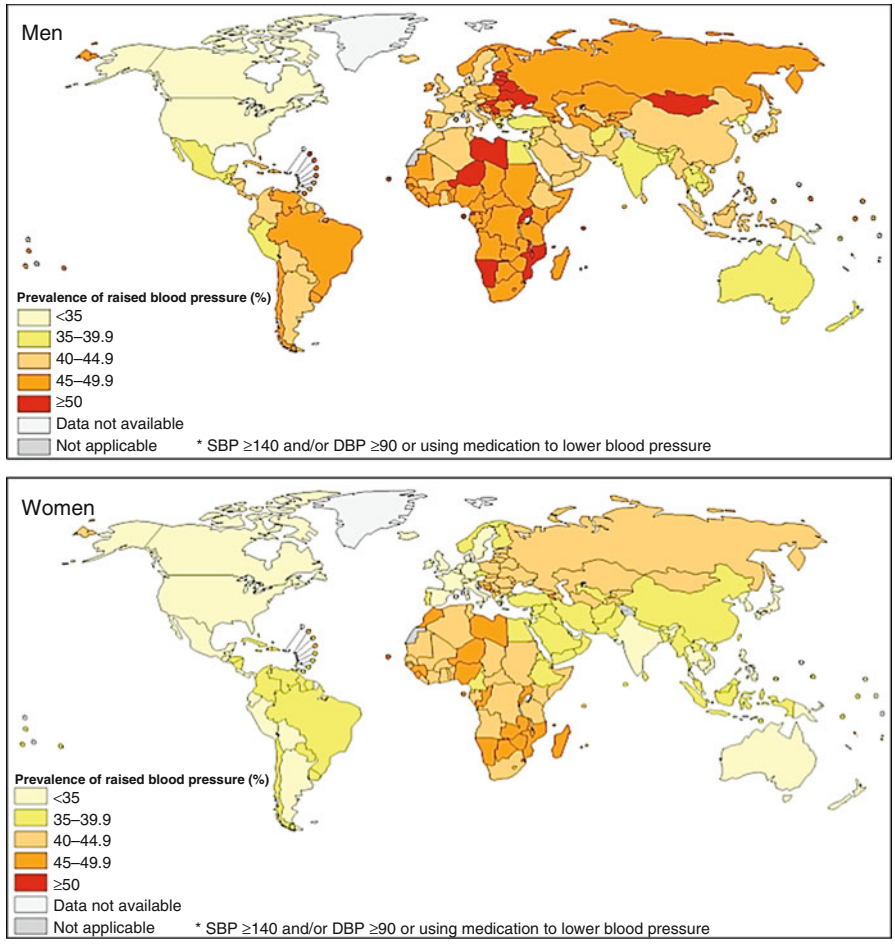

Fig. 4 Prevalence (%) of hypertension in adults 25 years or older in 2008 (World Health Organization Global Health Observatory Map Gallery http://gamapserver.who.int/mapLibrary/app/searchResults.aspx)

2002; Onat and Hergenc 2011). Activation of the renin-angiotensin system (RAS) in obesity has been linked to insulin resistance, inflammation, oxidative injury, ectopic fat accumulation, and hypertension (Frigolet et al. 2013).

Despite the controversies surrounding the definition of metabolic syndrome, there is little doubt about the close association of putative metabolic syndrome components and excess cardiovascular risk (Galassi et al. 2006). Hence, interventions to ameliorate obesity, hyperglycemia, dyslipidemia, and hypertension are likely to decrease the risk of developing cardiovascular diseases and other complications of metabolic syndrome. Successful weight loss from dietary management, adequate physical activity, pharmacotherapy, and surgery is highly recommended for metabolic syndrome patients. Available weight loss drugs in the United States include phentermine, extended release phentermine/topiramate, lorcaserin, orlistat, sustained release bupropion/naltrexone, and the glucagon-like peptide (GLP)-1 agonist liraglutide (Smith et al. 2010, 2013; Coomans et al. 2013; Apovian et al. 2013; Billes et al. 2014; Vilsboll et al. 2012). Metformin improves insulin sensitivity in patients with impaired glucose tolerance or T2D. GLP-1 agonists and sodium glucose co-transporter 2 (SGLT2) inhibitors improve glycemic control in T2D without increasing body weight and adiposity (Orchard et al. 2005; Bolinder et al. 2012). Statins are drugs of choice for atherogenic dyslipidemia, and fibrates can be

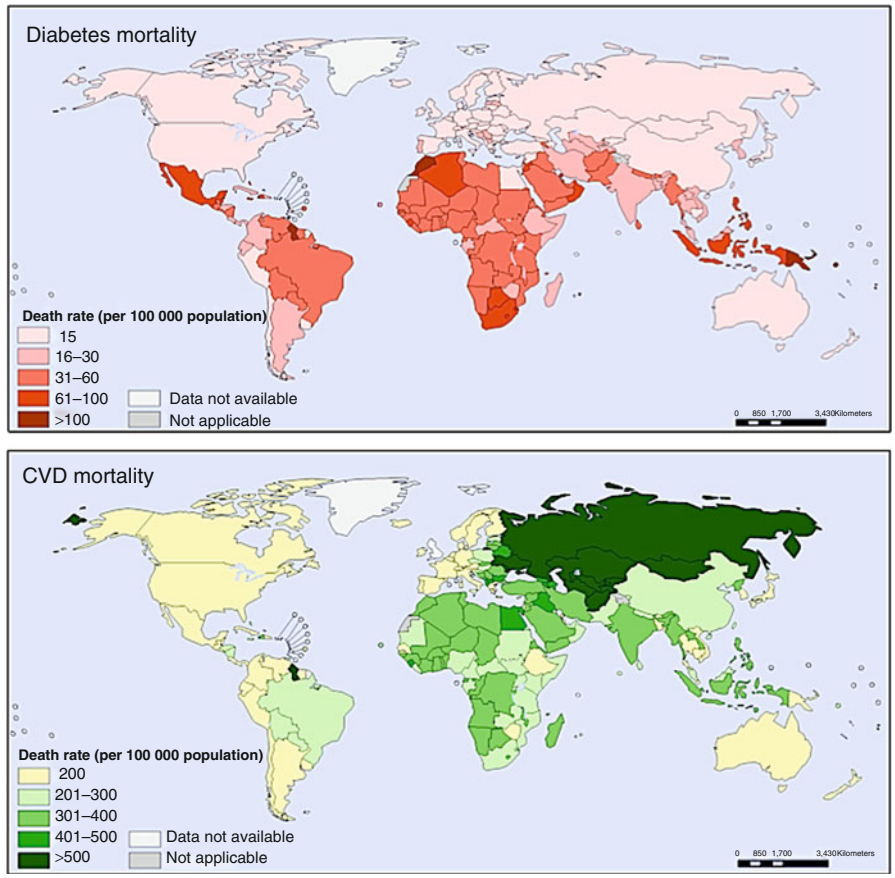

Fig. 5 Age-standardized mortality due to diabetes or cardiovascular diseases in 2012 (World Health Organization Global Health Observatory Map Gallery http://gamapserver.who.int/mapLibrary/app/searchResults.aspx)

used to decrease triglycerides and increase HDL-C (Colhoun et al. 2004; Baigent et al. 2005; Cholesterol Treatment Trialists et al. 2012; Koo 2014). Antihypertensive drugs, especially RAS blockers, are crucial for reducing blood pressure and cardiac complications (Chrysant et al. 2010; Borghi and Santi 2012; Watanabe et al. 2005; Zreikat et al. 2014).

This comprehensive reference book presents an up-to-date survey of the current scientific understanding of the metabolic syndrome, as well as an overview of the most significant advances in the field over the past 30 years. The references provide thorough information for obesity and metabolic syndrome and will prove an indispensable resource for clinicians, researchers, and students. The book covers a full range of scientific and clinical aspects: epidemiology, genetics, environmental factors, pathophysiology, diseases associated with obesity, and evidence-based management of metabolic syndrome.

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Epidemiology of Obesity in the United States

2

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Abstract

The prevalence of obesity has risen dramatically in the United States over the past several decades, leading to a public health crisis that disproportionately impacts racial/ethnic minorities and Americans of lower socioeconomic status. This chapter examines the historical trends in obesity, as well as the scientific evidence for specific behavioral and environmental correlates of this disease. The chapter also focuses on subpopulations impacted by obesity, including children. The idea of moving beyond body mass index (BMI) as an isolated measure of obesity is presented, along with evidence of the importance of other measures, such as waist circumference, particularly among certain ethnic groups. The obesity paradox – a finding that in observational data, some adults who are overweight or obese have lower mortality than their normal-weight counterparts – is reviewed as well. Finally, the chapter considers the implications of the obesity epidemic in an aging US population and the rising prevalence of more severe degrees of obesity in recent years.

Keywords

Obesity • Epidemiology • Body mass index • Prevalence

1 Introduction

In the early nineteenth century, the Belgian astronomer, mathematician, statistician, and sociologist Adolphe Quetelet described a standard for understanding the growth of children as they emerged into adolescents and adults. The weight of a child, Quetelet found, could be divided by the square of its height to monitor a child's progress and observe their growth trajectory with respect to their risk of stunting, wasting, or – more rarely in the nineteenth century – obesity (Hall and Cole 2006).

In the 1950s, the scientist Ancel Keys – known most famously for having conducted seminal studies on the importance of cholesterol to cardiovascular health – renamed weight per height squared "the body mass index" (BMI). The squared term appeared to correct growth curves for both height and age, providing a simple strategy for assessing growth and anthropometrics across the life-course and over entire populations. Yet the term did not gain widespread use until the late 1970s, when body mass index was observed to correlate with measures of body fat mass and more importantly to adverse health status among children (Cole 1979).

Today, BMI – particularly elevated BMI that we now term "overweight" (BMI $\geq$25 kg/m^2) or "obese" (BMI $\geq$30 kg/m^2) – has been correlated to a series of concerning health outcomes. Abundant studies have correlated elevated BMI to premature cardiovascular and metabolic disease markers – including hypertension, hyperlipidemia, and abnormal glucose tolerance (World Health Organization 2000). Notable variations, however, have been observed in the epidemiological literature relating obesity to long-term health, generating interest in whether the risks of overweight and obesity are contingent upon high BMI per se, or more on the site of body fat deposition, and biological mechanisms associating regional adiposity with heightened morbidity in some populations more than others – a dilemma we will discuss in detail in this chapter (Kissebah et al. 1989). Nevertheless, BMI remains the world's leading marker for abnormally heavy weight, being of particular importance as a risk factor for cardiovascular disease, which has become the leading cause of death worldwide (Lim et al. 2012). In addition to cardiovascular disease, obesity is increasingly related to rarer disease manifestations, ranging from pseudotumor cerebri, premature obstructive sleep apnea, and Blount's disease among children (Dietz 1998) to rising rates of knee and hip osteoarthritis among older persons (Zamboni et al. 2005). In addition, people with high BMI have been found to bear long-term psychological stigma for their body size and shape (Dietz 1998) – highlighting that the epidemiology of obesity is not merely a study of measurement, but a science that is intimately tied to very real social consequences for many individuals, families, and communities worldwide.

In this chapter, we will discuss the epidemiology of obesity in the United States, where – at the time of this writing – over one-third of adults are now classified as obese (Ogden et al. 2014). Our discussion will begin with an overview of the historical, sociodemographic, and environmental correlates to rising obesity in the United States and then proceed to emerging issues concerning the changing trajectories of obesity among both children and the elderly. We will focus in particular on epidemiological puzzles such as the variations in obesity and in obesity-health correlations among different sociodemographic groups and the "obesity paradox" in which some studies find lower mortality rates among overweight individuals. We also discuss emerging issues in the field such as sarcopenic obesity and the question of whether pediatric obesity is truly beginning to plateau or decline in the United States. Our presentation intends to touch upon the major questions emerging in the field around why obesity has risen dramatically in the United States, what epidemiological correlates to its rise may highlight opportunities for effective public health interventions, and how refinements of our understanding of body size and shape may further enhance our understanding of who is at greatest risk for the health consequences of excess body weight.

2 Historical Trends in Obesity

2.1 Obesity in the United States During the First Half of the Twentieth Century

Estimates of obesity prevalence during the first half of the twentieth century are difficult to obtain, owing to the lack of routine surveillance data on both height and weight in a representative sample of the population during this period. Nonetheless, some data are available to suggest that Americans were slowly gaining weight around the turn of the twentieth century. For example, repeated samples of men aged 30–34 years between the late 1800s and 1950 show that the average man of 5′8″ increased from a weight of 150 lbs to just over 160 lbs during that span, corresponding to a shift from a BMI near ideal body weight (22.8 kg/m^2) to one bordering on overweight (24.6 kg/m^2) by the mid-1900s (Van Itallie 1978).

According to USDA data, the per capita food supply actually declined during the first half of the twentieth century (Swinburn et al. 2011; Barnard 2010; Gortner 1975; US Department of Agriculture 2014) (Fig. 1). Although decreased production of wheat products during this time was arguably the most important driver of decreased caloric production, there was a similar decrease in availability of meats in the food supply that lasted from World War I through the Great Depression, only beginning to reverse course during the 1940s (Barnard 2010). Despite this period of declining food availability (and presumed lower caloric intake), as was suggested by the weight and height data from middle-aged men above, Americans did not become appreciably thinner during these decades. Some have hypothesized that a simultaneous decrease in energy expenditure, due to a shift away from hard labor jobs and greater mechanization of many processes, including transport, may have counteracted (or contributed to – through decreased hunger) decreased energy intake, to result in weight maintenance or a slow gain over time (Swinburn et al. 2011; Van Itallie 1978).

2.2 Obesity in the United States: 1960–1979

Beginning in 1960, more routine estimates of obesity prevalence in the United States were obtained through surveys conducted by the Centers for Disease Control and Prevention (CDC). The National Health Examination Survey (NHES) paved the way for later iterations of these critical health surveillance activities, including the National Health and Nutrition Examination Survey (NHANES, beginning 1971) and the Behavioral Risk Factor Surveillance System (BRFSS, beginning in 1984) (CDC 2011, 2013). Through these public health surveillance systems, data from self-report telephone interviews (BRFSS) and physical examinations (NHANES) on repeated samples representative of the US population have been compiled to yield prevalence

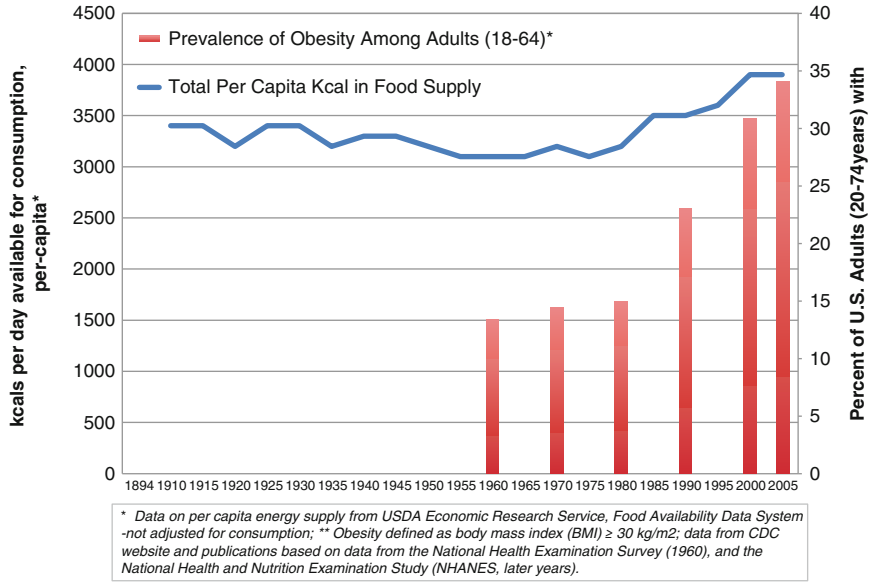

Fig. 1 Trends in per capita food energy and obesity prevalence in the United States

estimates for a number of different conditions, including obesity. Reviewing the prevalence of obesity among American adults over the latter half of the twentieth century is facilitated tremendously by these surveillance efforts.

In 1960, when NHES was originally conducted, the age-adjusted prevalence of obesity among adults aged 20–74 years was 13.4 %. By 1971, during the first wave of NHANES, the prevalence had risen only slightly, to 14.5 %. This upward creep in prevalence continued in the latter half of the 1970s, with NHANES II (1976–1980) estimating that 15 % of American adults were obese (Ogden 2010). Thus, for the entire two-decade period from 1960 to 1980, the prevalence of obesity among American adults rose by less than 2 %.

Although this rise seems gradual relative to the dramatic upswing in obesity that was to come beginning in the 1980s, it coincided with the beginnings of some major changes in the US agricultural and food supply systems. Whereas in the first half of the twentieth century, wheat products and caloric supply per capita were in decline, beginning in the 1960s, there was a reversal of this trend, such that year after year, more and more calories were becoming available for consumption by Americans (Swinburn et al. 2011). At the same time, physical activity levels remained low. This shift toward higher energy intake and lower energy expenditures has been referred to, by some experts, as "the energy balance flipping point" and is hypothesized to be a major driver of the obesity epidemic that was to follow (Swinburn et al. 2011).

2.3 Obesity in the United States: 1980–2000

The 1980s represented a critical inflection point in the upward trend of obesity among American adults. In contrast to the slow and steady rise that was exhibited in the previous 20 years, 1980–2000 was a period of dramatic increase in obesity prevalence. A review of data from NHANES shows that between the end of NHANES II in 1980 and NHANES III, which ended in 1994, the age-adjusted prevalence of obesity skyrocketed from 15 % of adults aged 20–74 to 23.2 %. This upswing continued in the 1990s, such that by 2000, 30.9 %, or nearly one-third of American adults, were considered obese (Ogden 2010).

Another emerging phenomenon from the 1980s onward was that of extreme obesity (BMI $\geq$40 kg/m^2). This phenotype was relatively rare in the 1970s, hovering around 1 % of the population. By the year 2000, however, a fivefold increase in this rate had been observed, with 1 in 20 American adults (5 %) classified as having extreme obesity (Ogden 2010). It is important to note that while the NHANES estimates referenced above represent an average trend, there were important differences between socioeconomic and demographic groups with respect to increasing obesity rates. Although all groups were affected to some degree, racial and ethnic minority groups, particularly African-Americans and Mexican-Americans, experienced a much steeper rise in obesity rates (Mokdad et al. 1999), a pattern that is addressed in detail in section "Sociodemographic/Geographic Correlates" of this chapter.

The historical context for this sharp upswing in obesity prevalence from 1970 to the 1990s includes some sweeping changes in the American food supply that have raised questions about specific dietary correlates, or even causes of obesity (section "Behavioral Correlates of Obesity" of this chapter). Data from NHANES show that, during this time period, American adults reported markedly higher energy intakes than in previous decades. For example, men aged 20–74 reported consuming an average of 2,439 kcal/day between 1976 and 1980 (relatively stable compared to the 2,450 kcal/day reported for the period 1971–1974), but by 1988–1994, when NHANES III was conducted, this same group reported consuming an average of 2,666 kcal/day, a daily increase of over 200 kcal, or nearly 1,600 kcal per week. Women reported similar increases, going from an average of 1,522 kcal/day reported during NHANES II (1976–1980) to 1,798 kcal/day during NHANES III (1988–1994) (Briefel and Johnson 2004).

2.4 Obesity in the United States: 2000–Present

From 2000 onward, public health surveillance systems have documented a slowing in the rise of adult obesity in the United States. Estimates of obesity prevalence have also been conducted with much greater regularity from 2000 onward, as NHANES has shifted to being done on 2-year cycles as opposed to the more spaced out and sporadic cycling of surveillance in the 1970s–1990s.

Between 2000 and 2007, the age-adjusted prevalence of obesity in adults aged 20–74 years rose from 30.9 % to 34.3 % (Ogden 2010). Pooled data from BRFSS, NHANES, and other CDC surveillance systems then show a relative leveling off of obesity rates among adults around 35 % from 2007 to 2013 (Johnson et al. 2014). Of concern, however, during the time period between 2005 and 2012, the average increase in obesity rates among children was 1.4 % per year, compared to 0.6 % per year for adults (Johnson et al. 2014). Also of concern, despite the relative plateauing observed for overall BMI in adults, rates of abdominal obesity, a key component of the metabolic syndrome (defined as a waist circumference greater than 102 cm in men or 88 cm in women), have continued to rise (Ford et al. 2014). Mirroring the obesity epidemic as a whole, abdominal circumference has displayed especially large increases among racial and ethnic minority groups such as non-Hispanic blacks and Mexican-Americans (Ford et al. 2014). Age-adjusted prevalence of abdominal obesity in adults went from 46.4 % during 1999–2000 to over half of Americans (54.2 %) in 2011–2012 (Ford et al. 2014).

3 Sociodemographic/Geographic Correlates

Differences in obesity epidemiology across sociodemographic groups offer important insights into why obesity has become so prevalent in the United States. For example, differences in BMI between the two sexes have changed dramatically over the last three decades in correspondence with changes in nutrition and physical activity behaviors. In the early 1970s, men had a mean BMI of 25.3 versus 24.4 among women; the two groups reversed trends in the mid-1990s, such that by the year 2000, men had a mean BMI of 27.6 versus

28.2 among women. These changes correspond to rising calorie intake and reduced physical activity among women at a greater pace than among men (Zhang and Wang 2004b).

3.1 Race/Ethnic Disparities

Even more pronounced are differences across race/ethnic and socioeconomic groups. The racial and ethnic disparities in obesity prevalence within the United States have generated a large literature in the field of epidemiology in part because they suggest differential risk of adverse outcomes in populations facing discrimination – implying that social or political factors unfairly put disadvantaged groups at risk. Because most information concerning obesity prevalence comes from the National Health and Nutrition Examination Survey (NHANES), however, the study of race/ethnic disparities in obesity across the United States is often limited by the race/ethnic categories used by the Centers for Disease Control and Prevention in the NHANES survey. These are defined as "non-Hispanic White," "non-Hispanic Black," "Mexican-American," "Other Hispanic," and "Other Race-including multiracial." Only the Mexican-American and non-Hispanic Black categories have sufficient sample size to track obesity prevalence over time. The changing composition of "Other Hispanic" and "Other race" also makes it difficult to understand whether obesity prevalence changes in these groups are real changes in body composition or changes in underlying demographic group due to immigration. Other surveys are available from Asian and Pacific Islanders or other race/ethnic minority groups, though much of the information is either self-reported (rather than directly measured) or from smaller regional surveys and cohort studies with limited age ranges.

The NHANES data reveal that since the 1970s, non-Hispanic Blacks and Mexican-Americans have had higher combined prevalence rates of obesity than non-Hispanic Whites, averaging about 10 percentage points higher through the 1990s and 2000s (Wang and Beydoun 2007). Most of this difference is driven by disparities among women. Age-adjusted obesity prevalence among adult men averaged around 12.5 % for Whites versus 15.7 % and 16.5 % for Mexican-Americans and Blacks, respectively, in the late 1970s (1976–1980 waves of NHANES) and then increased at a nearly linear rate to 31.1 % among Whites, 31.6 % among Mexican-Americans, and 34.0 % among Blacks in 2003–2004, after which prevalence rates increased by another 2–3 % among all groups during the 2000s through the most recent NHANES wave (2011–2012). Disparities were more pronounced among women, among whom age-adjusted prevalence among Whites was 15.4 % in the late 1970s versus 26.6 % among Mexican-Americans and 31 % among Blacks and then grew linearly among all groups to 30.2 % in Whites, 42.3 % in Mexican-Americans, and 53.9 % among Blacks by 2003–2004, and similarly slowing to a 2–3 % further increase over the 2000s until the most recent 2011–2012 study wave. In other words, all groups increased linearly in obesity, with Blacks starting at the highest prevalence rates and increasing the most and Whites starting lowest and increasing the least during the critical period of pronounced obesity rise in the 1980s and 1990s (Wang and Beydoun 2007; Ogden et al. 2014).

These data are supplemented by self-reported data from the nation's largest telephone survey, the Behavioral Risk Factor Surveillance System (BRFSS), which revealed similarly high prevalence rates among Native Americans as among Blacks, but consistently low prevalence (around 11 %) of obesity among Asian-Americans (Centers for Disease Control and Prevention 2015). Time trends to describe secular changes among these groups remain unreliable due to sample size and definitional changes.

3.2 Socioeconomic Disparities

Two critical questions have emerged in the epidemiological literature to understand the reasons behind race/ethnic disparities. First, are these disparities emblematic of socioeconomic disparities that are merely manifest as race/ethnic differences due to the correlation of socioeconomic class to race in the United States? Secondly, are these

differences consequential for health, meaning that the same degree of obesity has different health consequences among race/ethnic groups, or that the disparities in obesity are magnified in terms of their consequences for disease outcomes between groups?

To address the first question, several studies included both markers of socioeconomic status (e.g., wealth, annual income) and race/ethnic category as statistical predictors of obesity prevalence rates, finding consistently that socioeconomic status did not fully explain the race/ethnic disparities in obesity prevalence (Robert and Reither 2004; Zhang and Wang 2004a; Ogden et al. 2006; Wang and Zhang 2006). Nevertheless, low income was generally a significant risk factor for obesity. Within minority groups, socioeconomic status mattered less than among Whites; furthermore, low socioeconomic status has been most important for men and for middle-aged groups (Zhang and Wang 2004a; Chang and Lauderdale 2005).

But some of the socioeconomic and race/ethnic disparities have been in opposite directions from those typically hypothesized; for example, obesity prevalence increases among more educated Black women, possibly because rising incomes can correspond to increased overall calorie intake (Wang and Beydoun 2007). These findings influenced the field to further study community-level and environmental factors that would lead to social influences on obesity risk, not merely income alone, as we discuss further in the section "Environmental Correlates."

3.3 Different BMI Cut Points for Ethnic Minorities

To address the second issue – whether obesity may differ in health consequence among groups – a series of studies evaluated the risk of cardiometabolic disease among different race/ethnic groups based on BMI cut points. Some studies have shown that for the same BMI, Black children have less body fat than their White counterparts (Yanovski et al. 1996; Daniels et al. 1997), suggesting less consequential problems with higher BMI in this group, though the long-term morbidity and mortality implications of obesity (discussed below) seem to profoundly outweigh these findings. More extensive studies have found that race/ethnic differences in the implication of BMI for health are most important for South and East Asians rather than for the Black-White disparity. In particular, the risk of type 2 diabetes and associated cardiovascular outcomes appear at lower BMI among South and East Asians than among other race/ethnic groups (Deurenberg et al. 1998; Misra 2003; Chiu et al. 2011). This is thought to be due to the inability for BMI to fully capture risk among lower-height populations, in particular populations with more "abdominal" or "central" obesity in which the distribution and quantity of body fat is centrally located (Gallagher et al. 1996; Deurenberg-Yap et al. 2000); hence, waist-to-hip ratio has increasingly been used as a substitute for BMI among diabetes risk assessments in Asian populations (Chaturvedi et al. 2008; Kanaya et al. 2010). Studies of abdominal obesity at a population level in the United States using waist circumference measures have generally shown continued increases over time in obesity among all groups, as compared to the more stagnant prevalence trends among studies using BMI to assess obesity rates (Ford et al. 2014). Hence, the study of ethnic differences in BMI cut points contributed to the overall discovery that waist circumference or waist-to-hip ratio may be better for capturing ongoing epidemiological trends in body size and shape change in the United States, as opposed to BMI.

3.4 Environmental Correlates

Revisiting the issue of socioeconomic disparities in obesity risk, a series of studies over the last decade have found that the elevated risk of obesity among the poor may be better characterized as not merely linked to low socioeconomic status, but rather as a manifestation of the interaction between poverty and place. A consistent epidemiological observation is that spatial disparities across state, county, and local area obesity prevalence persist over time and remain robustly related

to larger socioeconomic and race/ethnic segregation in the country (Singh et al. 2008a, 2010). Indeed, area-level obesity prevalence disparities (e.g., disparities in obesity between zip codes) are larger than those associated with individual-level income markers or race/ethnicity (Drewnowski et al. 2007). Numerous studies have therefore correlated heightened obesity risk to interactions between low income, minority race, and local or regional environmental factors such as neighborhood or community features including: high prices of healthy foods (Drewnowski and Specter 2004), limited accessibility of healthy foods (Powell et al. 2007b; Ploeg et al. 2009), abundant availability of energy-dense low-quality foods (Powell et al. 2007a; Drewnowski 2010), and limited availability of built environment spaces conducive to physical activity (Gordon-Larsen et al. 2006; Sallis and Glanz 2006).

These mechanistic pathways linking these environmental factors to heightened obesity risk are plausible. What remains controversial is whether these correlates are necessarily consistent across the country or can persist despite biases in study design. For example, healthy foods studied in large databases are not as expensive as commonly believed and do not explain much of the variation in obesity prevalence rates across communities as implied by single-location studies (Rao et al. 2013). Food "deserts", or locations with poor healthy food access, also do not seem to explain as much of the variation in obesity as once believed, particularly when analyzed through large-scale rather than anecdotal data sources (An and Sturm 2012; Lee 2012). Similarly, selection effects may explain some of the relations between neighborhood built environment and physical activity (i.e., those people who are already more active seek out more activity-enhancing neighborhoods) (Boone-Heinonen et al. 2011).

Confounding and biasing factors make causal inference from epidemiological data challenging and may explain some disappointing results from early intervention trials that have attempted to improve nutrition and physical activity environments but have not generated significant obesity prevalence changes. For example, new supermarkets selling affordable healthy foods to low-income populations have not resulted the dietary or obesity effects intended (Cummins et al. 2005, 2014). Similar negative findings have been observed from interventions in the community that rely on education through health promotion messages to encourage use of physical activity spaces or available healthy food products (Ebrahim et al. 2006). The disappointing results suggest that while environment correlates may be statistically related to obesity risk, neutralizing their effects may require more attention to the complexities of how behaviors develop and persist in neighborhoods (Van der Horst et al. 2007). As discussed further in this volume, behavioral economic interventions such as taxes on high-calorie beverages have been of substantial interest because of their potential to produce a strong influence on food purchasing behavior, leading to the formation of healthier purchasing habits (Brownell et al. 2009; Powell et al. 2013). At the time of this writing, the further introduction and testing of such interventions to produce population-level obesity prevalence reductions remains a subject of active investigation (Wang et al. 2012; Basu et al. 2014).

4 Behavioral Correlates of Obesity

Evidence from numerous epidemiologic studies has begun to suggest that particular dietary and lifestyle factors may have played important roles in the development of the obesity epidemic in the United States. As was reviewed in section "Historical Trends in Obesity" of this chapter, American adults reported increasing their daily caloric intake by around 200 kcals per person between 1980 and the mid-1990s (Briefel and Johnson 2004). Interestingly, this change in intake appears to have been driven in large part by an increase in the consumption of certain types of foods but also by a shift toward eating more meals prepared away from home. Here we review evidence around several frequently discussed dietary and behavioral correlates of rising obesity rates in the United States.

4.1 Sugar-Sweetened Beverage Intake

The term "sugar-sweetened beverages" (SSBs) refers to a group of items that includes regular soft drinks, flavored waters, and juice drinks (Malik et al. 2013). In the past decade, policy makers and members of the public health research community have increasingly focused on SSBs as important correlates of obesity, as historic increases in SSB consumption across most age groups in the United States seem to run parallel to the steep increase in obesity rates. For example, between 1977 and 1994, survey data on the dietary behavior of US children and adolescents (aged 6–17 years) show a doubling in the daily intake of SSBs (from 5 oz/day up to 12 oz/day, on average) (Briefel and Johnson 2004). American adults also increased their consumption of SSBs during this period (Brownell et al. 2009). The timing of increased SSB intake also correlates with a major documented increase in fructose use by food manufacturers, mostly in the form of high-fructose corn syrup (HFCS). Namely, the per capita availability of HFCS increased by about 60 % between 1978 and 2004 (Marriott et al. 2009). Although SSB consumption has somewhat stabilized in recent years, it is still quite pervasive. As of 2012, BRFSS data showed that about a quarter of adults in surveyed states reported consuming at least one SSB daily (Kumar et al. 2014).

Most of the evidence supporting a link between SSBs and weight gain comes from observational cohort studies, although randomized controlled trial evidence has started to emerge (Ebbeling et al. 2012; de Ruyter et al. 2012). A recent large systematic review and meta-analysis on this topic suggested that, for both children and adults, there is a positive association between SSB consumption and weight gain over time (Malik et al. 2013) Some in the nutrition research community believe that SSBs may have a special causal relationship with weight gain. Several mechanisms to explain this weight-gain promoting effect of SSBs have been hypothesized. These include: (1) humans experience decreased satiety cues when calories are consumed in liquid form (beverage) as opposed to solid form (food) leading them to consume excess calories when SSBs are part of the diet; (2) SSBs have a high glycemic load, meaning they cause large insulin spikes and increase subsequent hunger; and (3) the liver metabolizes fructose (from high-fructose corn syrup in SSBs) differently than it does glucose, possibly leading to differential fat deposition when large amounts of fructose are consumed (Malik et al. 2013). Despite these hypotheses, research in this field is relatively nascent and requires further evaluation before a causal link between SSBs and obesity can be firmly established. Regardless, there is a clear correlation between the timing of increased SSB consumption in the United States and the sharp increase in obesity rates, leading public health professionals to recommend decreasing SSB consumption as one possible tactic to combat obesity (Hu 2013).

4.2 Fiber Intake

Another dietary factor that has been cited as a potential correlate of rising obesity rates is low fiber intake (Van Itallie 1978). It has been true for some time now that many Americans do not meet the recommendation of eating five servings of fruits and vegetables daily. Numerous public health campaigns have therefore focused on trying to increase fruit and vegetable intake, because, among other reasons, low fiber intake has been associated with the development of gastrointestinal, cardiovascular, and other health problems (Anderson et al. 2009; Threapleton et al. 2013). When it comes to obesity, researchers have posited that foods high in fiber may protect against weight gain by promoting satiety while contributing relatively small amounts of energy (Tohill et al. 2004; Alinia et al. 2009). The largest source of dietary fiber for most Americans has historically been vegetables, followed by fruit and bread (Block and Lanza 1987). Counter to what would be expected, however, fruit and vegetable intake has gradually increased in recent decades in the United States, alongside obesity prevalence. For

example, in 1989–1991 the average FVI for ages 2 years and up was 4.1 servings per day, which increased to 4.7 servings per day by 1994–1996 (Briefel and Johnson 2004).

Reviews on the topic of fiber intake and obesity have been inconclusive and are unable to demonstrate a clear correlation between total fiber (or fruit and vegetable) intake and weight gain (Tohill et al. 2004; Alinia et al. 2009). In part, this is probably due to the mostly epidemiologic nature of the data reviewed and potential confounders of the relationship between fiber intake and obesity, including socioeconomic determinants of diet and behavior, and the fact that diets low in fiber are often higher in other items (e.g., high-calorie density junk foods, SSBs) that do have a strong correlation with weight gain.

4.3 Fat Intake

The intake of dietary fats has been a controversial topic with respect to obesity. Analysis of longitudinal trends reveals that, coincident with the so-called low-fat craze (after dietary fats were linked to cardiovascular disease), American adults dropped their fat intake by about 11 % between 1977 and 1987, while obesity rates continued to rise sharply during that same period (Heini et al. 1997; Willett 2002). Despite this observed inverse relationship between population-level fat intakes and weight gain, there has been continued concern that fat intake could have a particularly strong impact on obesity. Because fat has a high energy density compared to carbohydrates and protein, it is hypothesized that decreasing the fat content of the diet should result in an overall calorie deficit and thus weight loss or diminished weight gain (Bray and Popkin 1998; Hill et al. 2000). Upon review of clinical trial and epidemiologic data, it appears to be true that reducing fat intake results in weight loss, provided that the fat is not replaced over time by a larger number of calories from other sources (Bray and Popkin 1998). However, at least in the United States, there is not compelling evidence that fat intake, in particular, has contributed to the increasing prevalence of obesity.

4.4 Eating Meals Away from Home

In addition to Americans changing *what* they eat or drink over the past few decades, there has also been a dramatic shift in *how* they eat. Many studies examining the sharp rise in obesity prevalence have identified a parallel trend among Americans toward eating more meals prepared outside of the home. This trend may have originated with a societal shift where more women entered the workforce beginning in the mid-twentieth century. Because of this shift, it is believed that the food marketplace began to demand more quick and convenient options for feeding families, as women had less time to devote to meal preparation (Cawley and Liu 2007).

The phenomenon of eating out or eating prepared meals appeared to really take off beginning in the 1970s. Across all age groups in the United States, the estimated energy intake from restaurants and fast-food establishments more than doubled between 1977 and 1996 (Nielsen et al. 2002). By the mid-1990s over half of Americans (57 %) reported eating at least one meal per day away from home (Briefel and Johnson 2004). Fast-food restaurants complicated the picture, representing a growing share of the food away from home market from the 1970s onward. Food and drink portion sizes at these fast-food restaurants increased sharply between the 1970s and 2000, more so than for other categories of food or drink (Briefel and Johnson 2004).

4.5 Reduced Physical Activity/ Sedentary Lifestyle

Starting in the early twentieth century, many Americans adopted sedentary lifestyles as more processes became mechanized, reducing the need for manual labor and active transport (Swinburn et al. 2011). It is believed that physical activity levels continued to drop throughout the century as more people relied on motor vehicles for transportation and the use of devices such as televisions and computers gradually increased (Jeffery and Utter 2003). By 2001, fewer than half of American adults met recommended levels of leisure time

physical activity (30 min per day on most days of the week) (Macera et al. 2005). Because reduced energy expenditure, coupled with stable caloric intake, would be expected to produce weight gain, this more sedentary modern lifestyle has been proposed as a driver of the obesity epidemic in the United States.

A sedentary lifestyle has been shown to correlate with obesity in cross-sectional and longitudinal epidemiologic studies (Giovannucci et al. 1995, 1996); however individuals who report more physical activity in these studies are also more likely to report other lifestyle choices, such as being nonsmokers and eating a more healthful diet. Physical activity does appear to have a strong correlation with an ability to maintain weight loss in previously overweight or obese individuals (Fogelholm and Kukkonen-Harjula 2000), but even in cohort studies designed to look at predictors of weight loss maintenance over time, the specific dose-response effect of exercise is difficult to tease out, with successful maintainers of weight loss displaying a wide array of activity levels (Catenacci et al. 2008). A general consensus has emerged that while a more sedentary lifestyle contributed to population-level weight gain over time, increased caloric intake probably played a stronger role in the obesity epidemic (Bleich et al. 2008). Importantly, there is a more nuanced view of physical activity emerging as a result of much of this research. Physical activity is now being viewed as a protective factor for health that varies according to a person's weight status (Michaud et al. 2001). The notion of "healthy obese" patients, whose BMI is in the overweight or obese category, but who are "fit" from a cardiovascular perspective due to regular exercise, has generated a new line of inquiry about the complex relationship between physical activity and weight (Kriska et al. 2003).

4.6 Summary of Behavioral Correlates

Although there were clear shifts in several aspects of the American lifestyle that correlated with rising obesity levels in the United States from the 1970s onward, it is quite difficult to isolate the individual influences of these different factors on weight, as they occurred contemporaneously, and to different extents across the population. Furthermore, beyond the changing diets and physical activity levels of Americans, there are a host of other changes we have not explored in this chapter but that have occurred broadly in our population during this same period. These include the widespread use of new chemicals that are known endocrine disruptors, the spread of medications that promote weight gain, the growing use of antibiotics in children, decreased sleep time, and many other factors that likely interact with an individual's genetics to promote obesity (McAllister et al. 2009). There is a clear need for further study on all of these topics, including more controlled trial data and studies using quasi-experimental designs, to better understand how physical activity level and diet behaviors interact with other factors to result in long-term changes in weight (Jeffery and Utter 2003).

5 Childhood Obesity

5.1 Choosing BMI Cut Points for Children

A major concern in tracking childhood obesity is how to appropriately set cut points for what is considered excess weight among children. Two critical dilemmas in the epidemiology of obesity are presented by studying children: first, weight and height do not increase perfectly in parallel through children's normal growth curves; secondly, early childhood weight is statistically a poor predictor of adult weight and health outcomes (Goldhaber-Fiebert et al. 2012). The risk of adult obesity is nevertheless twice as high for obese children as for non-obese children, but this finding appears to be driven by statistical correlations among older child and adolescent obesity and adult obesity, not early child obesity and adult obesity, in most assessments (Serdula et al. 1993; Power et al. 1997; Wright et al. 2001). Hence, it is important not to potentially stigmatize children who are simply

manifesting "normal variation" but also critical to not miss the opportunity to correct problematic early weight trajectories that may lead to adverse health outcomes that are difficult to reverse later in life.

The International Obesity Task Force (IOTF) is arguably the group that has most carefully reviewed the epidemiology of obesity among children and has defined BMI-for-age cut points specific to each sex that take into account the variability in weight per height squared across age groups from birth to age 18; these cut points gradually change with age to eventually match the conventional BMI cut points for overweight and obesity by age 18 (Dietz and Bellizzi 1999). The cut points are intended to capture individuals who exceed the 85th (overweight) or 95th (obese) percentiles to further identify pathological weight, normalizing individuals against historical peers to more precisely identify individuals with high body fat, given that BMI itself does not necessarily correspond to body fat among minority children (Yanovski et al. 1996; Daniels et al. 1997). Another problem with using BMI alone rather than calibrating BMI to age- and sex-specific cut points is that among populations with significant undernutrition, metabolic changes in early life may lead to high weight-for-height despite having a normal or low body fat content (Trowbridge et al. 1987).

5.2 Trends and Disparities Among Children

Using the standard IOTF cut points, which are incorporated into CDC growth charts used by pediatricians, it is evident that overall adult trends in obesity and disparities in obesity prevalence among race/ethnic and socioeconomic groups are developed during early childhood and adolescence. According to NHANES measures, over one-fifth of children are overweight or obese by the time they are in the 2–5-year-old age group, and the disparity across White, Black, and Mexican-American children is statistically significant by age 6 (Hedley et al. 2004). The rise in obesity among children corresponded to the rise among adults, with most of the increase occurring during the 1980s and 1990s (Freedman et al. 2006). Socioeconomic disparities among children and adolescents have been more complex. Socioeconomic disadvantage is associated with increased risk among young children but is not universally the case among adolescents, for whom higher-social class Black girls had a higher risk of obesity (Kimm et al. 1996; Gordon-Larsen et al. 2003; Whitaker and Orzol 2006). As among adults, the race/ethnic disparities in obesity among children are not fully explained by socioeconomic disparities among children, as the two factors of race/ethnicity and socioeconomic status seem to have some statistically independent and compounding effects on one another (Singh et al. 2008b). Furthermore, spatial variations in childhood and adolescent obesity follow the same trends as in adult obesity, in that geographic disparities between neighborhoods persist in association with income inequality, poverty, violence, and other socioeconomic clustering that manifests as both income and race/ethnic segregation between communities (Singh et al. 2008a).

5.3 Risk Factors and Consequences of Obesity Among Children

Studies of early child obesity have suggested that significant learning of dietary behaviors occurs during the transition from breastfeeding or formula feeding to the consumption of solid foods (Birch and Fisher 1998), as well as related transitions to the preschool period and the transition to adolescence when peer influences become particularly salient (Fowler and Christakis 2008). These data suggest that the natural predispositions toward sweet foods may be substantially influenced by parental (among younger and older children) and peer (among older children) social behaviors and the learning of appropriate social responses to internal cues of hunger, craving, and satiety (Birch and Fisher 1998; Campbell et al. 2007). Concordant with this notion, family-based obesity reduction interventions suggest that child weights tend to follow those of parents, which may be due both to household-level

nutrition and physical activity improvements, as well as secondary benefits through social modeling (Epstein et al. 1994; Wrotniak et al. 2004). Notably, there remains active debate about whether the correlations of "obesogenic" behaviors among peers are truly due to social network effects or due to common contextual factors that influence individuals without behaviors necessarily being "infectious" over networks (Cohen-Cole and Fletcher 2008), although the two possibilities are not mutually exclusive.

Although most risk factors for childhood obesity correspond to adult risk factors (poor nutrition and physical inactivity), some additional studies have suggested unique risk factors for children. Maternal BMI is predictive of early childhood BMI due in part to gestational obesity and diabetes (Butte et al. 2007), although whether the persistent association between material BMI and child BMI in older children is due to purely biological or mostly social reasons remains debatable. In addition, breastfeeding has been correlated to lower obesity rates, as opposed to formula feeding (Armstrong and Reilly 2002; Singhal and Lanigan 2007). A trial in Belarus, however, did not confirm these findings but was underpowered to find an effect (Kramer et al. 2007). The question therefore remains open as to whether breastfeeding may have a protective effect or if the epidemiological correlation between breastfeeding and lower obesity risk is driven by selection bias (e.g., as higher socioeconomic classes breastfeeding more commonly).

Additional behavioral predictors of obesity have been studied extensively in children and adolescents. Television watching and related sedentary behaviors have been found to be a key risk factor throughout childhood and adolescents, with a randomized trial suggesting that the risk is causal (Robinson 1999). Psychiatric comorbidities among adolescents have also been found to be predictive of heightened obesity risk. In particular, depression among adolescents was found to increase the risk of incident obesity and the persistence of obesity during adolescence (as opposed to only the converse finding of higher depression among those adolescents who are already obese); this is thought to manifest from unhealthy eating behaviors as a self-nurturing behavior for depressed adolescents or due to fatalism leading to unhealthy behaviors as long-term health prospects seem unimportant (Goodman and Whitaker 2002; Stice et al. 2005). Both binge eating and dieting among adolescents has been observed to increase the risk of future adult obesity, suggesting that steady self-regulation as a skill, as opposed to fluctuating and irregular eating behaviors, may be key to obesity prevention in this group (Tanofsky-Kraff et al. 2006).

Addressing these risk factors for childhood obesity appears important to reducing numerous premature adverse health events. In addition to manifesting early cardiovascular and metabolic disease risk factors (e.g., hypertension, hyperlipidemia, abnormal glucose tolerance), obese children appear to be at an increased risk for rarer diseases (e.g., pseudotumor cerebri) and for social problems arising from peer and adult stigmatization that potentially persists into adulthood (Dietz 1998). Health-related quality of life among obese children and adolescents is significantly lower than among their non-obese counterparts across all domains including physical functioning, emotional functioning, social functioning, and school functioning; the quality of life scores were similar to those among children with cancers (Schwimmer et al. 2003).

6 The Obesity Paradox

Any overview of obesity in the United States would be incomplete without discussing the so-called obesity paradox. This term refers to a pattern observed in epidemiologic studies whereby individuals whose weights are in the overweight (or even class I obese) category have lower mortality risk compared to individuals with normal BMI (Flegal et al. 2013; Romero-Corral et al. 2006). The finding has been particularly strong in selected patient populations with chronic illness, such as those with congestive heart failure (Horwich et al. 2001), and coronary artery disease (Kennedy et al. 2005). The finding is considered paradoxical because obesity and overweight are associated with a number of conditions that

should theoretically increase mortality relative to normal-weight individuals, including diabetes, hypertension, stroke, and cancer.

The notion of a paradoxical relationship between overweight or obesity and mortality has caused considerable debate in the obesity research community and spurred many studies in an attempt to sort out possible sources of bias or confounding that might lead to an erroneous association. For example, if smokers or patients with severe chronic disease such as cancer (groups with lower average BMIs but very high mortality risk) are included in the at-risk population, then it is likely that smoking or cancer acts as confounder or creates a situation of reverse causation in the BMI-mortality relationship. As a result, there have now been several large studies demonstrating that when smokers and those with known cancer are eliminated from the analysis, mortality increases in a linear fashion with weight for overweight, obese, and severely obese participants, relative to those in the normal-weight category (Berrington de Gonzalez et al. 2010; Tobias et al. 2014; Preston and Stokes 2014).

On the other hand, hypotheses about why overweight or mild obesity might be protective for some individuals have also been generated. These include the idea that extra adipose tissue could provide a "metabolic reserve" in times of acute illness (Doehner et al. 2010) or that it may allow patients to better tolerate certain medications (e.g., anticoagulation or blood pressure lowering in the case of treatment for acute myocardial infarction) (Kennedy et al. 2005). Other possible explanations for the findings include treatment bias that results in overweight or obese patients being more readily identified and treated for conditions such as cardiovascular disease than their normal-weight counterparts, thereby reducing their mortality due to the disease being treated earlier on (Greenberg 2013).

There have also been studies where adjusting for factors such as smoking status did not seem to resolve the obesity paradox (Flegal et al. 2013; Greenberg 2013), calling into question the general utility of BMI as a stand-alone predictor of health, particularly in chronically ill populations. Given that BMI does not provide an accurate measure of body fat distribution on its own, some experts have called for revisions to the way obesity is classified, asking that predictors of visceral adipose tissue, such as waist circumference or waist-to-hip ratio, be used in conjunction with BMI to provide a more complete picture of the cardiometabolic risk for a given individual (Carmienke et al. 2013).

7 What Does the Future Hold?

7.1 Obesity in an Aging Population

Among the critical issues facing obesity epidemiologists is the question of how obesity should be tracked among an increasing aging population. Emerging literature suggests that health risks related to weight among older adults cannot be accurately evaluated purely in terms of body fatness or fat distribution. Rather, because older adults have less bone and muscle mass, reduced body cell mass, and increased extracellular fluid volumes in their bodies, nonfat components of the body play critical roles in functional and physical functioning as well as comorbid disease risk. As a result, geriatricians and others studying obesity among older adults have increasingly used the term "sarcopenic obesity" to describe the phenomenon in which skeletal muscle atrophy (sarcopenia) in the context of elevated BMI is at greatest risk for morbidity and disability (Baumgartner 2000; Stenholm et al. 2008; Lim et al. 2010). Sarcopenic obesity appears to be associated with the incidence of disability independently from age, sex, physical activity level, prevalent morbidity, and length of follow-up, possibly due to reductions in anabolic metabolism and increased catabolism in older adults (Baumgartner et al. 2004), particularly due to pro-inflammatory cytokines (Schrager et al. 2007) and peptides produced by adipose tissue (Zamboni et al. 2005). Furthermore, reduced muscle mass decreases insulin-responsive tissue stores, which may promote insulin resistance and obesity (Roubenoff 2004). In some studies, however, obesity itself has been found to be more important than sarcopenia in

contributing to the lower capacity (Bouchard et al. 2009); similarly, sarcopenia itself is often not seen to cause disability apart from when it is accompanied by obesity (Rolland et al. 2009). Obesity itself also has also been linked to the onset of "frailty," which includes weakness, slowness, and exhaustion (Blaum et al. 2005).

7.2 Potential Plateau of Childhood Obesity Rates

Shortly before this writing, a new wave of NHANES data analyses suggested that while no significant improvements have occurred in obesity prevalence among most populations, there is a significant decrease in obesity among 2- to 5-year-old children (from 13.9 % to 8.4 %) (Ogden et al. 2014). The result was widely celebrated in both the popular and social media, even including attributions of causality to the White House "Let's Move" initiative, despite the likelihood that the prevalence changes actually occurred prior to the initiative's existence (Kass 2013). Among epidemiological observers, several concerns were raised about whether these findings were "real." In particular, differences in sampling over study waves (e.g., oversampling of Asians in the latest survey) and inadequate correction for multiple testing error (false findings by chance) may have produced a false sense of prevalence reduction in this young age group (Appel 2014; Rimm 2014). At the time of this writing, it remains premature to conclude that the finding is indicative of a true trend in improved obesity prevalence among children, which would be the first such decline observed in any developed country (Stuckler and Siegel 2011).

7.3 Trends in Severe Obesity

While overall obesity prevalence has plateaued, this may be due to the cut point for BMI that is defined as obese. That is, a large and stable population exceeds the cut point for obesity, but within this obese group, weight-for-height continues to increase. In particular, the prevalence of severe obesity (BMI GE 35 kg/m^2) continues to rise, with at least 14.5% of the American adult population meeting these criteria in 2011–2012 (Ogden et al. 2007, 2014).

Hence, obesity prevalence remains relatively stable, but the severity of obesity – and, in turn, the severity of complications related to obesity – continues to worsen among the general adult population (Andreyeva et al. 2004).

8 Cross-References

- Childhood Environment and Obesity
- Diet and Obesity (Macronutrients, Micronutrients, Nutritional Biochemistry)
- Diet, Exercise, and Behavior Therapy in the Treatment of Obesity and Metabolic Syndrome
- Obesity and Cardiac Disease
- Sarcopenic Obesity
- Social and Community Networks and Obesity
- The Built Environment and Obesity

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Obesity in Latin America

3

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Contents

Abstract

Obesity in Latin America has become a serious health problem. The highest prevalence in adults is now seen in Mexico (more than 30 %), and in children, it is seen in girls in Uruguay (more than 15 %). Obesity is the driving force for the epidemic of diabetes mellitus which has also extended to Latin America, and the increasing frequency of these two metabolic problems runs in parallel together with the metabolic syndrome. Abdominal obesity has been ill defined in Latin America until recently when the regional cutoffs for waist circumference were set at 94 cm for men and 88–90 cm for women. A high waist-hip ratio is associated with a two- to fourfold increase in the risk of having an acute myocardial infarction. Latin America is going through an accelerated urbanization process, and in some countries in Central America, this may lead to a steep rise in obesity and associated metabolic problems when the transition takes momentum. By the year 2030 overweight and obesity are expected to affect 50 % of males and 60 % of females in Latin America. Its burden reflects in the alarming increase of cases of diabetes, hypertension, CHD, stroke, cancer, and knee osteoarthritis. That could be minimized significantly if the mean BMI was reduced by 1 % and even more with a 5 % reduction and would save billions of US dollars in the next 30–40 years. A systematic review supports school-based interventions to improve lifestyle in children

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and healthcare interventions among overweight adults in Latin America. Many governments in Latin America are now developing innovative population strategies to reduce the obesity epidemic.

Keywords
Obesity • Latin America • Abdominal obesity

1 Introduction

Obesity in Latin America has become a serious health problem. Its frequency has rapidly increased in parallel with economic growth as a consequence of urbanization and industrialization, leading to changes in lifestyle including sedentarism and nutritional transition. The so-called coca-colonization entices even the most traditional communities where habits such as drinking bottled sweet drinks are now part of their lifestyle.

2 Epidemiology

Among the Latin American countries, Mexico has now the highest prevalence of obesity in adults. Their last national survey in 2012 (Barquera et al. 2013) revealed that 32.4 % of the adult population (ages ≥20 years) was obese (BMI ≥30 kg/m^2) and an additional 38.8 % was overweight (BMI 25–29.9 kg/m^2). Obesity was more prevalent in women and overweight in men. Greater proportion of both was observed in people with higher income, living in urban settings, and located in the north of the country (nearer to the USA). In the last 12 years, the prevalence of obesity and overweight had increased by 15.2 %. In Table 1 the Latin American countries are listed according to their age-standardized prevalence range of obesity estimated for 2013 (Ng et al. 2014).

In children, the prevalence of obesity as defined by the International Obesity Task Force is also increasing (Ng et al. 2014). It is alarmingly high in Uruguayan girls and high in most of the countries which also have the highest prevalence of obesity in adults. In Table 2 the Latin American countries are listed according to their age-standardized prevalence range of obesity in children estimated for 2013.

3 Obesity and Metabolic Disease

Obesity is the driving force for the epidemic of diabetes mellitus (DM) which has also extended to Latin America. Around 8 % of the adult population (20–79 years) in the SACA region of the IDF (excluding Mexico) has diabetes, and for each subject with the disease, there is roughly one with prediabetes (prevalence 7.5 %) (Aschner et al. 2014). In a cross-sectional study of adults (ages 25–64 years) in seven Latin American cities, Mexico City had the highest prevalence of diabetes (8.9 %) which coincided with the highest prevalence of obesity (31 %) and metabolic syndrome (27.2 %). Prevalence of diabetes in the other six

Table 1 Age-standardized prevalence of obesity (BMI ≥30 kg/m^2), adults ages ≥20 years, 2013 (Adapted from Ng et al. 2014)

Prevalence range (%)	Men	Women
30–40		Chile, El Salvador, Honduras, Mexico, Nicaragua, Paraguay
20–30	Argentina, Chile, Mexico, Paraguay, Uruguay	Argentina, Bolivia, Brazil, Colombia, Costa Rica, Cuba, Dominican Republic, Peru, Uruguay, Venezuela
15–20	Costa Rica, Cuba	Ecuador, Guatemala, Panama
10–15	Bolivia, Brazil, Colombia, Dominican Republic, Nicaragua, Panamá, Venezuela	
5–10	Ecuador, El Salvador, Guatemala, Honduras, Peru	

Table 2 Age-standardized prevalence of obesity (based on IOTF cutoffs), children 2–19 years, 2013 (Adapted from Ng et al. 2014)

Prevalence range (%)	Boys	Girls
15–20		Uruguay
10–15	Chile, Mexico	Chile, Costa Rica, Cuba
7.5–10	Argentina, Uruguay	Brazil, Mexico, Venezuela
5–7.5	Costa Rica, Cuba, Brazil, Paraguay, Venezuela	Argentina, Dominican Republic, El Salvador, Nicaragua, Panama, Paraguay
2.5–5	Bolivia, Colombia, Dominican Republic, Ecuador, El Salvador, Guatemala, Nicaragua, Panama, Peru	Bolivia, Colombia, Ecuador, Guatemala, Honduras, Peru
0–2.5	Honduras	

cities (Barquisimeto in Venezuela, Bogotá in Colombia, Buenos Aires in Argentina, Lima in Peru, Quito in Ecuador, and Santiago in Chile) ranged between 4.4 % and 8.1 %, obesity between 16.3 % and 26.6 %, and metabolic syndrome between 13.7 % and 25.8 % (Schargrodsky et al. 2008). The latter was diagnosed by the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATPIII) criteria.

4 Abdominal Obesity

The ATPIII criteria for diagnosing the metabolic syndrome include abdominal obesity defined by a waist circumference >102 cm in men and >88 cm in women (Grundy et al. 2005). The International Diabetes Federation (IDF) proposed to use ethnicity-specific values for the waist circumference in non-Europid groups (Alberti et al. 2005), and this was corroborated in the latest joint statement of the IDF and other institutions mainly from North America and Europe (Alberti et al. 2009). Nevertheless, since the ethnic-specific data for Latin America was not available, in the statement, it was recommended to use the Asian criteria in our region (abdominal obesity diagnosed by a waist circumference ≥90 cm in men and ≥80 cm in women) until new data appeared.

The IDEA study, which compared the waist circumference of more than 160,000 primary care patients from 63 countries around the world, clearly showed that the mean values for Asian men and women were around 10 cm lower than the rest of the regions, including Latin America (Balkau et al. 2007). The mean circumference value for our region was comparable to Eastern Europe. We analyzed our regional data in more than 28,000 patients and found a strikingly high frequency of abdominal obesity in women with normal BMI (42 %) using the IDF criteria for Asia, suggesting that an evidence-based definition of abdominal adiposity was needed (Aschner et al. 2009). Recently, we investigated the waist circumference value that identified subjects with excess visceral fat measured by CT scan using a standardized method in 457 voluntaries from five Latin American countries (Colombia, El Salvador, Mexico, Paraguay, and Venezuela), and by ROC curves, we found that the cutoffs for waist circumference in our population were 94 cm in men and 90 cm in women (Aschner et al. 2011). There have been other attempts in Latin America to establish the cutoffs using cardio-metabolic endpoints (lipids, blood pressure, CVD surrogates), but they have been limited to local populations, and the cutoff values for waist circumference were similar to those found in our study (Sanchez-Castillo et al. 2000; Perez et al. 2003; Bastos Barbosa et al. 2006; Medina-Lezama et al. 2010). A multinational study of almost 4,000 postmenopausal women attending routine consultation at 12 gynecology centers in major Latin American cities found that the optimal WC cutoff value best predicting at least two other components of the metabolic syndrome was 88 cm (Blümel et al. 2012). In the INTERHEART case-control study, the waist-hip ratio (higher vs. lower tertile) in Latin American population was associated with

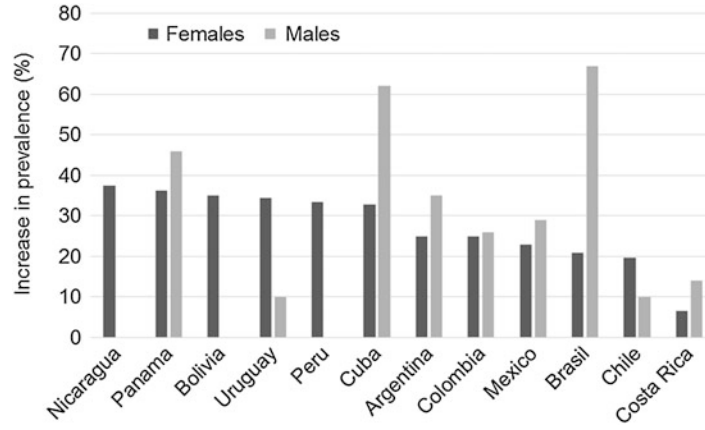

Fig. 1 Estimated increase in the prevalence of overweight and obesity from 2010 to 2050 in some Latin American countries (Adapted from Webber et al. 2012; Rtveladze et al. 2013a, b)

a twofold risk of having an acute myocardial infarction in men and a fourfold risk in women, and the population attributable risk was 36 % and 63 %, respectively (Lanas et al. 2007).

5 Burden of Obesity

Many countries in Latin America are still going through an accelerated urbanization process. Although in some countries such as Argentina, Uruguay, and Venezuela more than 90 % of the population lives in the cities, there are still countries in Central America such as Guatemala, Honduras, and Nicaragua where more than 40 % of the population lives in the rural area (Aschner et al. 2014). Overweight and obesity affect more people living in urban than in rural areas, and the latter are expected to be more physically fit. Obesity has been associated with low socioeconomic status and low educational level, but in communities where the transition is taking place, it penetrates first households with higher income (Rivera-Andrade et al. 2014). In that population being moderately fat is a sign of wealth, prosperity, and good health. It is worrisome that those Central American countries where the proportion of rural population is still high have also the highest prevalence of obesity (Table 1) and diabetes (12.5 % in Nicaragua and 10.9 % in Guatemala) (Aschner et al. 2014) which means that the problem can get much worse when full transition occurs.

Overweight and obesity are expected to affect 50 % of males and 60 % of females by 2030 in Latin America. The increase in the prevalence of overweight and obesity was estimated in some Latin American countries, and the highest projected rates for males were in Brazil and Cuba and for females in Nicaragua and Panama (Webber et al. 2012; Rtveladze et al. 2013a, b; Fig. 1). In Brazil the high rates of obesity have been associated with a significant increase in the burden of other chronic diseases. Prevalence of diabetes and knee osteoarthritis will double between 2010 and 2050. Hypertension will increase more than 1.5-fold, and CHD, stroke, and cancer will triple. A reduction of 1 % in the mean BMI of the Brazilian population would save in 2050 nearly 10,000 cases of cancer and over 222,000 cases of CHD/stroke as well as over 0.7 million cases of knee osteoarthritis, nearly 0.8 million cases of type 2 diabetes, and 1.6 million cases of hypertension. If the mean BMI decreased by 5 %, the figures would be 21,000, 600,000, 2.5 million, 2.1 million, and 5.4 million, respectively. A 1 % reduction in mean BMI by 2050 would lead to a reduction in healthcare expenditure, saving over US$ 27 billion which would increase to US$ 56 billion with a 5 % decrease in mean BMI (Rtveladze et al. 2013a). A similar result was found in Mexico where obesity-related CHD, stroke, cancers, and diabetes are projected to more than double between 2010 and 2050. The rates will also nearly double for hypertension and knee osteoarthritis. A reduction of 1 % in the

mean BMI will result in 28,277 fewer cases of cancer, 400,227 fewer cases of CHD/stroke, and 877,311 fewer cases of diabetes in 2050. With a 5 % reduction in BMI, there would be a reduction of 82,655, 1.2 million, and 2.5 million cases of cancer, CHD/stroke, and diabetes, respectively. Such a reduction would save US$ 85 million in 2050 (Rtveladze et al. 2013b).

6 Strategies to Reduce Obesity

Unfortunately, few trials have been reported on the efficacy of obesity-related interventions in Latin America. In a recent systematic review of such interventions in Latinos in the USA and in Latin America (mostly Mexico, Brazil, and Chile) which was published between 1965 and 2010, the authors found sufficient evidence to recommend school-based interventions to improve physical activity, particularly those which included a component for parent participation (Lobelo et al. 2013). They also found evidence to recommend interventions to improve healthy eating and physical activity in the healthcare context for children who are already overweight or obese. In this context, the most successful interventions included longer intervention time (e.g., 16 weeks) and a multidisciplinary approach involving psychologists, physical trainers, and endocrinologists. The healthcare setting may have a stronger influence on individuals' health behaviors in developing countries and for cultures that hold physicians in high regard. The authors also found sufficient evidence to recommend healthcare interventions aimed at improving physical activity and healthy eating among overweight adults in Latin America but not to support prevention interventions for adults (Holub et al. 2013; Mehta et al. 2013). In fact, promoting better nutrition in undernourished communities without educating on healthy lifestyle may lead to obesity, particularly if the aid is given in terms of extra income (Forde et al. 2012).

There are initiatives ongoing on prevention of obesity at the population level in Latin America (Elder and Arredondo 2013). The Centre for Disease Control (CDC) in the USA has been developing a guide to obesity prevention in Latin America and the USA (project GOL) in collaboration with the Mexican National Institute of Public Health (Instituto Nacional de Salud Pública, INSP) to better understand, assess, and develop evidence-based strategies and recommendations to effectively prevent obesity in Latin American communities and populations (Project GOL 2015). The project has examined and synthesized published literature related to policy, community, and organizational change strategies to promote physical activity and healthy diets (Holub et al. 2013), and now it has focused on different methods that would promote water consumption in elementary school students, including the Water for Kids project aimed at increasing the accessibility of water to children by providing each student with a water bottle. The walk and water team was derived from the previous study that provided students with water bottles and classroom education on drinking water and physical activity. The study utilized a system to monitor students' physical activity by counting the number of laps each student ran or walked. In general they have succeeded in changing some lifestyle habits (Project GOL 2015). The Mexican government has also launched the National Agreement on Nutritional Health (Acuerdo Nacional para la Salud Alimentaria, ANSA) which includes ten strategies based on increased physical activity; access to drinking water; reduced consumption of sugar and fat in beverages; increased consumption of fruits, vegetables, whole grain cereals, and fiber; food labeling; promotion of breastfeeding up to 6 months; reduction of added sweeteners; reduction of saturated and trans fats; reduction of portion sizes; and less sodium in the diet (ANSA 2015). Following a similar trend, Brazil launched a strategic plan for preventing chronic disease supported by national legislation that will scale up physical activity promotion programs built around community classes to 4,000 municipalities in Brazil. This appears to be the largest and most comprehensive national commitment to physical activity promotion in the world to date (Pratt et al. 2014). Colombia has been doing this through a program called Ciclovía Recreativa in which streets are closed to

motorized transport, transforming them into temporary linear parks focused on recreational activities. It started in Bogotá more than 40 years ago, and now during Sundays and festivity days, more than one million individuals walk, jog, run, or cycle along the main streets which are closed for vehicles. The Ciclovía program has been incorporated into the Colombian National Public Health Plan as a strategy for promoting physical activity and reducing chronic diseases, and since 2009, it became part of the national obesity law. It serves as a model for more than 300 programs in Colombia and beyond. Studies conducted in Bogotá and in the USA show that users of the open streets or Ciclovía programs are more likely to meet physical activity guidelines and that Ciclovía programs are cost beneficial (Montes et al. 2012).

Latin America is in a strong position to implement prevention strategies. Most Latin American countries have strong and well-established infrastructures, health systems, education, communications, and an active and engaged civil society. In general there is abundant availability of fruits and vegetables all year-round. There is still an opportunity to preserve some of the traditional lifestyle advantages such as home cooking and walking. Thus, there is every reason to believe that, with appropriate planning and implementation, Latin America can reduce obesity prevalence (Editorial 2014).

7 Cross-References

- Body Composition Assessment
- Global, National, and Community Obesity Prevention Programs
- Prevention and Treatment of Childhood Obesity and Metabolic Syndrome
- Type 2 Diabetes: Etiology, Epidemiology, Pathogenesis, Treatment

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Obesity in Sub-Saharan Africa

4

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Contents

Abstract

This chapter outlines the epidemiology of overweight and obesity in sub-Saharan Africa, their determinants, and the relationship with cardiovascular diseases (CVDs) and diabetes. The review shows that overweight and obesity rates are increasing in all African regions with Southern African region being the most affected. The rate of overweight and obesity is higher among women than among men and in urban areas compared to rural areas. Socio-economic status, age, parity, marital status, physical inactivity, body weight perceptions, and increased energy are powerful predictors of overweight and obesity in sub-Saharan Africa. The rapid urbanization accompanied by nutrition transition is changing the disease landscape in sub-Saharan Africa with CVD and its related risk factors gaining prominent position. The rising levels of overweight and obesity in sub-Saharan Africa are likely to exacerbate the burden of CVD and diabetes if measures are not taken to curb the problem. Public health strategies focusing on healthy diet, physical activity, weight reduction, and maintenance strategies are urgently needed in sub-Saharan African countries.

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Overweight • Obesity • Cardiovascular diseases • Diabetes • Gender • Sub-Saharan Africa

1 Introduction

Obesity is a significant contributing factor for various chronic diseases such as cardiovascular diseases (CVD), type 2 diabetes (T2D), musculoskeletal disorders, and some cancers (Prospective Studies Collaboration 2009). Obesity and its related conditions lead to reduced quality of life and premature death. A meta-analysis of 97 studies, for example, showed that, compared with normal weight, being obese was associated with higher all-cause mortality for all grades of obesity combined (Flegal et al. 2013). Obesity is truly a global burden. In 2014, more than 1.9 billion adults were overweight. Of these over 600 million were obese (WHO 2015).

The fundamental cause of *overweight* and obesity is an energy imbalance between calories consumed and calories expended. The nutrition transition, characterized by the change from diets of high nutritional quality to those in low poor diets, is occurring globally (Popkin et al. 2011). The nutrition transition coupled with the epidemiological and demographic transitions has set population health toward high prevalence and incidence of obesity and related sequelae such as hypertension, diabetes, strokes, cancers, heart attacks, and other *chronic noncommunicable diseases* (NCDs) (Lancet 2011; Martorell et al. 2000; Rutter 2011). Africa is also experiencing these transitions (Abubakari et al. 2008; Awuah et al. 2014; Steyn and McHiza 2014).

In *Africa*, a complex coexistence of undernutrition and overnutrition has been reported. Between 1992 and 2005, the prevalence of overweight and obesity increased by almost a third in sub-Saharan Africa (Ziraba et al. 2009). Until recently, this increase was reported among women and urban residents (Martorell et al. 2000); however, current data show consistent increase in overweight and obesity among men and rural residents as well (Afolabi et al. 2004; Kimani- Murage et al. 2011). The trend toward rising overweight and obesity poses both health and socioeconomic challenges to individuals and the region.

Reviews examining the prevalence of overweight and obesity have been limited in African nations (Chukwuonye et al. 2013; Micklesfield et al. 2013) and regions of Africa (Abubakari et al. 2008; Steyn and McHiza 2014). However, given the fast increasing prevalence of overweight- and obesity-related illnesses such as T2D, it is highly relevant to map the current information about overweight and obesity prevalence in Africa to help health workers, government agencies, and policy makers toward setting priorities and for designing interventions. In this chapter, therefore, we aimed to outline the *epidemiology* of overweight and obesity in *sub-Saharan Africa*. Secondly, we examined the determinants of overweight and obesity and their impact on CVDs and diabetes.

Box 1 Search Strategy
Two kinds of data were used for this review study: the World Health Organization (WHO) Global InfoBase on overweight and obesity (https://apps.who.int/infobase/Index.aspx) and a review of determinants of overweight and obesity in Africa. *WHO Global InfoBase database* was used to provide prevalence estimates by sex, region, residence, and socioeconomic status and to depict trends of overweight and obesity over time in various African regions. In addition, we conducted a review on determinants of overweight and obesity in Africa using several electronic databases including ScienceDirect, EBSCOhost, Academic OneFile, eLibrayUSA, PubMed, JSTOR, and AJOL. In webpages where the advanced search option was allowed, the search was limited to English language, human studies, and peer review journal articles.

1.1 Measurement of Overweight and Obesity

Body mass index (BMI) is a simple index of weight for height that is commonly used to classify adult with overweight and obesity. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2). A BMI of 25–29.9 kg/m^2 is classified as overweight and BMI $\geq$30 kg/m^2 is classified as obesity.

2 Prevalence and Overweight and Obesity in Africa

Figure 1a, b shows *prevalence* of overweight in 46 *WHO African countries*. Among men (Fig. 1a), the prevalence of obesity ranged from 3.5 % in Eritrea to about 64 % in Seychelles in 2010. The top five countries with the highest prevalence of overweight were Seychelles (64 %) followed by Mauritius (44.8 %), Cameroon (43.9 %), Botswana (41.6 %), and South Africa (41 %). Conversely, the top five countries with the lowest rates include Eritrea (3.5 %), Democratic Republic of Congo (5.7 %), Kenya (7.7 %), Central African Republic (8.0 %), and Rwanda (8.1 %). Women in general have higher prevalence of overweight than men in all countries with the prevalence rates ranging from 3.7 % in Ethiopia to 74 % in Seychelles. The top five countries with the highest prevalence of overweight were Seychelles (73.8 %), Lesotho (70.8 %), South Africa (68.5 %), Mauritania (56.8 %), and Mauritius (53.5 %). The top five countries with the lowest rates include Ethiopia (3.7 %), Eritrea (6.3 %), Democratic Republic of Congo (15.8 %), and Central African Republic and Zambia with 20 %.

Figure 2a, b shows the prevalence of obesity in various WHO African countries. The prevalence of obesity ranged from 0 % in Eritrea to about 21 % in Seychelles in men and from 0 % in Ethiopia to about 43 % in Seychelles in women. In men, only two countries (Seychelles and Cameroon) out of the 46 countries had obesity prevalence of more than 10 %. Among women, however, 17 countries of the 46 countries (37 %) had prevalence of obesity of more than 10 %.

2.1 Regional Differences Overweight

Figure 3 shows the time trend prevalence of overweight in various African regions. Overweight has been on the increase in all regions since 1990, although the extent of the increase has differed between regions. In 1990, the prevalence of overweight was highest in the *Northern Africa* (7.5 %) followed by *Southern Africa* (6.4 %), *Eastern Africa* (4.5 %), *Middle Africa* (3.7 %), and *Western Africa* (2.6 %). There has been a staggering increase of overweight in Southern African region since 1990 with average prevalence rate of 21 % in 2015 (330 % increase in the last 25 years) compared to other regions. Northern African region has also experienced rapid increase in overweight since 1990 with prevalence of 13 % in 2015 (73 % increase in the last 25 years). In other regions, the percentage increase in the last 25 years has been modest ranging from 9 % in Eastern Africa to 70 % in Western Africa.

2.2 Urban and Rural Differences in Overweight and Obesity

Urbanization has been linked to increased risk of overweight and obesity in Africa; therefore, most urban populations have higher overweight and obesity rates than rural populations (Benkeser et al. 2012; Agyemang et al. 2009; Abubakari et al. 2008; Amoah 2003; Kandala and Stranges 2014). This reflects on the clear differences in the prevalence of obesity between rural and urban communities across sub-Saharan African countries (Fig. 4). As Fig. 4 shows, the percentage difference in the prevalence of obesity ranges from 4 % higher in rural Chad to about 10 % higher in *urban* Lesotho and Uganda compared with *rural* communities in these countries.

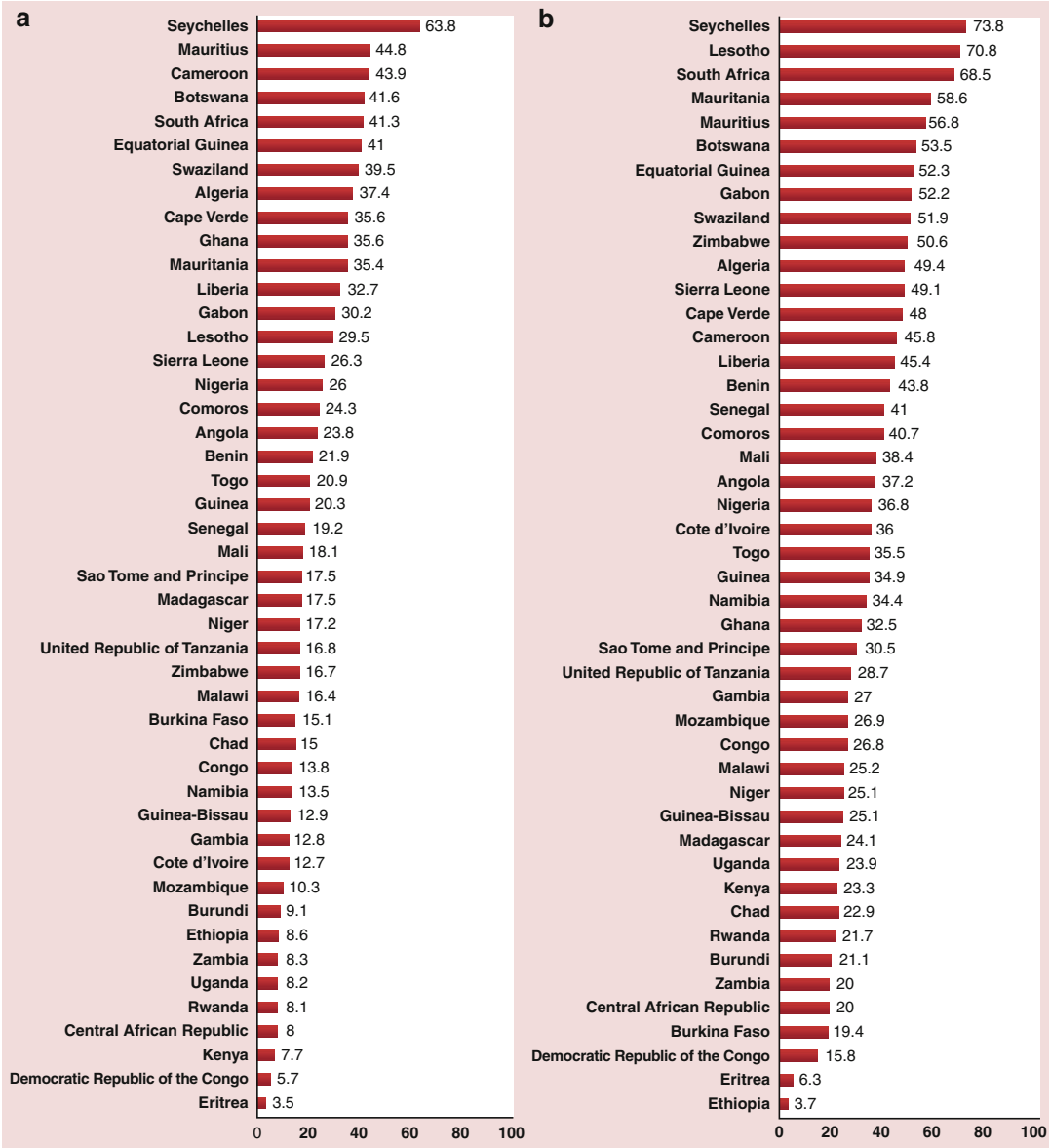

Fig. 1 (**a**) (men) and (**b**) (women): estimated overweight and obesity (BMI ≥25 kg/m^2), prevalence, males, aged 15+, 2010 (Source: WHO Global InfoBase)

3 Determinants of Obesity

From the review the determinants of overweight and obesity were categorized into three: sociodemographic factors, *socioeconomic status*, and perceptions of weight and lifestyle factors.

3.1 Sociodemographic Factors and Obesity

Generally, obesity rates are higher among females than among males in Africa as indicated above. In 2006, obesity was six times as common in women as in men in Ghana, four times in Morocco, and in

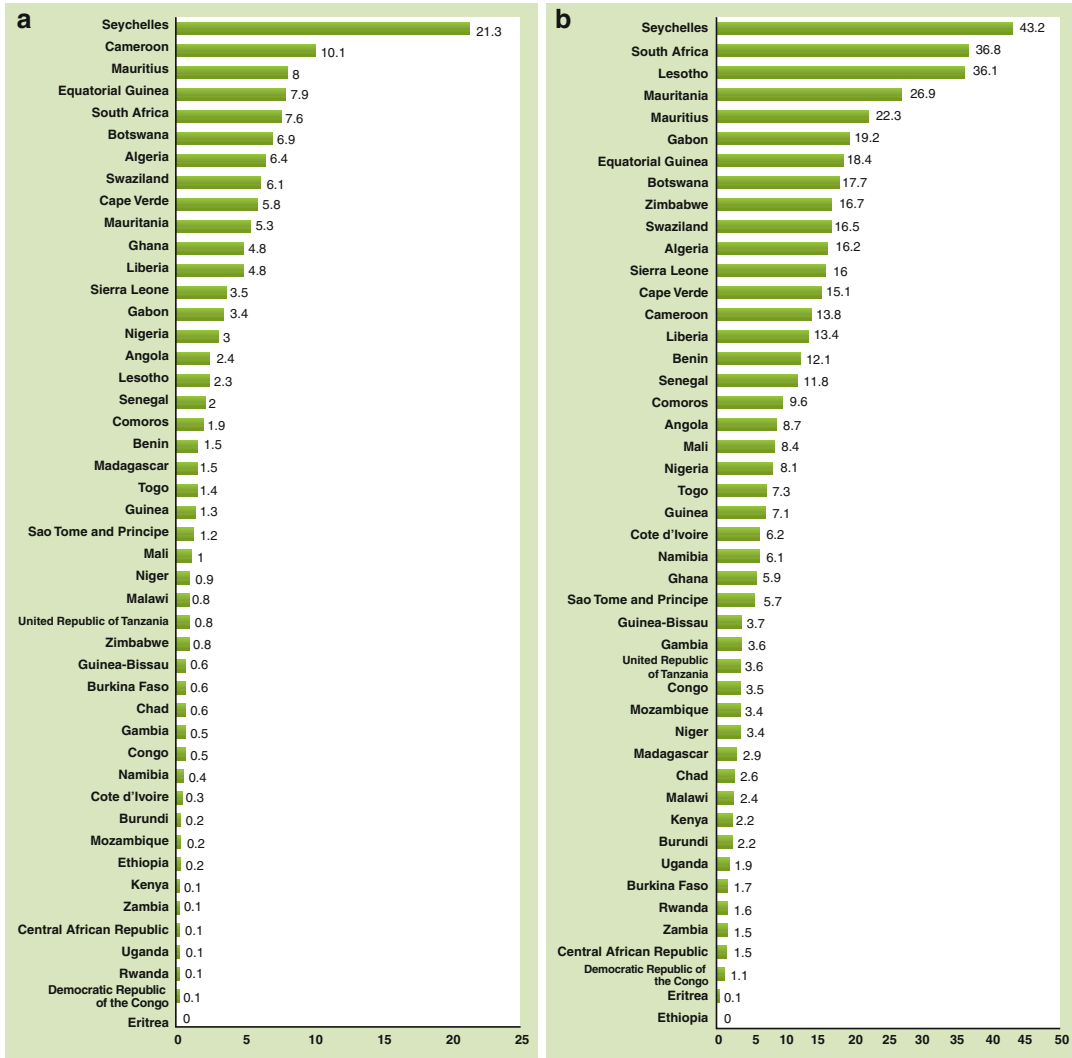

Fig. 2 (**a**) (men) and (**b**) (women): estimated obesity (BMI ≥30 kg/m^2), prevalence, males, aged 15+, 2010 (Source: WHO Global InfoBase)

South Africa three times as common in women as in men (Prentice 2006). Pereko et al. (2013) in Ghana reported that females were about eight times more likely to be overweight/obese than males. In addition, Njelekela et al. (2009) reported that Tanzanian women were 4.5 times more likely to be obese compared to men. Similarly, obesity prevalence was higher among South African women compared with men (Malhotra et al. 2008).

Although body weight varies by *sex*, it is related to a specific stage of life. A number of studies in Africa have reported a positive association between *age* and obesity (Biritwum et al. 2005; Amoah 2003; Duda et al. 2007; Muhihi et al. 2012; Dake et al. 2010; Pobee et al. 2013; Iloh et al. 2011; Pereko et al. 2013; Atek et al. 2013; Shayo and Mugusi 2011; Masibo et al. 2013). While obesity increases with age, it increases up to a certain age and declines afterward. For instance, six papers reported that obesity prevalence increases for women from age 35 to 64 and declines after 64 years of age. For men, obesity increases until age 45 and usually remains constant.

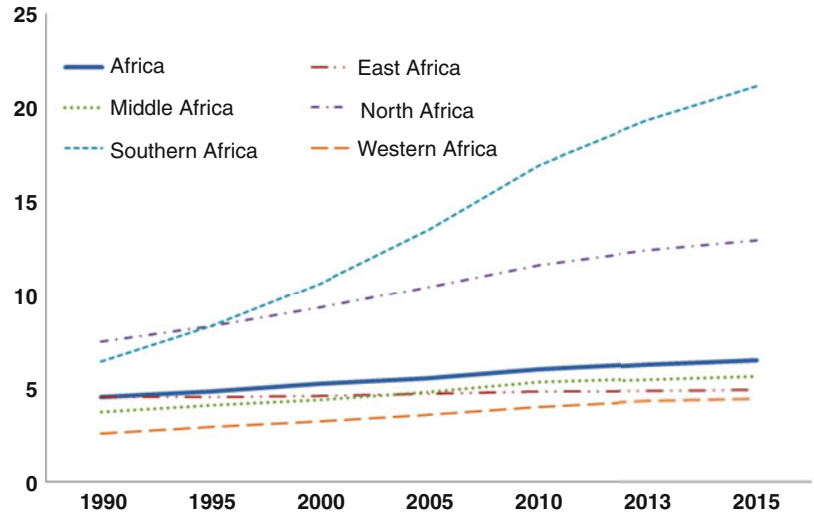

Fig. 3 Time trend of overweight prevalence by African region (Source: WHO Global InfoBase)

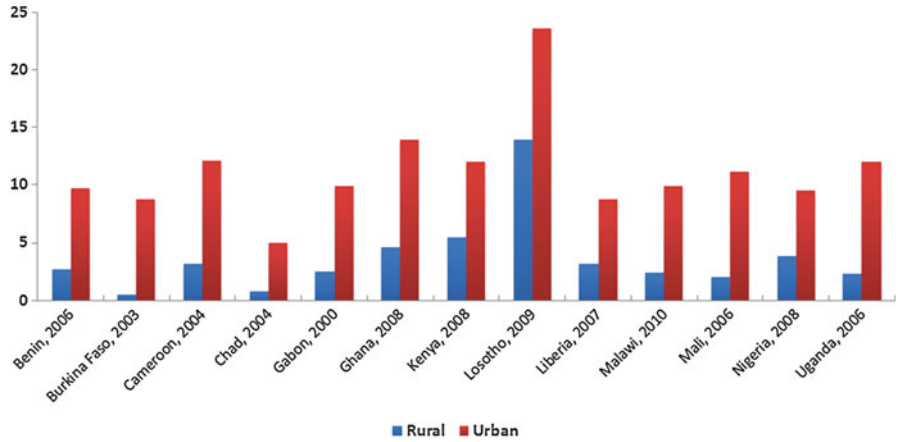

Fig. 4 Prevalence of obesity by rural and urban residence in selected African countries (Source: WHO Global InfoBase). The year represents the period the study was done

Marital status is also an important determinant of obesity on the continent. Being married increases the likelihood of being overweight or obese. Mogre et al. (2014) in a study among Ghanaian medical students found that individuals who were married were nearly six times more likely to be obese compared to those who were never married. Other Ghanaian studies including Pobee et al. (2013), Benkeser et al. (2012), Pereko et al. (2013), and Dake et al. (2010) found that married women were more likely to be obese compared to unmarried women). In South Africa, Malhotra et al. (2008) and Case and Menendez (2009) reported that never married participants were at a lower risk of being overweight/obese than those currently married. In Tanzania, married and cohabiting respondents showed significant increase risk for obesity compared to unmarried respondents (Shayo and Mugusi 2011). Similarly, Masibo et al.'s (2013) study in Kenya reported that women who were currently married were 1.9 times more likely to be overweight/obese compared to those who were not married.

Obesity also increases with *parity*. Women who had one or more children were more likely

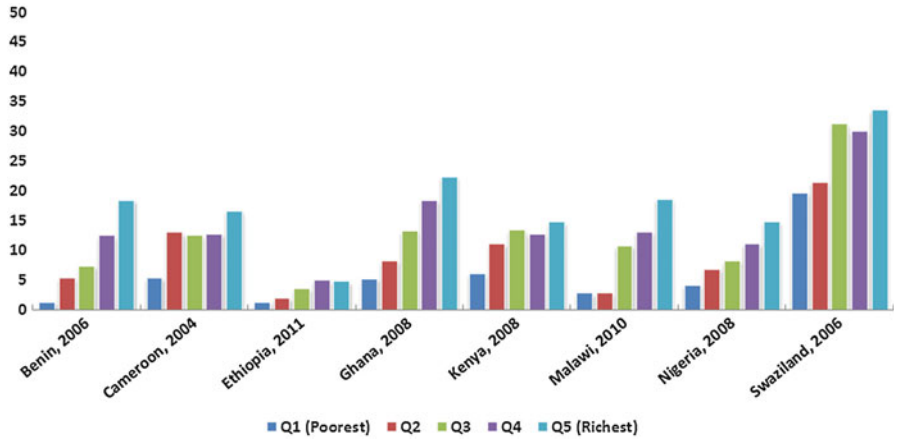

Fig. 5 Prevalence of obesity by wealth quintiles in selected African countries (Source: WHO InfoBase). The year represents the period the study was done

to be overweight or obese compared to those with no children (Dake et al. 2010; Pobee et al. 2013; Appiah et al. 2014; Agbeko et al. 2013).

3.2 Socioeconomic Status and Obesity

Among studies that examined the influence of *SES* on obesity, the results were inconsistent. Studies that used the wealth index as measure of SES in relation to obesity consistently found higher prevalence of obesity in rich households than poor households (Fezue et al. 2006; Case and Menendez 2009; Steyn et al. 2011), while studies that used the level of education as measure of SES found mixed results (Alaba and Chola 2014; Amoah 2003). As Fig. 5 shows, in all the regions, obesity rates were higher in rich households compare to the poor households. In some countries such as Benin, the richest quintile of the population has nearly 17 % higher prevalence of obesity than the poorest quintile of the population.

Women with secondary or higher *education* were about 60 % more likely to be obese than those with no formal education, and working women were 13 % more likely to be obese compared to those who were not working (Ziraba et al. 2009). Agbeko et al. (2013) in Ghana also reported that women with higher education were about two times more likely to be overweight or obese compared to those with no formal education. However, a study among Ibos in Nigeria by Anyanwu et al. (2010) observed a negative relationship between education and obesity. Although obesity was worse for all females of the various education groups, it was worst for those in the least educated group. A negative association between education and obesity has also been observed in South Africa and Ghana (Alaba and Chola 2014; Amoah 2003).

3.3 Perception of Body Size and Obesity

Preferred body size has been associated with obesity particularly among African women. In some parts of Africa, obesity is associated with *wealth*, *beauty*, good health, strength, and respect (Holdsworth et al. 2004; Prentice 2006; Siervo et al. 2006; Amoah 2003). Appiah et al. (2014) reported that a point increase in preferred body size increases the likelihood of being overweight or obese. However, recent studies indicate that this *perception* is changing (Duda et al. 2007; Tlili et al. 2008; Puoane et al. 2013). In Tanzania, women associated obesity with greediness and the likelihood to develop chronic diseases such as

diabetes, heart disease, and cancer. Majority (77.9 %) of overweight and obese women therefore indicated preference for a slimmer body size (Tlili et al. 2008). Puoane et al. (2013) observed a contradictory opinion of body size preference among South African adolescent girls. Although participants expressed positive feelings about being thin and being fat, majority (63 %) expressed preference for a low body weight. A Ghanaian study among women indicated the desire for a moderate or healthy weight, and this was influenced by the weight strategies of their partners. Moreover, obese women were more likely to have a greater dissatisfaction score with their bodies than women of all other categories (Duda et al. 2007).

3.4 Lifestyle Factors and Overweight and Obesity

Unhealthy diet, *physical inactivity*, *smoking*, *and alcohol consumption* are among the lifestyle factors that have been shown to be associated with overweight and obesity in sub-Saharan Africa. Regarding diet, the consumption of calorie-dense foods, low intake of fruits and vegetables, and drinking of tea have been related to obesity (Manyema et al. 2014). In Ghana, consuming less servings of fruit has been shown to be associated with increasing the likelihood of being overweight and obese (Biritwum et al. 2005). Physical inactivity also has a negative effect on obesity. Individuals who engaged in vigorous activities had lower risks for obesity as compared to those who did less rigorous activities (Shayo and Mugusi 2011).

The association between alcohol consumption, smoking, and obesity is not consistent. While some studies report a positive association, others report the inverse. Women who consumed alcohol were 1.37 ($p = 0.002$) times more likely to be overweight or obese compared with those who did not consume alcohol (Agbeko 2013). In Malawi, however, the proportion of current drinkers who were obese (22.9 %) was less likely than nondrinkers (17.3 %) to be obese (Msyamboza et al. 2013). In terms of smoking, obesity was high among smokers. In Malawi, nonsmokers were 24 % more likely to be obese compared to 10 % of current smokers.

3.5 Relationship Between Overweight and Obesity and CVD and Diabetes in Africa

Obese individuals develop more CVD risk factors than persons of normal weight (Ayah et al. 2013; Njelekela et al. 2009; Okpechi et al. 2013). Six of the papers included in the review examined the impact of obesity on CVD risk and diabetes in Africa. Among the risk factors of CVD, obesity was considered the most dominant. Overweight and obese persons had higher systolic *blood pressure* and diastolic blood pressure compared with normal weight persons (Msyamboza et al. 2013). The data suggest that the risk is higher for men than for women (Mufunda et al. 2006; Njelekela et al. 2009). In Tanzania, a unit increase in BMI was associated with a 10 % increase odds of *hypertension* (Njelekela et al. 2009). In Nigeria, a BMI greater than 25 increased the odds of hypertension by 12 % (Okpechi et al. 2013). In addition, the risk of diabetes was higher among obese than normal weight people (Tibazarwa et al. 2009). In Kenya, the age-sex adjusted odds for *diabetes* increased by 3.2 % among obese compared to persons of normal weight (Ayah et al. 2013). Obesity was also positively related to hypercholesterolemia. In South Africa, the total cholesterol levels of overweight women increased by 3 % compared to the normal weight (Tibazarwa et al. 2009).

4 Discussion

The aim of this study was to outline the epidemiology of obesity in sub-Saharan Africa, obesity determinants, and the risk of CVDs and diabetes due to obesity. The review shows that obesity rates have been increasing in all African regions. In addition, the rate of obesity is higher among women than among men and in urban areas compared to rural areas. Sex, age, marital status and

parity, socioeconomic status, body weight perceptions, and lifestyle factors are among the determinants of obesity. The study also identified that obesity increases the risk of CVDs and diabetes.

The increasing prevalence of obesity in Africa over the last few decades could be explained by changes in livelihood and economic conditions. During the late 1980s, for example (a period described as the lost decades), the continent was in *economic crisis*: living standards fell and deprivation increased for a growing number of citizens in affected countries (Aryeetey et al 2012; Agyei-Mensah and de-Graft Aikins 2010). The first major wave of rural-urban migration occurred during this period (Agyei-Mensah and de-Graft Aikins 2010). There was a corresponding challenge of limited *food availability* and quality, and the region recorded high prevalence of undernutrition for both children and adults. This period was also characterized by the advent of the *HIV/AIDS crises* (Iliffe 2006). During this period the stigma attached to thinness intensified as thinness became associated not only with deprivation but also with HIV/AIDS status (Kruger et al. 2005). At the turn of the millennium, economic growth was reported in some African countries (Aryeetey et al. 2012). Globalization changed the sociocultural landscape of many countries with food market globalization playing a major role. African countries signed trade agreements that allowed increased importation of processed foods high in fat, sugar, and salt into the continent, the availability of which lessened the appeal and consumption of traditional wholesome foods (Agyei-Mensah and de-Graft Aikins 2010). The change in economic growth in combination with globalization forces led to changes in demographic profile, urban population, weight perceptions, and lifestyle behaviors. These factors are currently fuelling Africa's obesity crisis.

In demographic terms, socioeconomic status of individuals was first affected. For example, school enrolment rates increased on the continent. Between 1999 and 2008 gross enrolment ratios increased from 19 % to 27 % for upper secondary and 3 % to 6 % for tertiary education (UNESCO Institute for Statistics 2010). This educated population contributed to the growth of the urban wealthy who had access to a globalized food economy and engaged in sedentary work patterns and *lifestyles*. As a result this group may have maintained a positive energy balance over a long period of time (Addo et al. 2009; Mogre et al. 2012). It is not surprising therefore that until recently, wealthy persons were at higher risk of obesity in Africa compared to the poor (Ziraba et al. 2009). In terms of gender, research suggests that the gap between men and women can be explained by the low levels of physical activity among women (Amoah 2003; Averett et al. 2014; Puoane et al. 2003). In urban areas, processed foods high in fat, sugar, and salt are accessible, easy to cook, and preferred to traditional meals (Freidberg 2003; Kgaphola and Viljoen 2004; Kifleyesus 2002). As a result there is an increase in consumption of these *calorie-dense foods* but without the needed *physical activity* (Delisle et al. 2012).

The positive relationship between wealth and obesity reflects the *epidemiological transition* in sub-Saharan Africa (Agyei-Mensah and de-Graft Aikins 2010). The pattern is generally in line with the "diffusion theory" of the *epidemic of coronary heart disease* (CHD) as demonstrated in high-income countries (Mackenbach et al. 2000). The 'diffusion theory' postulates that the rise of CHD starts in high socioeconomic groups, because they are the first groups who can afford diets rich in saturated fats and associated with overweight and obesity, which in turn increase the risk of CHD. With time, the disease spreads to lower socioeconomic groups as living standards improve for all. When the CHD epidemic starts to decline, the higher socioeconomic groups are once again the first groups to reap the benefit as they are the first to adopt healthy behavioral changes. Accordingly, it is expected that the current socioeconomic gradient in obesity which favors the poor in sub-Saharan Africa will reverse as standards of living improve unless measures are put in place to protect the poor. Evidence from Egypt suggests that the gradient is changing in favor of the rich. In Asfaw's (2007) study, poor people who had lived in urban areas for long periods were more likely than their rich peers to be obese due to their access to relatively inexpensive calorie-dense foods.

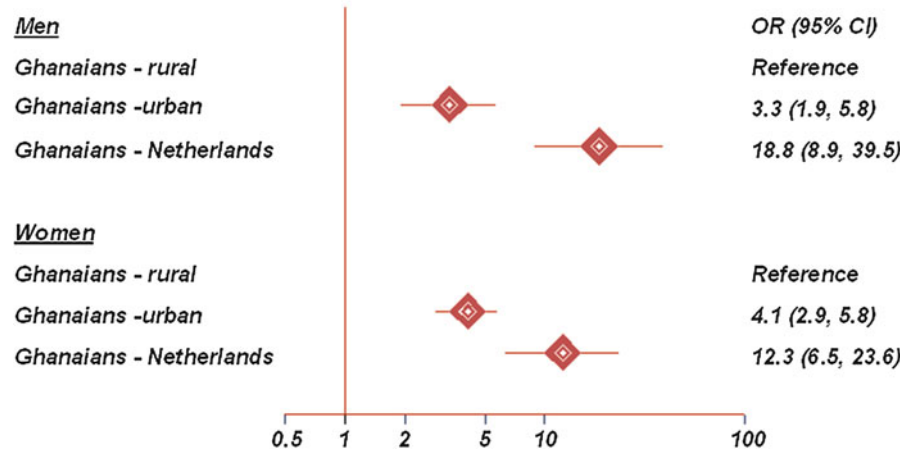

Fig. 6 Age-adjusted odds ratios (95 % CI) of overweight/obesity among Ghanaians living in different locations

In terms of perceptions of body weight, the association of fat with wealth, health, and beauty has coexisted with the *stigmatization* of *thinness* in many African countries over a long period. The HIV/AIDS pandemic intensified the stigmatization of thinness, as strong associations were made between the emaciated body and HIV/AIDS status. Yet, current evidence suggests that perceptions of body weight and of fatness, in particular, are more nuanced than originally reported. In a number of empirical studies, lay communities appear to value healthy body weight, which corresponds to a *buxom* rather than obese body size (Benkeser et al. 2012; Brown 1991; Duda et al. 2006). There is also increasing awareness of the relationship between obesity and health risks including diabetes and CVD.

Evidence shows that obesity increases the risk of CVDs and related intermediate risk factors such as hypertension, diabetes, and hypercholesterolemia in several African countries (Agyemang 2006; Medeiros et al. 2012). The increasing burden of CVDs has increased in line with the rising levels of obesity in Africa. These conditions reduce the quality of life through disabilities and deaths (Bertram et al. 2013; Mayosi et al. 2009). The increasing burden of CVD is occurring at a time when infectious diseases are still highly prevalent, placing a great demand on the overburdened and impoverished *healthcare systems* in most of these countries. Given the rising numbers of urban population, accompanied by nutrition transition throughout sub-Saharan Africa (Population Reference Bureau 2013), the prevalence of obesity and its related problems such as diabetes and hypertension are likely to increase further if measures are not taken to address the problem head on (Sanuade et al. 2014). The potential impact of the changing *environment* on obesity has been demonstrated among sub-Saharan African *migrants* in Europe. In Agyemang et al.'s study (2009), the odds of overweight and obesity among Ghanaian migrant men and women in Amsterdam were 19 times and 11 times higher than their compatriot men and women living in rural Ghana (Fig. 6).

5 Conclusion

The rapid urbanization accompanied by *nutrition transition* is changing the disease landscape in Africa with CVD and its related risk factors gaining a prominent position. The rising levels of overweight and obesity in African are likely to exacerbate the burden of CVD if measures are not taken to curb the problem. *Public health* strategies focusing on healthy diet, physical activity, weight reduction, and maintenance strategies are clearly needed in sub-Saharan African countries, particularly in urban areas. Strategies must include measures such as price reduction for healthy foods (e.g., fruits and vegetables) and promotion of

physical activity in workplace and schools. These strategies need to take gender, socioeconomic, and culturally specific factors into account.

6 Cross-References

- Genetics of Obesity
- Obesity in East Asia
- Obesity in Latin America
- Obesity in Middle East

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Obesity in Middle East

5

Zlatko Nikoloski and Gemma Williams

Contents

Abstract

The Middle East and North Africa region (MENA) encompasses 18 countries at various levels of economic development – high-income (Qatar, Saudi Arabia), upper-middle-income (Jordan, Morocco), and lower-middle-income countries (Yemen). As in the rest of the world, rising obesity prevalence has also been documented in the MENA countries, with roughly one fifth of the adult population in the region considered as obese. Against this background, this article (i) documents the prevalence of obesity in the region (both from the literature and official statistical sources), (ii) identifies the major correlates of obesity, and (iii) assesses and documents the literature that links obesity with some of the most prevalent noncommunicable diseases (inter alia, diabetes and cardiovascular diseases). We argue that the levels of obesity in the region are high and still increasing, with gender, age, income, education, nutrition patterns, and urbanization acting as the most prominent and robust correlates of obesity in the MENA region. Finally we argue that, in the context of MENA countries, there is robust link between obesity and certain chronic conditions (e.g., diabetes).

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1 Introduction

The Middle East and North Africa region (MENA) encompasses 18 countries at various levels of economic development – high-income (Qatar, Saudi Arabia), upper-middle-income (Jordan, Morocco), and lower-middle-income countries (Yemen). The global obesity epidemic has also engulfed the MENA countries with roughly 19 % of the people living in the Eastern Mediterranean region considered obese (i.e., having BMI index higher than 30) (WHO 2008). Globally, the literature has distilled a few important correlates of obesity – income, age, and gender are the most prominent ones. The fast pace of urbanization and the associated sedentary lifestyle have both played a role in exacerbating the obesity pandemic. These factors, as this literature review shows, act as significant correlates of obesity in the MENA region as well, particularly in countries that had undergone a rapid economic growth and development due to their richness with natural resources (e.g., the Gulf countries). Finally, the rising global obesity rates are responsible for the substantial increase in the overall global burden of disease associated with noncommunicable diseases (NCD). In the MENA region, roughly three quarters of the total deaths are due to noncommunicable diseases (WDI 2014). Moreover, the percentage of people living with NCDs particularly associated with obesity (e.g., diabetes, cardiovascular disease) is high. For instance, WHO reports that 11.3 % of adults older than 25 years report raised fasting blood glucose levels, hence satisfying the basic diagnostic conditions for diabetes (WHO 2008).

Against this background, the aim of the literature review is to take stock and synthesize the current knowledge on obesity in the countries of the MENA region. In doing so, we have organized the review in three major parts: (i) a section that documents the overall prevalence of obesity across the countries in the region, (ii) a section that sheds light on the main correlates of obesity in the MENA region, and (iii) a final section that documents the literature on the risk factors associated with obesity such as diabetes, cardiovascular diseases, stroke, and cancer.

In conducting this literature review on obesity, correlates of obesity, and obesity-related diseases, we grouped the countries of the Middle East and North Africa (MENA) region in three major groups corresponding to their level of development: lower-middle-income countries, upper-middle-income countries, and high-income countries. The country classifications correspond to the latest updates provided by the World Bank Research Department. Accordingly, the groups include the following countries:

(i) Lower-middle-income countries (Djibouti, Egypt, Morocco, Syria, the Palestinian National Authority, and Yemen)
(ii) Upper-middle-income countries (Algeria, Iran, Iraq, Jordan, Lebanon, Libya, and Tunisia)
(iii) High-income countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates)

Before moving onto summarizing and discussing the literature on obesity and obesity-related diseases in the region, we present a snapshot of the economic development (as captured by GDP per capita and the Human Development Index) in the three respective country groups.

From Fig. 1, we see a significant discrepancy in GDP per capita among the countries in the region, with the average per capita GDP ranging from 6109 USD in the lower-middle-income countries, 14517 USD in the upper-middle-income countries, and 67657 USD in the high-income countries. In order to "control" for the effect of abundance of natural resources and their impact on the overall GDP per capita in the

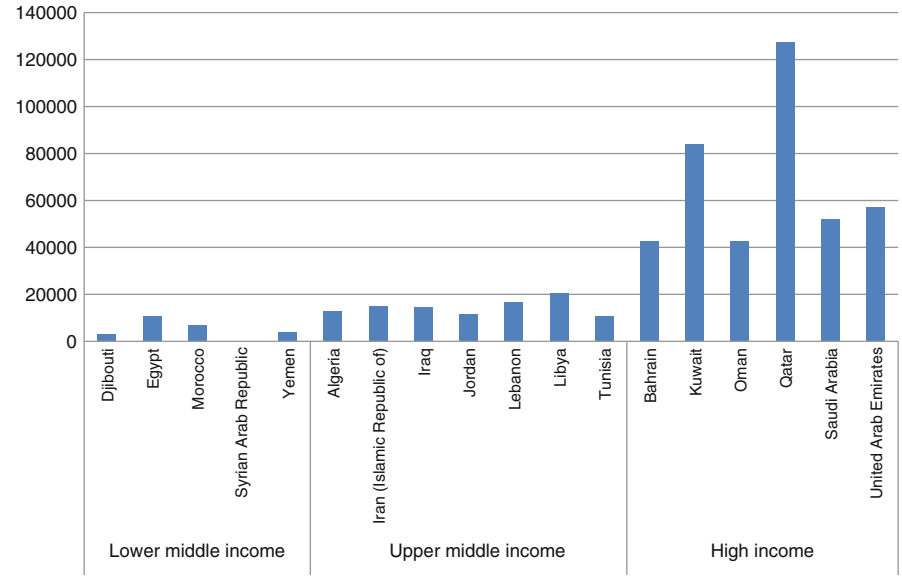

Fig. 1 MENA countries: GDP per capita (international USD, constant), 2013 (Source: World Development Indicators and authors' calculations)

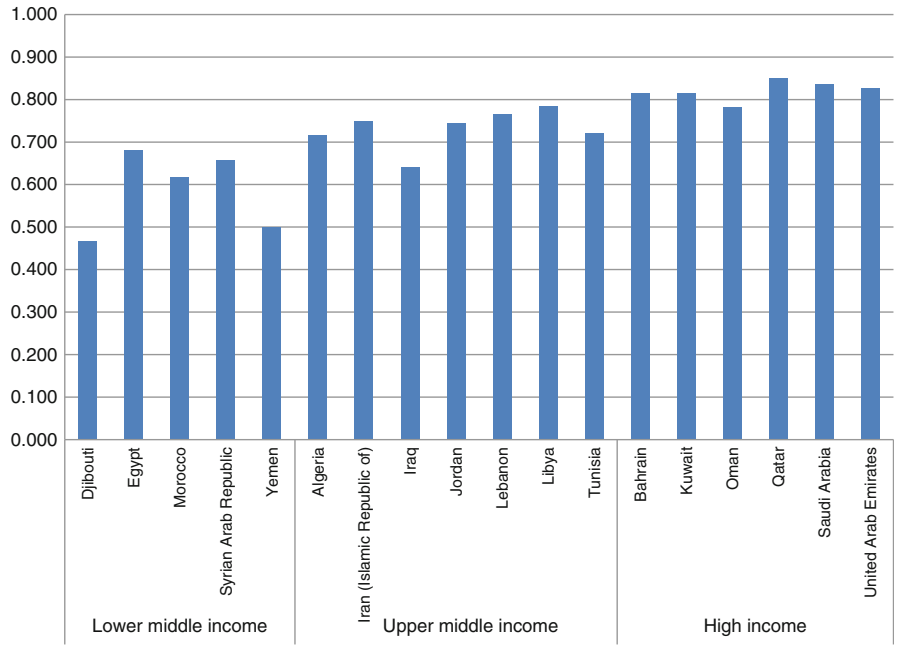

Fig. 2 MENA countries: Human Development Index, 2013 (Source: UNDP and authors' calculations)

respective countries, we also present the latest figures for the UNDP's Human Development Index (HDI). Here again, we see significant gap between the country groups in the region, with HDI ranging from 0.585 in the lower-middle-income countries, 0.732 in the upper-middle-income countries, to 0.821 in the high-income countries (Fig. 2).

2 Evidence on Obesity in the Middle East and North Africa Region

2.1 Evidence from Official Sources

Figure 3 captures the obesity rates per country, and it also provides the averages for the three country groups (Data for Fig. 3 comes from the World Health Organization (WHO)). There are a few observations that stem from Fig. 3. First, we see a positive correlation between the level of obesity and the level of economic development. Indeed, as we move up the income ladder, the obesity prevalence increases. For instance, the average prevalence of obesity in the lower-middle-income countries is 20.5 %, 25.4 % in the upper-middle-income countries, and 33.1 % in the high-income countries. Second, in the lower-middle-income country group, there is a significant variation in the prevalence of obesity (for instance, the obesity prevalence in Djibouti is 10.4 %, while it is as high as 33 % in Egypt – almost as high as in some of the countries in the Gulf). The variation of the obesity prevalence rates is much smaller for the upper-middle-income and high-income country groups.

2.2 Evidence from the Literature

2.2.1 Lower-Middle-Income Countries

While there is no harmonized data on prevalence of obesity in the lower-middle-income countries in MENA, isolated studies point to a rising obesity trend, especially among the urban population (Musaiger et al. 2011). Obesity prevalence in some countries such as Egypt and Morocco has been rapidly increasing and risks reaching levels similar to the ones found in Gulf countries (Musaiger et al. 2011). For instance, a study has found that obesity prevalence rates in Morocco are as high as 31.2 % (Berraho et al. 2012). Similarly, a study on Syria found that 43 % of the population was obese (Al Ali et al. 2011), while the prevalence of obesity among the Palestinians has reached the level of 22.1 % among men and 37.2 % among women (Abu-Rmeileh et al. 2013).

2.2.2 Upper-Middle-Income Countries

The existing literature also indicates that obesity rates in the upper-middle-income countries in the region are high (Al-Kaabi et al. 2009). Overweight and obesity prevalence in the upper-middle-income countries have been reported as high as 40 %. Similarly high and alarming

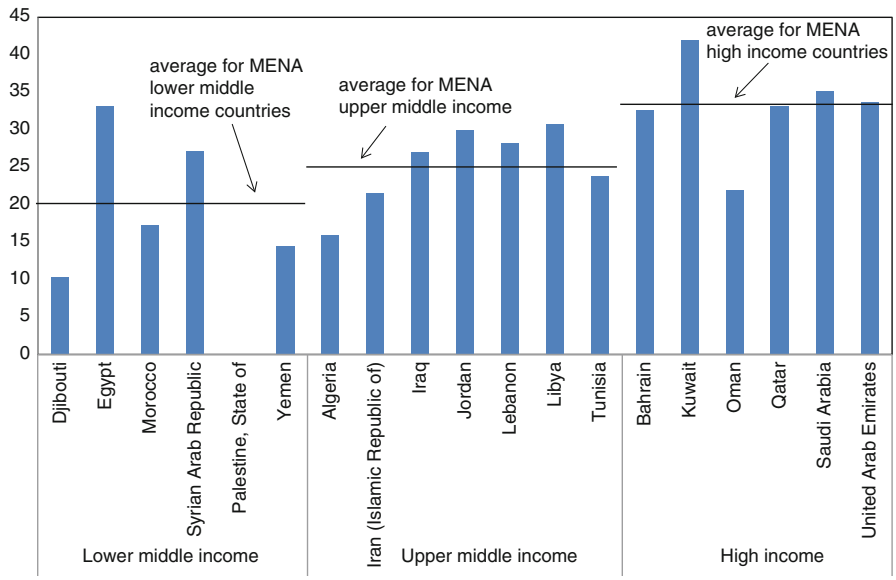

Fig. 3 Selected MENA countries: % of population that is obese (BMI >30), 2008 (Source: WHO and author's calculations)

overweight and obesity prevalence rates are also registered among school children (Musaiger et al. 2011). More specifically, prevalence of obesity has been particularly high in Algeria (30.1 % among women and 9.1 % among men) and Tunisia (37 % among women and 13 % among men) (Atek et al. 2013). Finally, a significant body of knowledge has documented the high and rising obesity rates in Iran (Ayatollahi and Ghoreshizadeh 2010).

2.2.3 High-Income Countries

The literature documents the high prevalence of obesity among Gulf countries, especially in Saudi Arabia (Mandil et al. 2013; Ahmed et al. 2014). A recent study has reported that the obesity rates in Saudi Arabia reached 40 %, with prevalence higher among women than men and among nationals than expatriates (Al-Daghri et al. 2011; Amin et al. 2014). High prevalence of obesity has also been reported in Oman (Al-Sharafi and Gunaid 2014; Al-Saadi et al. 2011) and Qatar (Ali et al. 2014).

3 Correlates of Obesity in Middle East and North Africa Region

3.1 Gender

An overview of the existing literature reveals that gender is one of the main correlates of overweight and obesity, with women being more prone to being overweight and obese (Mandil et al. 2013). For instance, obesity prevalence in Syria among women reached 51.8 % (high prevalence has also been reported in Saudi Arabia and Bahrain, reaching levels of 80 % in Bahrain) (Mandil et al. 2013). A literature review on the topic of gender and obesity has found higher prevalence of obesity among women in Algeria, Egypt, Morocco, and Tunisia (Bos and Agyemang 2013). Similar findings stem from a study by Zenki et al. (2012). In addition, a significant number of studies conducted in Iran have found higher obesity prevalence among women compared to men (Ayatollahi and Ghoreshizadeh 2010). Moreover, studies in Iran have found that the trend of obesity among women has worsened over the last two decades (Mirzazadeh et al. 2009).

There are a number of reasons why prevalence of obesity is particularly high among women in the Middle East. Marriage and unemployment (which, as evidenced by the existing literature, is found to be negatively correlated to the obesity rates) are considered as the most important correlates of weight gain among women. A study on Kuwait, for instance, shows that roughly half of the unemployed women were obese, compared to only a third of the employed ones. Similar findings stem from studies on Saudi Arabia and Tunisia, though with different ratios (79 % and 53 % in Saudi Arabia and 24 % and 15 % in Tunisia) (Musaiger 2007). Other significant correlates of weight gain among women include higher inactivity rates and cultural factors. Due to cultural and religious reasons, the access to exercises venues for women is limited. Hence, television and the Internet have become the main leisure activities among women in the region, further exacerbating the growing obesity rates. In addition, given the level of affluence in the Gulf countries as well as the availability of foreign workers, most of the women from affluent families in the region employ domestic helpers (Musaiger et al. 2011). All of these factors lead to somewhat sedentary lifestyles and increase in the rates of overweigh and obesity (Al Nohair 2014). Finally, the cultural norms associated with large families and hence leading to multiple pregnancies are another reason why women in the region gain weight (Al Nohair 2014).

3.2 Age

Age is another important correlate of obesity, and the extant literature points to a nonlinear relationship between age and obesity. A study on Morocco finds that the turning point of the inverted U curve that depicts the relationship between age and obesity occurs at year 64 for women and somewhat earlier (45–54 years) for men (El Rhazi et al. 2011). These findings from the Moroccan study were mirrored in other studies

from Kuwait and Yemen (Al-Sharafi and Gunaid 2014; Ahmed et al. 2012).

3.3 Income and Socioeconomic Class

Income (proxied either by socioeconomic class, parents' education, or material possessions) is another important correlate of obesity in the Middle East. Higher income is associated with higher consumption, which in turn puts wealthier individuals at higher risk of becoming overweight and obese (Fatemeh et al. 2012). For instance, a study on Kuwait has found that affluent households in Kuwait consume more dairy products and meat, compared to the poorer households (Al Nohair 2014). Obesity is found to increase with household wealth in both Algeria and Tunisia (Atek et al. 2013). A positive link between income and obesity was also found in a study on Morocco (El Rhazi et al. 2011). A study on Palestine has found that child obesity is higher among children who come from better off families (Mikki et al. 2009). A study among students in UAE has documented that students coming from richer households have higher propensity of becoming overweight and obese (Katsaiti and Anshasy 2014). Given the cultural importance of housing in the Middle East, the extant literature has often proxied income by the quality of a household's housing. Using quality of housing as a benchmark for income, a study on Morocco has found that individuals living in better houses tend to have higher probability of being obese compared to those living in slums or similar poor housing conditions (El Rhazi et al. 2011).

3.4 Education

The existing literature on global level suggests that education is negatively linked with obesity (Ahmed et al. 2012), and this link is resonated among countries in the MENA region. Studies in Iran (Hajian-Tilaki and Heidari 2006) and Kuwait (Al Isa 1997) noted a negative link between levels of education and the likelihood of obesity (Ahmed et al. 2012). Similar findings stem from a study conducted in Morocco. The study finds that the prevalence of obesity and overweight was highest in illiterate women and lowest in women who had obtained a university degree (El Rhazi et al. 2011). Over time, the highest increases in prevalence of obesity were registered among women who had no education or only had primary education (Aitsi-Selmi et al. 2012). Similar findings were observed in the rest of the region. For instance, 28 % of Syrians with university education are obese (compared to 51 % of the illiterate ones). In Jordan, people with less than a high school education (less than 12 years of formal education) are roughly twice more likely to be obese compared to those who have, at least, completed a high school education. Almost identically, in Lebanon, the prevalence of obesity is negatively correlated with the years of formal education (Al Nohair 2014).

3.5 Exercise/Activity

Lack of exercise is another important correlate of obesity in the MENA region. Hot climate coupled with increased air pollution and rapidly increased urbanization and industrialization has led to a significant decrease of physical activity among the people in the region. In addition, and as evidenced from the introductory part of the chapter, the rapid economic development has allowed the Gulf countries to achieve some of the highest levels of development in the world. This rapid economic development, however, brought with itself significant changes in the lifestyle, with more and more households relying on cars and mechanical appliances for work and television and the Internet for leisure, leading to sedentary lifestyle and hence increasing the prevalence of obesity in the region. A study on Saudi Arabia, for instance, has found that more than half of boys in Riyadh do not participate in some form of physical activity. Same source goes on to argue that the percentage is much higher among adults, with roughly four fifths of adults being physically inactive (FAO 2008).

Similarly, in UAE, the inactivity rates among young urbanites are as high as 40 % and as high as

70 % among older residents of urban areas (Hajat et al. 2012). Among children, those with sedentary lifestyle are almost twice as likely to become obese (Bamoshmoosh et al. 2013). In Morocco, the prevalence of obesity was lower among study participants who undertook at least 30 min of physical activity per day than in other individuals (El Rhazi et al. 2011). A study on Egypt has documented that among the leisurely activities performed on a daily basis, physical exercise was the least favorite. Roughly 2 % of respondents have reported practicing some sport on a daily basis (though almost 10 % have reported that they practice regular physical activity during weekends) (Yasin 1998). The situation is even worse in Saudi Arabia where roughly half respondents of a study did not participate in any physical activity lasting for roughly 10 min (Al-Hazzaa 2007). Low levels of physical activity have been noted in other countries in region. A study on six MENA countries has found that the inactivity rate is highest among Saudis (roughly 86 %) and lowest among Syrians (33 %) (WHO 2009). Similar trends on the physical activity/obesity nexus have also been documented among young people (Al-Hazzaa et al. 2012; Sweeting 2008).

3.6 Nutrition

The changes in lifestyle marked over the last few decades and closely connected with the economic development of some of the MENA subregions have also brought with itself changes in the nutrition patterns among the countries in the region. However, as documented by the literature, the changes in the nutrition patterns have not been same across the region. Changes in nutrition patterns have been most drastic in the high-income countries, where traditional diet that consists of fiber (fruits and vegetables) and milk and limited intake of dairy products have been replaced with a diet marked by heavy intake of calorific food, especially fat and carbohydrate. This has resulted to an average daily caloric intake in the Gulf countries amounting to 3,000 kcal per adult individual. Interestingly, sugar and fat combined now comprise roughly 45 % of the daily energy intake of an adult living in the high-income countries in the MENA region (Musaiger et al. 2011). In Saudi Arabia, for instance, a recent study has documented that the intake of fresh fruits and vegetables occurs only twice weekly. The consumption of fried food has been found to be relatively high (Al-Rethaiaa et al. 2010; Bazhan et al. 2011).

Changes in the caloric intake have also been noted in the upper-middle-income countries in the region (Musaiger et al. 2011). While the situation is not as drastic as in the high-income countries, roughly 28 % to 45 % of the daily calorific intake in the countries of the region comes from sugars and fat combined, while cereals contribute to roughly a half of the daily caloric intake, leaving little space for fruits, vegetable, and other foods high in fiber (FAO 2008).

The nutrition patterns in the lower-middle-income countries in the region have remained broadly stable resembling those of the rest of the developing world. The sugar and fat consumption is moderate, while cereals represent the staple food. However, the extant literature documents that higher social classes in these countries have similar food intake patterns to individuals in the high-income countries of the Middle East (FAO 2008).

3.7 Fat Intake

As evidenced from the previous section, fat intake, especially in the upper-middle-income and high-income countries in the region, has increased. In addition, studies point out that the fat intake has particularly increased in the high-income countries in the region, with fat calories increasing much more rapidly compared to the increase of the total daily caloric intake. In some of the countries in the region, the increase in the daily intake of fat calories has been as high as 50 % (FAO 2008). Moreover, a special strand of the literature has emerged that has documented the type of fat consumed by households in the MENA region. A study in Egypt, for instance, found that almost 40 % of the fat consumed by women was saturated fat (Mahmood 2004). Similar findings emerge from a study in Bahrain, which points out that almost half of the

school children intake more saturated fat than they should (Gharib and Raseed 2011).

3.8 Fiber Intake

As indicated in the previous sections in this review, one of the reasons for increased prevalence of obesity in the MENA region is the change in nutrition patterns that, inter alia, involved increase in the daily intake of fat and decrease in daily intake of fiber. Indeed, data on Saudi Arabia suggests that the average daily intake of fiber is alarmingly low averaging roughly 25 g, with most of the daily intake coming from vegetables, cereals, and fruits. In addition, the low intake of fiber is further exacerbated by the food preparation practices, thus involving boiling and peeling of fruits and vegetables, ultimately reducing the daily average intake of fiber (Musaiger 2002). A cross-country survey in the region has found that the low intake (below five servings per day) of fresh fruit and vegetables (food that is high in fiber) ranged as high as 80 % in Egypt and 96 % in Syria (WHO 2014). Moreover, the intake of fiber-rich foods by children and adolescents in most Arab countries is alarmingly low. The literature documents that school children and adolescents follow similar nutrition patterns as adult individuals (Musaiger et al. 2011).

3.9 Urbanization

In contrast to the high-income countries in the West, across the MENA region, obesity is higher among the urban population. This is connected with some of the correlates mentioned above – urbanization is highly correlated with Western living and eating habits as well as sedentary lifestyle which significantly contribute to rising obesity rates. A study in Jordan has found that almost 60 % of urban residents are obese compared to 45 % in rural areas. Studies on Tunisia, Morocco, Oman, and Egypt have documented similar trends (Musaiger 2011). The existing research evidence points to the fact that adult urban women in UAE are more prone to being obese compared to women living in rural areas (Ng et al. 2011). Finally, the literature has documented that individuals that have maintained their Bedouin lifestyle (in selected countries in the region) and have remained living in small isolated villages have lower rates of overweight and obesity (Malik and Bakir 2007).

4 Obesity-Related Noncommunicable Diseases in the MENA Region

The rapidly increasing prevalence of overweight and obesity in the MENA region, coupled with progressively poorer diets and insufficient physical activity, has contributed to a significant transition in health risks in MENA countries (Bank 2011; Rahim et al. 2014; Diabetes UK 2014). Over the past 30 years, the burden of noncommunicable diseases (NCD) in the region has increased substantially to overtake the disease burden from communicable diseases and maternal mortality (GBD 2013; Rahim et al. 2014). In 2008, approximately 1.2 million people in the MENA region died from NCDs, accounting for 60 % of all deaths (Rahim et al. 2014). The increased prevalence of these NCDs is partly attributable to a rise in life expectancy but is primarily driven by an upsurge in population exposure to modifiable risk factors such as poor diet, obesity, lack of physical activity, and tobacco use (Bank 2011; Rahim et al. 2014; Hauner 2010). Excess weight remains the primary modifiable risk factor for development of NCDs in the region, with overweight and obesity estimated to be responsible for 8 % of all deaths in the Eastern Mediterranean region in 2004, the fourth leading risk factor in the region after high blood pressure (15 % of deaths), underweight (10 %), and high blood glucose (9 %) (WHO 2009a). In this section, we explore the available evidence on the association between rising obesity rates in the MENA region and prevalence of a number of major obesity-related NCDs, including diabetes, cardiovascular disease, chronic kidney disease, and cancer.

4.1 Diabetes Prevalence in the MENA Region

4.1.1 Evidence from Official Sources

The International Diabetes Federation estimates that 35 million people aged 20–79 were living with diabetes in MENA countries in 2013, with 48.0 % of these cases undiagnosed (IDF 2014). The age-standardized average prevalence of 10.9 % of adults living with diabetes represents the highest regional prevalence globally. By 2035, projection modeling indicates that diabetes prevalence in the region will almost double to affect 67.9 million people (IDF 2014).

WHO data indicates a positive correlation between the prevalence of diagnosed diabetes in adults aged 25 years and over and level of economic development (Fig. 4). In 2008, average diabetes prevalence was 9.7 % in lower-middle-income countries, 11.6 % in the upper-middle-income countries, and 12.4 % in high-income countries. Diabetes prevalence varies widely between countries, ranging from 6.5 % in Egypt to 12.9 % in Syria among lower-middle-income countries, from 8.0 % in Algeria to 14.4 % in Jordan and Libya in the upper-middle-income group, and from 9.5 % in Qatar to 21.8 % in Saudi Arabia in the high-income country group (WHO/EMRO 2015).

In a number of high-income countries, diabetes prevalence has risen dramatically in the last 5 years (IDF 2014). In 2013, diabetes prevalence in adults aged 20 years and over was estimated to be over 19.0 % in Bahrain, Kuwait, Qatar, and the United Arab Emirates (UAE) and had reached 23.9 % in Saudi Arabia (IDF 2014). Kuwait, Qatar, and Saudi Arabia now rank among the top 10 countries globally with the highest diabetes prevalence (IDF 2014).

4.1.2 Evidence from the Literature

A number of systematic reviews have been conducted on diabetes in the MENA region, with these reviews indicating that diabetes prevalence varies widely between countries and has increased substantially in the last two decades, particularly in high-income Gulf countries. For example, a meta-analysis of studies on type 2 diabetes in Arabian Gulf states found that overall estimated prevalence of diabetes was 14.9 %, ranging from 5.9 % in the UAE to 32.1 % in Saudi Arabia (Alharbi et al. 2014). Over time, the prevalence of diabetes among the Saudi population more than doubled from 12.4 % in 1987 to 27.7 % in 2011. Although this study found no significant difference in the prevalence of diabetes between males and females, the rate of increase of diabetes prevalence was reported to be significantly higher in men than women. A further review on type 2 diabetes in the Eastern Mediterranean region also found that diabetes prevalence has increased rapidly over time (Musaiger and Al-Hazzaa 2012). In Tunisia, the prevalence of diabetes was reported to have doubled in the past 15 years, while in Jordan diabetes prevalence increased by 31.5 % from 1994 to 2006. The highest prevalence of raised blood glucose in the EMR was found among Saudi men (22 %) and women (21.7 %). A third review found that diabetes prevalence ranged from 15.8 % in Beirut, Lebanon, to 31.6 % in Riyadh, Saudi Arabia (Zabetian et al. 2013). High prevalence rates were also found in urban areas of Bahrain (28.1 %), Kuwait (21.4 %), Jordan (17.1 %), and Qatar (16.7 %). Over time, diabetes prevalence was shown to have increased from 2.5 % in Saudi Arabia in 1982 to 31.6 % in 2011.

Additional studies from low- and upper-middle-income countries show that diabetes prevalence is lower than in high-income countries but still represents a significant health issue of concern. In Syria, a study using household survey data from 2006 showed that diabetes prevalence was 15.6 % (Al Ali et al. 2011), with a study from the Palestinian National Authority reporting that diabetes prevalence among refugees aged 40 years or over was 10.5 % in the West Bank and 11.8 % in the Gaza Strip (Husseini et al. 2009). In Yemen, the age-standardized rate of diabetes prevalence was reported to be 6.3 %, while the age-standardized rate of having either impaired fasting glucose or impaired glucose tolerance was 9.0 % (Gunaid and Assabri 2008). In Jordan, previously diagnosed diabetes prevalence was 9.0 % compared with 16.9 % diagnosed by laboratory testing (Zindah et al. 2008). In Lebanon, prevalence of laboratory diagnosed type

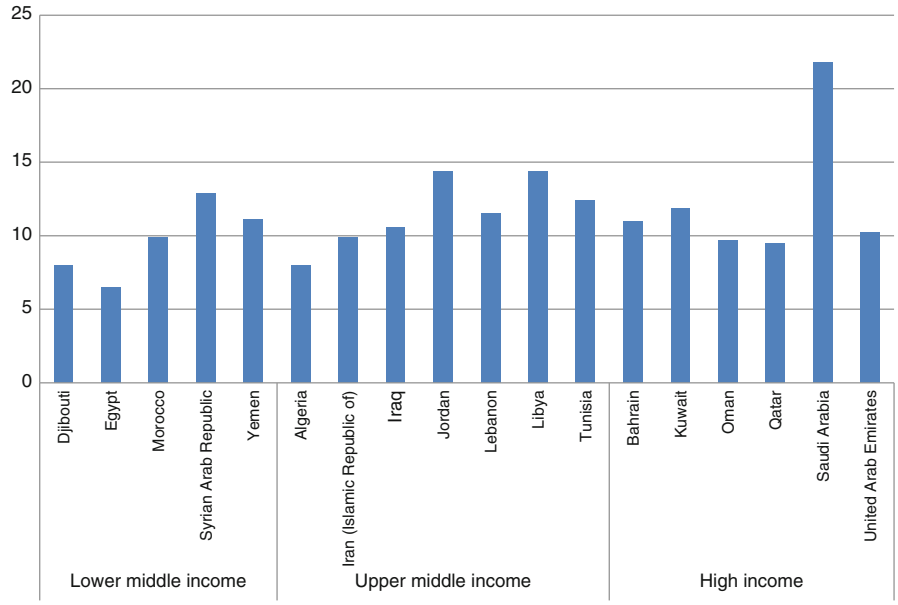

Fig. 4 MENA countries: raised blood glucose levels (>7 mmol/L or on medication), 25 years and up, age standardized, 2008 (Source: WHO and author's calculations)

2 diabetes in adults aged 25 or over was found to be 8.5 % (Costanian et al. 2014).

Studies from Iran suggest that the country has a relatively low prevalence of diabetes in comparison to other MENA countries. For example, in one study, diabetes prevalence was found to be 3 and 7 % in rural and urban areas, respectively (Azimi-Nezhad et al. 2009). In two longitudinal studies using data from the Tehran Lipid and Glucose Study (TLGS), 3.7 % of study subjects developed diabetes after 3.6 years of follow-up (Hadaegh et al. 2007; Hosseinpanah et al. 2007). However, as found in other MENA countries, there has been a significant upward trend in diabetes prevalence over time, with one study demonstrating that diabetes prevalence almost doubled from 2.5 % in 1999 to 4.6 % in 2007 (Esteghamati et al. 2010).

4.1.3 Association Between Diabetes and Excess Weight in the MENA Region

The existing literature shows a strong correlation between excess weight and diabetes risk in the MENA region. In a review of diabetes in MENA countries, diabetes prevalence was found to be significantly associated with living in urban areas, older age, and lower educational attainment but was most commonly associated with higher body mass index (Zabetian et al. 2013). Similarly, a further review reported that diabetes prevalence in Middle Eastern countries was significantly and positively correlated with obesity in all included studies assessing the association between the two variables (Motlagh et al. 2009).

In lower-middle-income countries, age and waist circumference were found to be significantly and positively related to total glucose intolerance in Yemen (Gunaid and Assabri 2008). However, a Syrian study from 2006 found that although diabetes diagnosis was significantly and positively correlated with hypertension, it was not significantly related to obesity (Al Ali et al. 2011). In upper-middle-income countries, the risk of having diabetes was found to be significantly and positively associated with BMI in Jordan (Zindah 2008) and Lebanon (Costanian et al. 2014). In a longitudinal study from Iran, general obesity and high waist-to-hip ratio were shown to significantly raise the risk of developing diabetes in individuals aged less than 60 years, while high waist circumference was the only

independent predictor of diabetes in individuals aged 60 years or over (Hadaegh et al. 2007). A further Iranian longitudinal study showed that BMI was significantly and positively associated with risk of diabetes; after adjusting for other socioeconomic and health factors, excess weight was found to account for more than half of the diabetes burden in the study (Hosseinpanah et al. 2007).

In high-income countries, overweight or obese individuals aged over 50 in Kuwait were reported to be 40 % more likely to have diabetes than counterparts with a normal BMI (Badr et al. 2013). An additional study from Kuwait further demonstrated that risk of diabetes was significantly associated with obesity prevalence (Alarouj et al. 2013). In a study from Saudi Arabia, a BMI of ≥25 was associated with greater risk of diabetes, although this relationship was not significant (Alqurashi et al. 2011). A further study from Saudi Arabia conducted laboratory testing and found that risk of diabetes was lower in females and was significantly associated with older age and previous diagnosis of hypertension; however, obesity and physical activity were not shown to be associated with risk of developing diabetes (El Bcheraoui et al. 2014). In Qatar, diabetes risk in two studies was found to be significantly higher in individuals with BMI of ≥25 (Ali et al. 2014; Christos et al. 2014). Christos et al. (2014) estimated that eliminating obesity and improving educational attainment could reduce diabetes cases by one third for all Qatari residents and by 50.0 % for Qatari nationals.

4.2 Cardiovascular Disease and Hypertension

Cardiovascular disease (CVD) is the leading cause of death in the MENA region, with ischemic heart disease and stroke accounting for two of the top five causes of death in all country income groups (GBD 2013; Rahim et al. 2014). WHO estimates indicate that hypertension is the primary CVD risk factor globally, accounting for 13 % of global CVD deaths (WHO 2009a). The causes of the majority of hypertension cases are unknown; however, the condition has been linked to excess salt intake, lack of physical activity, and overweight and obesity (Kang 2013; Kotchen 2008). Excess weight has also been shown to be an independent risk factor for CVD in general and is estimated to be the primary cause of 5 % of CVD deaths globally (WHO 2009a).

4.2.1 Hypertension

Evidence from Official Sources

WHO estimates indicate that the global prevalence of hypertension ranges from an average of 35 % in the WHO Region of the Americas to 46 % in the WHO Africa Region (WHO 2009a). In the MENA region, the prevalence of hypertension is relatively low in comparison to other regions, with 31.2 % of individuals aged 25 years or over estimated to have raised blood pressure (SBP >140 or DBP > 90) (Fig. 5). There is little variation between country income groups, with the percentage of individuals with high blood pressure ranging from 30.5 % in the high-income country group to 32.0 % in the lower-middle-income group. In Djibouti and Morocco, raised blood pressure was found in over 35.0 % of individuals, while Libya had the highest regional percentage of raised blood pressure at 42.2 %.

Evidence from the Literature

Estimates of hypertension prevalence in the MENA region varies markedly between published studies. A systematic review of CVD risk factors in Gulf countries found an estimated average hypertension prevalence of 29.5 % (Tailakh et al. 2014), similar to the percentage calculated using WHO data (Fig. 5). However, a clinical study of outpatients across the region found that the prevalence of hypertension was above 40.0 % in a number of MENA countries, including Algeria, Egypt, Jordan, Kuwait, Lebanon, Saudi Arabia, and UAE (Alsheikh-Ali et al. 2014). In Iran, the prevalence of hypertension in urban and rural areas was found to be 28.8 % and 26.5 %, respectively (Azimi-Nezhad et al. 2009). Conversely, a further Iranian study on CVD risk factors found a far lower age-adjusted prevalence of hypertension

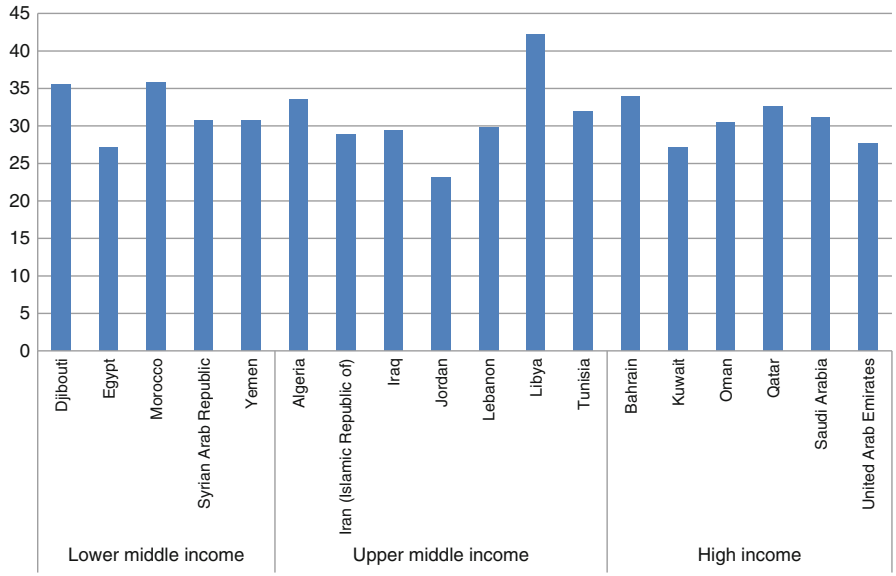

Fig. 5 MENA countries: raised blood pressure (SBP >140 or DBP >90), 25 years and up, age standardized, 2008 (Source: WHO and author's calculations)

of 9.6 % (Fakhrzadeh et al. 2008). In a study from Kuwait, prevalence of hypertension was found to be 52.0 % in men and 49.0 % in women, far higher than WHO estimates (Badr et al. 2013).

Hypertension was shown to be correlated with excess weight in the few studies that explored the association between these factors. In an Iranian study of women aged between 18 and 74 years, BMI and waist circumference were found to be significantly and positively associated with hypertension (Bahrami et al. 2006; Esmaillzadeh et al. 2006). In a study from Jordan on healthy male adults aged 30–50 years, prevalence of hypertension was found to be significantly and positively correlated with BMI (Alboqai et al. 2006). Similarly, a study from Kuwait found that risk of hypertension was significantly and positively related to BMI (Badr et al. 2013).

4.2.2 Cardiovascular Disease

The existing literature provides mixed evidence on the prevalence of CVD and its association with obesity in the MENA region. In the Palestinian National Authority, cardiac diseases were reported to be the leading cause of death in 2005, accounting for 56.5 deaths per 100 000 people and 21.0 % of all deaths (Husseini et al. 2009). In a systematic review of CVD mortality in Syria, overall mortality ranged from 45.0 % to 49.0 % in included studies (Barakat et al. 2012). In an Iranian study, the prevalence of ischemic heart disease according to ECG findings was 36.5 %, and the prevalence of myocardial infarction according to ECG findings and clinical evidence was 4.9 % (Fakhrzadeh et al. 2008). In a study from Kuwait, cardiac diseases were identified in 21.0 % of men and 15.0 % of women (Badr et al. 2013).

No clear patterns are observed in studies exploring the relationship between excess weight and CVD. In Syria, obesity was found to be the primary risk factor for CVD in the majority of individuals, with the exception of men aged over 65 years, where smoking and hypertension were the most common risk factors (Barakat et al. 2012). In Iran the prevalence of ischemic ECG changes was significantly higher in patients with hypertension, but was not significantly related to BMI (Fakhrzadeh et al. 2008). However, an additional Iranian study showed a significant and positive association between waist circumference and incidence of ischemic heart disease (Talaei et al. 2012). In

Kuwait, one study found that being overweight or obese was not significantly associated with risk of developing cardiac disease (Badr et al. 2013). In contrast, another Kuwaiti study found that being obese and aged over 40 years and having diabetes mellitus, positive family history of diabetes, hypertension, or dyslipidemia were all significant independent risk factors for developing CVD (Alarouj et al. 2013).

In a systematic review of stroke in Arabic countries, stroke incident ranged from 27.5 per 100,000 population in Kuwait to 63 per 100,000 in Libya (Benamer and Grosset 2009). In a systematic review of stroke in Iran, the annual stroke incidence was reported to range from 23 to 103 per 100,000 population (Hosseini et al. 2010). In both reviews, the most common risk factors for stroke were identified as hypertension, diabetes, smoking, and cardiac disease, but it was not frequently found to be independently associated with overweight and obesity.

4.3 Chronic Kidney Disease

Chronic kidney disease (CKD) is a growing issue of concern in the MENA region and represents a major public health challenge. Studies on the Global Burden of Disease estimate that the prevalence of CKD rose significantly between 1990 and 2010 to become one of the top ten most common causes of death in the upper-middle-income and high-income MENA countries (GBD 2013; Rahim et al. 2014). Although CKD can be caused by a number of conditions such as infection, inflammation, and inherited conditions, the two principal causes of CKD globally are hypertension and diabetes (Turner et al. 2012). Excess weight remains the primary modifiable risk factor for CKD, largely due to the increased risk of hypertension and diabetes in overweight and obese individuals (Kopple 2010; Wickman and Kramer 2013). However, obesity also has independent effects on CKD risk through its impact on renal physiology and metabolism, making obese people more likely to suffer CKD and end-stage renal failure (Kopple 2010; Wickman and Kramer 2013).

Despite representing a significant and rapidly growing burden of disease, little research has been conducted on CKD in the MENA region and its association with obesity (Shaheen and Souqiyyeh 2010). Some evidence from Iran is available, showing mixed results on the association between CKD and obesity. In one Iranian cohort study, 18.0 % of participants developed CKD after 9 years of follow-up (Barzin et al. 2014). Changes to waist circumference over this period were not found to be significantly associated with the risk of developing CKD in women, but a mild to moderate increase in waist circumference in men raised the risk of developing CKD by 70.0 %. A further cohort study found a crude cumulative incidence of 21.8 % of stage 3–5 CKD after 10 years of follow-up (Tohidi et al. 2012). Age over 50 years, hypertension and known diabetes were reported to be significantly associated with raised CKD risk, but abdominal obesity was not shown to be an independent risk factor for disease development. In contrast, a cross-sectional Iranian study reported that BMI was strongly and positively correlated with risk of CKD in both men and women (Khajehdehi et al. 2014). A further Iranian study exploring the association between metabolic syndrome and CKD in people aged 60 and over found a strong, positive, and independent correlation between metabolic syndrome and risk of developing CKD (Fakhrzadeh et al. 2009).

4.4 Cancer

Cancer represents an increasing burden of disease in the MENA region. WHO mortality statistics indicate that cancer is responsible for 270,000 deaths per year in the EMR and is the fourth leading cause of death overall (WHO 2009b). By 2035, it is predicted that the prevalence of cancer in the region will increase by between 100 % and 180 % (Rastogi et al. 2004; WHO 2009b). This rise is partly due to an expected increase in life expectancy but is also linked to increased prevalence of modifiable risk factors including smoking, unhealthy diets, lack of physical activity, and obesity.

Despite the growing burden of cancer in the region, evidence from published studies on the

relationship between modifiable risk factors, including overweight and obesity, and cancer in MENA countries is sparse. In one of the few studies exploring cancer risk factors, breast cancer in Iran was shown to be significantly and positively associated with BMI in both pre- and postmenopausal women, while waist circumference was significantly and positively associated with risk of breast cancer in premenopausal women only (Hajian-Tilaki et al. 2011). A further study on colon cancer in rapidly developing countries linked increased prevalence of the disease to rising levels of physical activity, obesity, alcohol consumption, smoking, and high consumption of red meat and fat (Bener 2011).

5 Conclusion

Over the past 30 years, the MENA region has undergone a rapid economic transformation that has generated increased modernization and dramatic improvements in living standards. However, these changes have led to a proliferation in unhealthy behaviors linked to developed economy lifestyles; levels of physical activity have declined substantially, and consumption patterns have evolved away from traditional diets containing fruit, nuts, and seeds, toward diets with a high fat, sugar, and salt content. The adoption of these behaviors has led to an alarming increase in overweight and obesity, which has become an important health threat in many countries in the region. In high-income Gulf states, obesity levels have increased substantially, and many countries now rank among the most obese countries in the world. Although overall obesity prevalence is lower in low- and upper-middle-income MENA countries, rates of overweight and obesity are still high and are rapidly increasing. Across countries of all income levels, obesity is more prevalent in richer, urban areas where sedentary lifestyles and Western diets are predominant. Furthermore, in the majority of countries, the obesity epidemic disproportionately affects women as cultural factors restrict access to sports and exercise activities and employment opportunities.

The rapid increase in overweight and obesity in the region has contributed to a rising prevalence in a number of noncommunicable diseases. Available evidence strongly indicates that excess weight is the primary modifiable risk factor driving the alarming increase in diabetes in the region. Although evidence on the relationship between obesity and other NCDs is less clear, it has been linked to a considerable recent rise in the prevalence of hypertension, cancer, chronic kidney disease, and cardiovascular disease in a number of countries. These NCDs are now the leading causes of morbidity and mortality in the region and represent a critical and growing public health challenge. If the rapid upward trend in obesity prevalence in the MENA region continues, it is likely to contribute to a substantial increase in premature deaths and morbidity from these leading NCDs, generating significant costs for health systems and potentially reversing recent gains in life expectancy (Finucane et al. 2011; GBD 2013; WHO 2009).

In order to respond appropriately to the obesity epidemic and manifest increase in NCDs, it is important that all MENA countries fully understand the epidemiology of obesity in their country. However, there is currently little evidence on the importance of excess weight on the etiology of NCDs in the MENA region. Few studies have been conducted on the relationship between overweight and obesity and the development of chronic kidney disease, CVD, and cancer. Studies that do exist are primarily concentrated on Iran and high-income Gulf states and largely neglect lower- and upper-middle-income countries. It is therefore important that more studies are available from a wider range of countries to help inform appropriate national responses to the growing obesity crisis and NCD burden. Future research should also explore how socioeconomic factors, in particular gender and education, may affect the relationship between excess weight and NCD outcomes. These research findings can be used to develop targeted prevention and outreach campaigns to reduce the disproportionate burden of obesity among women and other vulnerable groups.

Responding quickly and appropriately to the alarming rise in obesity and obesity-related NCDs

is fundamentally important in MENA countries of all income levels. A significant first step to respond to the crisis in the region was taken in 2012 with the development of the Riyadh Declaration on healthy lifestyles in the Arab World and Middle East (Riyadh Declaration 2012). However, it is now imperative that momentum from this Declaration is continued and recommendations from the resolution implemented. National policies targeting fat, salt, and sugar content in food and the introduction of labeling systems on fast-food items should be considered in all countries. Furthermore, health education campaigns should be developed to increase awareness of the benefits of healthy diets, physical activity, and maintaining a healthy weight. Lastly, health systems should be developed to ensure that NCDs can be appropriately treated and managed (Rahim et al. 2014). Investing in effective measures to curb the rise in overweight and obesity and obesity-related NCDs will ultimately improve the health of the region and reduce long-term health-care spending.

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Metabolic Syndrome in South Asians

6

Mohsin Wali and C. Venkata S. Ram

Contents

Abstract

Cardiovascular disease (CVD) is an important global health problem causing significant morbidity, disability, and premature mortality. The overall impact of CVD on the society is enormous – chronic disease burden, frequent hospitalizations, loss of productivity, and impairment of quality of life. While multiple individual risk factors such as hypertension, diabetes, hyperlipidemia, obesity, and tobacco consumption can cause CVD, it is the constellation of these risk factors (termed metabolic syndrome) which creates the milieu for atherosclerosis and other manifestations of CVD. The problem of metabolic syndrome is escalating all over the world irrespective of cultural, genetic, gender, and geographical differences. Thus, metabolic syndrome can be labeled as a merciless equal opportunity killer. This chapter covers the epidemiology of metabolic syndrome in South Asians and the implications for the society. The escalating prevalence and degree of metabolic syndrome in South Asians required applicable public health interventions at the societal level to decrease chronic disease burden.

Keywords

Hypertension • Body weight • Prevalence • Morbidity • Mortality • Disability • South Asia

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1 Introduction

Metabolic syndrome is a major public health problem in South Asia requiring urgent preventive and therapeutic actions. Paradoxically, metabolic syndrome in South Asia is equally prevalent in the obese and non-obese subjects. The escalating prevalence of metabolic syndrome in South Asia correlates with rising incidence of hypertension, diabetes, and premature cardiovascular disease (CVD). The universal criteria to define metabolic syndrome may not be applicable to South Asians because CVD complications occur at lower body mass index (BMI) and waist circumference (WC). It is timely and appropriate to address the epidemic of metabolic syndrome in South Asia and to create a private-public consensus to establish policies for early detection and prevention of this dangerous problem. Until refined guidelines emerge, the health-care providers should manage metabolic syndrome effectively to reduce the disease burden on the country.

Cardiovascular disease (CVD) remains the most common cause of death in developed countries. However, cardiovascular disease is not limited to developed countries, and multiple epidemiologic studies have demonstrated a dramatic increase in the incidence, prevalence, and severity of atherosclerosis in developing countries and so-called emerging economies (Reddy and Yusuf 1998). Vascular disease is a syndrome with various risk factors, and a unifying hypothesis which explains all aspects of the initiation and progress of vascular disease has remained inconclusive. The concept of risk factor identification and gradation is necessary for the early identification of subjects who have an increased likelihood for atherosclerosis prior to a clinical event. Observational studies have demonstrated that risk factors appear in clusters in certain individuals. Pioneering studies performed over two decades ago demonstrated the clustering of multiple risk factors such as obesity, hypertension, and dyslipidemia with the theory that insulin resistance is the unifying factor in these apparently disparate hemodynamic or metabolic conditions (Reaven 1988). The term insulin resistance syndrome was initially introduced to encompass these multiple risk factors and mechanisms. The term metabolic syndrome was subsequently proposed as an alternative term to avoid the implication that insulin resistance is the sole cause of the syndrome (Grundy et al. 2004). While the controversy remains, the term metabolic syndrome has gained credence as a means to identify multiple risk factors which appeared to share metabolic pathways and clusters in individuals more often than would be expected by chance alone. The increasing incidence of cardiovascular disease in South Asia has given rise to considerable interest in the role of the metabolic syndrome as a predisposing factor for atherosclerosis in developing countries.

A significant clinical and pathological connection between insulin resistance and cardiovascular risk factors was revealed nearly three decades ago. The latest definition of metabolic syndrome appeared in the Adult Treatment Panel III (ATP-III) report of the National Cholesterol Education Program (NCEP). The standard diagnosis of metabolic syndrome requires the presence of at least three out of five criteria: increased fasting plasma glucose level >110 mg/dL, waist circumference >30 in. in men and >35 in. in women, blood pressure >130/85 mmHg, triglyceride level >150 mg/dL, and a low concentration of HDL (<50 mg/dL in women and <40 mg/dL in men).

2 Metabolic Syndrome

The metabolic syndrome is a grouping of several interrelated risk factors which have been demonstrated to be associated with an enhanced hazard ratio for the development of premature or accelerated CVD. The conceptual model of the metabolic syndrome is supported by the common soil hypothesis for the development of atherosclerosis (Donati 2010). The common soil hypothesis was proposed following the determination that inflammation and oxidative stress coexist in the early phase of multiple risk factors – hypertension, dyslipidemia, diabetes, and obesity. The prevalence of these risk factors has been increasing in a worldwide distribution due to lifestyle changes such as increased caloric consumption with resultant obesity coupled with the reduction in physical

activity common with urbanization. Controversy has been generated relative to the prognostic utility of the diagnostic criteria which had been utilized to define the metabolic syndrome when compared to established algorithms such as the Framingham Risk Score (Reaven 2011). However, a consensus has arisen that the concept of risk factor clustering is useful and allows a focused approach to risk reduction. The term syndrome is defined as a clustering of factors which coexist at a higher rate than would be explained by chance alone and have an uncertain pathogenesis. The clinical usefulness of the term metabolic syndrome is supported by epidemiologic studies which have demonstrated that patients who met the diagnostic criteria for the metabolic syndrome have been shown to exhibit a twofold risk for the development of CVD (Alberti et al. 2009). Moreover, the lifetime risk for the development of atherosclerosis would be considered to be significantly increased in subjects with prolonged exposure to the components of the metabolic syndrome. The American Heart Association has established criteria for the clinical diagnosis of the metabolic syndrome (Grundy et al. 2005). The diagnosis of the metabolic syndrome requires any three of the five major criteria:

1. Waist circumference: Increased waist circumference greater than or equal to 102 cm (greater than equal to 40 in.) in men or greater than or equal to 88 cm (greater than or equal to 35 in.) in women (see Table 1).
2. High-density lipoprotein (HDL cholesterol): HDL cholesterol less than 40 mg/dL (1.03 mmol/L) in men or less than 50 mg/dL (1.3 mmol/L) in women. Additionally, the utilization of pharmacologic therapy for low HDL is also considered a diagnostic criterion.
3. Hypertriglyceridemia: Elevated triglycerides in excess of or equal to 150 mg/dL (1.7 mmol/L) or pharmacologic treatment for hypertriglyceridemia is considered a diagnostic criterion.
4. Hypertension: Elevated blood pressure is defined as measurements greater than or equal to 130 mm Hg systolic pressure or greater than or equal to 85 mm Hg diastolic pressure. Additionally, the use of antihypertensive therapy in a patient with a history of hypertension is also considered a diagnostic criterion.
5. Hyperglycemia: Elevated fasting blood glucose in excess or equal to 100 mg per deciliter or drug therapy for hyperglycemia.

Table 1 Ethnic factors for abnormal waist circumference

Ethnic group		Waist circumference
Europids	Male	≥94 cm
	Female	≥80 cm
South Asians including Indians	Male	≥90 cm
	Female	≥80 cm
Chinese	Male	≥90 cm
	Female	≥80 cm
Japanese	Male	≥90 cm
	Female	≥80 cm

Multiple other criteria have been proposed for inclusion as criteria of the metabolic syndrome including inflammatory markers, prothrombotic state, body mass index, urinary albumin excretion, and others although controversies exist as to the usefulness of these additional or interdependent markers (Third Report of the National Cholesterol Education Program (NCEP) 2002).

3 General Implications of the Metabolic Syndrome

The diagnosis of the metabolic syndrome has several clinical implications for therapy and prevention. Obesity is a major predisposing or accompanying cause for the development of CVD, and the Adult Treatment Panel (ATP-III) of the National Cholesterol Education Program (NCEP) has recommended that reduction of increased body mass index be a primary therapeutic target to reduce cardiovascular risk. The recommendation from the ATP-III for the primary focus on weight reduction in management of the metabolic syndrome stems a large body of clinical and epidemiologic data which links increased body mass index with insulin resistance, hypertension, dyslipidemia, and coronary heart disease risk (Abbasi et al. 2002). The reduction of body

weight by calorie restriction and increased level of physical activity may secondarily improve dyslipidemia, blood pressure, and glucose levels. Additionally, weight loss has been associated with a reduction in inflammatory markers and prothrombotic mediators. Insulin resistance has been long been recognized as a major underlying factor in the pathogenesis in several components of the metabolic syndrome (Ferrannini et al. 1991). Insulin resistance has been demonstrated to be a major factor in the pathogenesis of dyslipidemia in the metabolic syndrome. Individuals with insulin resistance exhibit increased production and impaired catabolism of triglyceride-rich lipoproteins with resultant hypertriglyceridemia. The reduction in the catabolism of very low-density lipoprotein and secondary hypertriglyceridemia is correlated with low levels of HDL due to the resultant impaired transport of cholesterol between these two lipoproteins. Insulin resistance may be a primary phenomenon or secondarily related to increased body mass index. The concept of improvement of insulin resistance by hygienic interventions is theoretically attractive in the management of subjects with the metabolic syndrome. Dietary restriction of caloric intake and increased physical activity have clearly been demonstrated to improve insulin sensitivity with the potential to improve metabolic parameters. Pharmacologic agents have also been an attractive approach to insulin resistance in subjects who do not optimize metabolic parameters by weight loss or exercise. The two major pharmacologic agents which have been demonstrated to alter insulin sensitivity are metformin and the thiazolidinediones (TZDs). The insulin sensitizers such as the thiazolidinediones are theoretically attractive although the use of these agents has become controversial as a means to improve cardiovascular outcomes. A controversial meta-analysis has demonstrated an increase in myocardial infarction but without a concomitant increase in cardiovascular or total mortality with rosiglitazone (Nissen and Wolski 2010; Schernthaner and Chilton 2010). Furthermore, another meta-analysis of 16 clinical studies which evaluated 810,000 subjects has suggested an increase in sodium retention and congestive heart failure with these agents (Loke et al. 2011). Metformin therapy has been utilized for diabetes for many years. The United Kingdom Prospective Diabetes Study (UKPDS) did demonstrate a reduction in the incidence of coronary heart disease with metformin administration in subjects with increased body mass index coupled with the presence of type 2 diabetes (Krentz and Bailey 2005). Additionally, in the Diabetes Prevention Program, individuals who demonstrated impaired glucose tolerance and received metformin therapy were demonstrated to exhibit reduction in the onset of type 2 diabetes (Knowler et al. 2009). However, while specific prospective-controlled clinical trials in subjects with the metabolic syndrome had not been performed utilizing metformin therapy, it would appear that this agent would be a logical therapy. Additionally, individuals who have impaired glucose tolerance have been demonstrated to exhibit a delayed onset of type 2 diabetes following the implementation of metformin therapy.

Dyslipidemia is a major feature of the metabolic syndrome. Subjects with the metabolic syndrome frequently exhibit the atherogenic lipid phenotype which is characterized by a relatively normal total cholesterol but elevated triglycerides, low HDL, and small dense low-density lipoprotein (Eckel et al. 2010). The use of non-HDL cholesterol targets Apo B-containing particles and has been advocated as a therapeutic target for optimization of the lipid profile. The utilization of non-HDL cholesterol has been demonstrated to be a more accurate predictor of cardiovascular risk than LDL cholesterol alone (Liu et al. 2005). A proposed advantage of the utilization of non-HDL cholesterol as a therapeutic target obviates the controversy relative to the role of isolated hypertriglyceridemia as a cardiovascular risk factor. Non-HDL cholesterol levels are frequently abnormal in subjects with the metabolic syndrome. The administration of statin therapy has a predominant effect on low-density lipoprotein but also improves HDL and lowers triglycerides albeit to a lesser degree. Statin therapy should be considered to be a mainstay

intervention for the pharmacologic management of dyslipidemia in subjects with metabolic syndrome whose lipid profiles are not optimized by lifestyle modification. Subgroup analysis of statin trials demonstrates a reduction in cardiac events in patients who fit the diagnostic criteria of the metabolic syndrome (Ballantyne et al. 2001). The use of fibric acid derivatives is also theoretically attractive as the mechanism of PPAR agonists is to increase the activity of lipoprotein lipase with reduction in triglycerides and an increase in HDL. Post hoc analysis of primary prevention trials with gemfibrozil demonstrates a reduction of cardiac events in individuals with the lipid triad (Manttari et al. 1990). However, the Fenofibrate Intervention and Event Reduction in Diabetes (FIELD) trial which employed fenofibrate in diabetic subjects was disappointing although methodological problems were encountered in the trial design (Keech et al. 2005).

Elevated blood pressure is a major factor in the determination of cardiovascular risk in subjects with the metabolic syndrome. Lifestyle interventions are always considered to be the first line of therapy in risk factor management. Lifestyle changes should always be given an adequate trial prior to consideration of antihypertensive pharmacologic therapy. Modulators of the renin-angiotensin system (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) are theoretically advantageous in the metabolic syndrome as there are no adverse effects on lipids or glucose tolerance. Factors governing the modulators of the renin-angiotensin system has not been evaluated in prospective trials with cardiovascular endpoints have not been performed specifically in subjects with the metabolic syndrome. However, the use of ramipril in the Heart Outcomes Prevention Evaluation (HOPE) trial appeared to demonstrate the decrease on the incidence of diabetes mellitus in normotensive patients with multiple risk factors (Sleight et al. 2001). However, no class of antihypertensive agents is considered to be globally efficacious in subjects with the metabolic syndrome.

4 Metabolic Syndrome in Asians

Epidemiologic studies from South Asia have demonstrated a progressive and alarming increase in the incidence of cardiovascular disease over the past several decades. Additionally, the incidence and prevalence of type 2 diabetes has also been demonstrated to be significantly increasing which has profound implications for the development of coronary artery disease. Epidemiologic studies have demonstrated that the prevalence of type 2 diabetes has increased twofold over the past 30 years in South Asia (Gupta et al. 2003; Ramachandran et al. 2001). The reasons which underlie this disturbing trend are multifactorial and have been related in varying degrees to urbanization, lifestyle alterations (diet and exercise), economic influences, and increased life expectancy. The availability of Western fast-food outlets which supply foods high in both calories and content of saturated fat has proliferated over the past two decades in South Asia. Additionally, observational studies have documented a reduction in the level of physical activity which is particularly manifest in children. The lifestyle changes occurring in South Asia have progressively been manifest by an increasing prevalence of the components of the metabolic syndrome. The progressive urbanization has been a major factor in the increased incidence and prevalence of the metabolic syndrome in South Asia. The bulk of epidemiologic data analyzing the prevalence of the metabolic syndrome and its cardiovascular implications have been conducted in India. Epidemiologic studies conducted in Indian population centers have estimated a prevalence of the metabolic syndrome to encompass approximately one third of subjects residing in large cities (Ramachandran et al. 2003).

The prevalence rate of the components of the metabolic syndrome may also have a genetic basis with different expressions in various populations although quantification of the relative contribution of lifestyle modifications relative to interactions of genetic tendencies is difficult to separate. However, several studies have analyzed that the phenotypic expression of body mass index and fat

distribution have significant differences in the Indian population. South Asians who do not live in urban centers tend to have a low body mass index when compared to other populations. However, the progressive urbanization in the Indian subcontinent has been demonstrated to exhibit a modification of body phenotype when compared to rural populations. Individuals and their progeny who migrate to urban centers have been demonstrated to exhibit a significant increase in body mass index. Additionally, South Asians tend to have a higher prevalence of truncal obesity, fatty infiltration of the liver, and ectopic fat deposition. South Asians tend to have a higher percentage of body fat compared to other populations despite the lower-average BMI values. Importantly, excess adiposity in South Asians appears to manifest by an increased prevalence of the major components of the metabolic syndrome including hypertension, diabetes, and dyslipidemia (Misra et al. 2007; Basit and Shera 2008). The anatomic distribution of adiposity may also be different in South Asians. Abdominal obesity is increased especially when associated with a body mass index of greater than 25 kg/m^2 (Vikram et al. 2003). The distribution of intra-abdominal adipose tissue is increased in South Asians. Intra-abdominal adipose tissue has been demonstrated to be metabolically active and is associated with increased release of free fatty acids into the circulation with a secondary increase in the degree of hypertriglyceridemia and impaired glucose tolerance. The term metabolically obese has been utilized to explain these risk factor alterations in the presence of a relatively normal body mass index (Misra and Khurana 2008). The recognition of differing metabolic characteristics has resulted in a revision of normal values for South Asians. The National Obesity and Metabolic Syndrome Summit presented a consensus paper on diagnostic cutoffs for body mass index and waist circumference. The normal values for South Asian body mass index in kilograms/meter squared were established to be 18–22.9 kg/m^2. The definition of an overweight body mass index was 23–24.9 kg/m^2 and the diagnosis of obesity was established if the body mass index exceeded 25 kg/m^2. Additionally, the waist circumference for males was considered to be abnormal when the measurements exceeded 90 cm. The abnormal value for waist circumference in women was defined as greater than or equal to 80 cm (Misra 2003).

The role that diet and exercise play in body mass index and waist circumference in South Asians has been not adequately studied. The traditional Indian vegetarian diet was low in saturated fat and simple carbohydrates and is accompanied by a relatively higher level of insoluble dietary fiber. The consumption of the traditional diet has gradually declined with the progressive urbanization of the subcontinent with a resultant increase in insulin resistance and the metabolic syndrome (Misra et al. 2009a; Wasir and Misra 2004). Despite the fact that the diet is considered to be "vegetarian," Asian Indians have been demonstrated to consume a higher concentration of saturated fats and hydrogenated oils which may negate the nutritional benefit of a pure vegetarian diet (Popkin et al. 2001). Additionally, South Asians had been demonstrated to have a reduced consumption of omega-3 polyunsaturated fatty acids and monounsaturated fatty acids coupled with a higher intake of omega-6 polyunsaturated fatty acids when compared to Caucasians. The increase in simple carbohydrates and fat intake coupled with a reduction in fiber intake has been postulated to play a significant role in the interrelationship between obesity and type 2 diabetes which has been documented in the Indian population. Additionally, the progressive urbanization which is prevalent on the Indian subcontinent has led to a more sedentary lifestyle relative to other ethnic groups.

Societal factors and metabolic syndrome in South Asians

1. Increased affluence
2. Urbanization
3. Rural-urban population shifts
4. Change in dietary habits, fast high-calorie foods
5. Decreased physical activity

Certain characteristics of metabolic syndrome in South Asians

1. Metabolic obesity with normal or low BMD
2. Truncal obesity
3. Increased intra-abdominal adipose tissue
4. Higher percentage of body fat
5. Comorbid conditions like diabetes and hypertension with normal BMI

The increasing prevalence of a sedentary lifestyle has led to a consensus statement recommending a nationwide increase in aerobic activity as a means to reduce the risk for the development of the metabolic syndrome and other cardiovascular issues (Misra et al. 2009b). Additionally, the type of leisure-time activity practice by Indians has shifted from aerobic outdoor sporting activity to more sedentary forms of entertainment. The shifts in leisure activities which have occurred as a result of socioeconomic and behavioral changes have resulted in a significant increase in central obesity which is especially manifest in women (Ghosh 2006). In addition to the alteration of dietary and physical activities in the urban Indian population, a number of genetic factors may interplay with lifestyle changes in the development of the metabolic syndrome in Asian Indians.

The presence of several gene polymorphisms which are present in South Asians has been demonstrated to alter lipid and carbohydrate metabolism and may play a significant role in the development of the components of the metabolic syndrome. For instance, the glucokinase enzyme system is involved in the facilitation of the phosphorylation of glucose to glucose-6 phosphate. The glucokinase enzyme system plays a pivotal role in carbohydrate metabolism by acting as a glucose sensor. Polymorphisms of glucokinase exist which play a role in insulin sensitivity and diabetes. The glucokinase gene polymorphisms are present in Asian Indians and may have a significantly adverse impact on hepatic and whole body insulin sensitivity (Chiu et al. 2000). Additionally, the presence of increased levels of plasma cell glycoprotein (PC)-1K121Q and insulin receptor substrate-1 G972A polymorphisms are associated with primary insulin resistance, and the gene frequencies have been demonstrated to increase in South Asians and provide a genetic predisposition for the development of glucose intolerance (Abate et al. 2003). Triglyceride-rich lipoproteins such as very low-density lipoprotein and chylomicrons carry both Apo CII and Apo CIII on their surface. Apo CII is an agonist for lipoprotein lipase and the resultant enhanced catabolism of very low-density lipoproteins and is a major factor in the metabolism of both chylomicrons and very low-density lipoprotein. Conversely, Apo CIII is an inhibitor to lipoprotein lipase and results in impaired catabolism of very low-density lipoprotein and chylomicrons with resultant circulating hypertriglyceridemia. South Asian subjects who express polymorphisms of the Apo CIII gene complex are characterized by an increased predisposition for the development of dyslipidemia due to impaired catabolism of very low-density lipoprotein and subsequent increases in triglyceride levels (Miller et al. 2007). Additionally, a predilection for elevated blood pressure coupled with a subsequent enhanced risk of the metabolic syndrome has been described in South Asians who express these polymorphisms. Abnormal indices of vascular inflammation and thrombosis have been described in South Asians with metabolic syndrome (Kain et al. 2003; Wasir et al. 2007).

Dyslipidemia is felt to be a major modifiable cause of the excess burden of atherosclerosis in Asian Indians. Dyslipidemia is a major consequence of the dietary increase in the quantity and percentage of saturated fat, genetic tendencies, reduced level of physical activity, and increased body mass index which has been demonstrated in South Asians. The characteristic lipid pattern of the metabolic syndrome is a triad comprised of the combination of hypertriglyceridemia, low HDL cholesterol, and small dense LDL particles. The total cholesterol may be normal or only slightly elevated despite the presence of the atherogenic lipid phenotype. The lipid phenotype of the metabolic syndrome is highly atherogenic and has been demonstrated to have characteristic

differences in the South Asian population. However, difficulty has arisen in defining the true normal level of the various lipoprotein fractions which has become controversial both in the general population and in subjects with the metabolic syndrome. The average level of LDL cholesterol in normal humans is 50 mg/dL at birth. LDL cholesterol levels of 50 mg/dL appear to be sufficient to supply all of the metabolic needs of the body relative to the production of steroid hormones, membrane synthesis, neuron integrity, etc. The level of low-density lipoprotein in urban India has significantly increased in the recent years (Joseph et al. 2000). The high prevalence of a vegetarian diet would be predicted to be associated with a relatively low total cholesterol levels. However, while vegetarianism was previously the rule, the recent trend in urbanization has altered conventional dietary habits. The Asian Indian population has been analyzed for dietary trends, lipid phenotypes, and the subsequent risk for coronary artery disease. Epidemiologic studies have demonstrated that vegetarian and non-vegetarian Indians express a similar lipid phenotype and risk for the development of coronary artery disease which would appear to be counterintuitive. The precise mechanism for the lack of an improved lipid profile in vegetarians is multifactorial and may be secondary to alteration of the traditional methods in the preparation of food. One explanation for the failure of South Asian vegetarians to exhibit an improved lipid profile is in the utilization of high quantities of saturated fats and *trans*-fatty acids in the process of deep frying of vegetables. Additionally, the practice of overcooking has been demonstrated to result in the destruction of multiple nutrients including folic acid. The reduced level of circulating folic acid has been linked to risk for coronary artery disease. The components of the lipid profile may also be different in Asian Indians. Low-density lipoprotein exists in a family of circulating particles which vary in size, lipid composition, density, and risk for the development of atherosclerosis. The larger, more buoyant subforms of low-density lipoprotein have been associated with a relative decrease in cardiovascular risk when compared to the smaller more dense particles. Low-density lipoprotein is composed of a family of seven definable subforms. However, for clinical purposes the low-density lipoprotein fraction may be divided into large buoyant forms (type A) and small dense forms (type B). The plasma level of small dense LDL cholesterol is correlated with a significant statistically increased risk for the development of coronary artery disease relative to the larger, more buoyant forms. The mechanism by which the presence of small dense LDL induces atherosclerosis is multifactorial. Small dense LDL particles are cytotoxic and induce endothelial dysfunction. The endothelial damage associated with increased levels of small dense LDL reduces the endothelial barrier function for circulating lipoproteins and allows increased migration into the subendothelial space. Additionally, small dense LDL particles are more susceptible to oxidation which enhances recognition by the scavenger receptor and subsequent uptake by the monocyte macrophage system. The progressive unregulated uptake of oxidized LDL particles generates the foam cell which is the first pathologic marker of atherosclerosis. The precise quantification of the levels of small dense LDL requires sophisticated measurement techniques such as nuclear magnetic resonance (NMR). However, the presence of small dense LDL particles can be predicted on clinical grounds by the presence of hypertriglyceridemia (greater than or equal to 150 mg/dL). Additionally, HDL cholesterol levels lower than 35 mg/dL are also associated with the presence of small dense LDL particles. The utilization of the triglyceride/HDL ratio has also been recommended as a means to estimate the presence of small dense LDL particles. Ratios in excess of 3.8 have been determined to be indicative of the presence of small dense LDL in South Asian individuals and may provide an indication for intensive lipid modification (Bhalodkar et al. 2006). The utilization of both statin therapy and fibric acid derivatives has been demonstrated to alter the structure of low-density lipoprotein to a less atherogenic phenotype (Sirtori et al. 2005; Superko et al. 2005). Hypertriglyceridemia is frequently associated with an atherogenic lipid profile. However, the role of hypertriglyceridemia as an independent

risk factor for the development of coronary atherosclerosis is controversial. Hypertriglyceridemia frequently coexists with obesity, tobacco usage, diabetes mellitus, reduced physical activity, and medications (such as nonselective beta-blockers), and its independent contribution to cardiovascular risk is difficult to quantify due to statistical issues. Very low-density lipoprotein is the major endogenous triglyceride-rich particle produced by the liver. Very low-density lipoprotein does carry Apo B which is considered to be a significant marker for particle atherogenicity. Clinical data is accumulating that the atherogenicity of partially metabolized very low-density lipoprotein remnant particles is significant and associated with increased cardiovascular risk. Genetic conditions such as familial dysbetalipoproteinemia are characterized by the persistence in the circulation of partially metabolized very low-density remnant particles and are associated with increased cardiovascular risk (Smelt and de Beer 2004). The utilization of non-HDL cholesterol may be employed as a marker for cardiovascular risk and circumvents the problems associated with remnant particles which are common in the metabolic syndrome due to the impaired catabolism associated with endothelial dysfunction in combination with impaired clearance. Non-HDL cholesterol would include very low-density lipoprotein, lipoprotein remnant particles, and low-density lipoprotein and lipoprotein (a). The utilization of the degree of non-HDL cholesterol elevations has gained credence as a therapeutic target for the dyslipidemia associated with the metabolic syndrome. The non-HDL cholesterol goals are 30 mm per deciliter higher than the targets for LDL cholesterol levels. Asian Indians appear to have generally similar levels of non-HDL cholesterol when compared to Americans and Europeans (Enas et al. 1996). However, when hypertriglyceridemia is associated with an increase in non-HDL cholesterol which includes all Apo B-containing lipoproteins, an increase cardiovascular risk has been determined.

High-density lipoprotein also exists in a family of particles with a variable impact on cardiovascular risk. The level of HDL cholesterol is generally inversely related to cardiovascular risk and has been classified as a negative risk factor by the ATP-III of the National Cholesterol Education Program. However, significant exceptions to rule exist and the measurement of HDL cholesterol in and of itself does not determine the physical characteristics of the particle, functionality, or relation to risk. Reverse cholesterol transport involves the mobilization of cholesterol from peripheral stores by high-density lipoprotein and is felt to be the major mechanism by which HDL exhibits protection from atherosclerosis. The large HDL particles such as HDL-2 are higher in cholesterol and imply more efficient reverse cholesterol transport activity. Conversely, smaller HDL particles such as HDL-3 are relatively depleted in cholesterol which would suggest an impaired removal of cholesterol from peripheral stores. Asian Indians have been demonstrated to exhibit a significant decrease in the larger more protective HDL particles coupled with an increase in smaller particles (Cromwell 2007; Bhalodkar et al. 2004). An unknown factor is the interpretation of the prognostic implications of elevated HDL cholesterol is the concept of dysfunctional HDL (Farmer and Liao 2011). Despite relatively normal levels of HDL cholesterol, its exposure to inflammation and oxidative stress has been demonstrated to be associated with a decreased functionality of this particle. HDL is a naturally occurring antioxidant which protects low-density lipoprotein from oxidation. Exposure to inflammatory stimuli has been demonstrated to be associated with a reduction in a variety of antioxidant enzymes associated with HDL such as paraoxonase which is associated with reduced protective functionality of the particle.

Lipoprotein (a) is a complex lipoprotein which consists of a LDL molecule coupled to Apo (a) by the presence of sulfhydryl groups (Scanu 2003). The levels of lipoprotein (a) are primarily genetically determined and display minimal response to pharmacologic therapy (with the exception of nicotinic acid and estrogens), diet, or physical activity. The role of lipoprotein (a) in the pathogenesis of atherosclerosis is complex. Lipoprotein (a) is felt to provide a pathophysiologic link between dyslipidemia, atherosclerosis, and the thrombolytic cascade. The presence of the low-density

lipoprotein moiety in the lipoprotein (a) molecule provides the capacity to deliver cholesterol to the subendothelial space where it may be scavenged by the monocyte macrophage system. Additionally, Apo (a) exhibits a structural similarity to plasminogen although lipoprotein (a) is lacking in serine protease activity. High circulating levels of lipoprotein (a) interfere with the capacity of tissue plasminogen activators to lyse an intravascular clot. Individuals who exhibit high levels of lipoprotein (a) are at risk for atherosclerosis and this particle is generally not measured in standard lipid profiles. Asian Indians have been demonstrated to have increased circulating levels of lipoprotein (a) with a mean level of 20 mg/dL which is considered to be the threshold for increased atherosclerotic risk (Enas et al. 2006). Determinations of lipoprotein (a) in Asian Indians have been correlated with the presence and severity of atherosclerosis. However, the quantification of the atherosclerotic risk transmitted by lipoprotein (a) is complicated by the presence of a variety of isoforms which have a variable impact on risk and are not generally determined with standard biochemical assays.

Elevated blood pressure is the most common risk factor for cardiovascular morbidity and mortality. The prevalence of hypertension is progressively increasing in developing countries due to lifestyle modifications, increased body mass index, reduced physical activity, increased sodium intake, and increased survival to older age groups where vascular pathology is more prevalent. Developing countries that are in economic transition have been demonstrated to express a significant increase in the incidence and prevalence of elevated blood pressure. Epidemiologic studies which were conducted in the decade including the 1940s demonstrated a prevalence of hypertension of 1.2–4.2 % in India. However, the prevalence of elevated blood pressure has risen to a rate of 15–25 % in the decade encompassing the 1990s (Gupta 1997). The increase in blood pressure in Asian Indians is not limited to adults. School-age children in the 11–17-year-old age group have a prevalence of hypertension of 6.6 % in urban areas which would be predicted to increase if trends in obesity and reduced physical activity continue (Mohan et al. 2004). The burden of hypertension in South Asia and its underlying causes are multifactorial. The high prevalence of diabetes and insulin resistance in India may play a significant role in the risk for the development of hypertension. The prevalence of type 2 diabetes mellitus was estimated to be 23 million subjects in the year 2000 with a projected increase to 57 million by the year 2025 (King et al. 1998). The presence and severity of insulin resistance may play a significant role in the pathogenesis of hypertension in South Asian subjects. Elevated levels of insulin have been demonstrated to have multiple adverse effects on blood pressure which include endothelial dysfunction, increased sympathetic tone, enhanced proximal renal absorption by the kidney, and vascular remodeling. The presence of endothelial dysfunction has been demonstrated to result in a significant alteration of flow through both resistance and conduit vessels. The endothelial dependent dilation is partially a function of the balance between the local production of vasoconstrictors such as thromboxane and vasodilators such as prostacyclin. The resultant effect of insulin resistance on endothelial function is impaired vasodilation which can be measured clinically. The presence of endothelial progenitor cells and endothelial progenitor cell colony-forming units (which are a marker of endothelial function) has been demonstrated to be lower in healthy South Asian individuals compared to Caucasians. The presence of endothelial dysfunction, insulin resistance, and reduced endothelial progenitor cells may contribute to the increased vascular risk from hypertension in South Asians (Murphy et al. 2007). The role and physiologic implications of endothelial function may be assessed in both conduit and resistance vessels by utilizing flow-mediated dilation in response to a variety of stimulants. Both conduit and resistance vessels had been demonstrated to exhibit impaired dilation in dyslipidemia, obesity, tobacco usage, and diabetes. The impaired vascular function in South Asians relative to Caucasians may play a role in progressive vascular remodeling which has been implicated in the pathogenesis of hypertension. The presence of endothelial dysfunction in South Asians has also been linked to an increase prevalence of visceral and abdominal

obesity when compared to Caucasians (Chambers et al. 1999). The presence of endothelial dysfunction would have multiple implications for the pathogenesis of hypertension and subsequent vascular disease in the metabolic syndrome.

Dietary influences have also been demonstrated to play a major role in the pathogenesis of hypertension in South Asia. Studies performed in urban centers of India have demonstrated a significant increase in sodium intake with resultant hypertension (Radhika et al. 2007). The mean dietary intake was determined to be 8.5 g per day which is significantly higher than the amount recommended by the World Health Organization of 5 g per day. The progressive rise in elevated blood pressure in South Asian has implications for the development of the metabolic syndrome, coronary artery disease, and cerebrovascular disease. However, epidemiologic data for the prevalence of severity and hypertension is conflicting when comparing South Asians to other ethnic groups. Epidemiologic studies performed in the UK have demonstrated an increased prevalence of elevated blood pressure in South Asian individuals although the data is not striking (McKeigue et al. 1991; Cappuccio et al. 1997). Additionally, meta-analysis of multiple blood pressure studies in South Asians has provided conflicting results. The heterogeneity within different South Asian ethnic groups has been reflected in multiple variables including differences in smoking, physical activity, dietary factors, and socioeconomic conditions (Bhopal 2002).

4.1 Implications

The term metabolic syndrome was initially proposed to describe a grouping of cardiovascular risk factors which appeared to coexist with a greater frequency than would be expected by chance alone with the implications for metabolic pathways. The metabolic syndrome is characterized by hypertension, hypertriglyceridemia, low HDL cholesterol, increased waist circumference, and glucose intolerance. National organizations have established differing criteria for the diagnosis of the metabolic syndrome. The epidemiologic data has demonstrated that the prevalence of the metabolic syndrome is significantly increased in South Asians. The cardiovascular risk relative to risk factor clustering is significantly increased in the South Asian population and begins at an early age. The rapidly occurring impacts of rapid urbanization, mechanization, and socioeconomic factor alterations of traditional diet have been felt to play a major role in the increased incidence and prevalence of the metabolic syndrome in South Asian populations which has been demonstrated across the age spectrum and in both rural and urban populations. The metabolic syndrome in South Asians is correlated with a distinct phenotype including excess body fat, abdominal obesity, truncal subcutaneous fat, and ectopic fat deposition. Prevention relative to the alteration of trends occurring in dietary intake of fat in simple carbohydrates and reduced physical activity is the primary thrust in the reduction of the incidence of the metabolic syndrome. Community-based programs aimed at creating awareness relative to the various aspects of lifestyle modifications had been recommended as a means to reduce the prevalence of the metabolic syndrome of and lifestyle and exercise (Misra and Khurana 2009).

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Obesity in East Asia

7

Yong-Moon Mark Park and Junxiu Liu

Contents

Abstract

The prevalence of obesity has been dramatically increased for the last three decades worldwide.

Since there is a difference in defining obesity, especially in abdominal obesity, direct comparison of the obesity prevalence may not be appropriate between Asian countries and others. However, based on data for the recent two decades, obesity epidemic is also observed in the countries in East Asia in parallel with marked environmental and lifestyle changes. This review focuses on the recent trends of general and abdominal obesity in East Asian countries including China, Japan, South Korea, and Taiwan.

In addition to data for obesity epidemic, a large body of evidence on the "metabolically obese" phenotype in a normal weight population has been reported in the population in east countries. This phenotype is important in the public health perspective, because normal weight individuals with metabolic obesity may have obesity-related morbidities as well, especially in an Asian population who are more liable to increased visceral fat and insulin resistance than any other race or ethnicity with the same level of body mass index. In the other way, "healthy obesity" in an obese population has been proposed, based on the fact that not all obese individuals are uniformly affected with cardio-metabolic abnormalities; however, this may not be the case in East Asian population.

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1 Definition of Obesity in East Asia

For the epidemiological purpose, general obesity and abdominal (central) obesity measured by body mass index (BMI) and waist circumference, respectively, are the commonly used anthropometric measurements. By the recommendation from the International Obesity Task Force (IOTF) and the World Health Organization (WHO) Regional Office for the Western Pacific Region, general obesity has been defined as BMI $\geq$ 25 kg/m^2 (World Health Organization 2000). WHO expert consultation also proposed an alternative criterion for general obesity in Asians as BMI $\geq$ 27.5 kg/m^2 (WHO, Expert Consultation 2004).

However, there is no consensus on a standard definition for abdominal obesity. Thus, several cutoffs have been proposed to determine abdominal obesity according to different countries or ethnicities. Each country in East Asia has its own recommended waist circumference threshold for abdominal obesity (Table 1). In addition to this recommendation, a number of studies have been conducted to identify the appropriate cutoff for abdominal obesity in East Asian countries, based on reflecting or predicting metabolic syndrome or its components (Lee et al. 2007; Bao et al. 2008; Oka et al. 2008; Baik 2009; Seo et al. 2009; Wang et al. 2010; Kawada et al. 2011; Lim et al. 2012; Hou et al. 2014), multiple cardiovascular risk factors (Narisawa et al. 2008; Kashihara et al. 2009; Nakamura et al. 2011; Zeng et al. 2014), or insulin resistance (Koh et al. 2010; Park et al. 2010; Kamezaki et al. 2012). However, most studies had cross-sectional design in which inaccurate conclusions could not be ruled out in the association between abdominal obesity and health outcomes. Well-designed prospective studies with representative populations would be warranted to determine optimal cutoff values for abdominal obesity.

2 Obesity Prevalence and Trend in East Asia

Due to the shifts in diet and lifestyle resulting from rapid socioeconomic transition and urbanization, the epidemic of obesity from childhood to adulthood has become a substantial public health issue in eastern Asia including China, Japan, South

Table 1 Recommended waist circumference thresholds for abdominal (central) obesity

Population	Organization	Male, cm	Female, cm
Europid	IDF	≥94	≥80
Caucasian	WHO	≥94 (increased risk) ≥102 (higher risk)	≥80 (increased risk) ≥88 (higher risk)
United States	AHA/NHLBI (ATP III)	≥102	≥88
Asian	IDF/WHO	≥90	≥80
Korea	KSSO	≥90	≥85
China	Cooperative task force	≥85	≥80
Japan	Japanese obesity society	≥85	≥90
Middle East, Mediterranean, sub-Saharan Africa	IDF	≥94	≥80

Adapted from Yoon, Rev Endocrinol Metab 2014;29:418–426 with permission from Korean Endocrine Society (Yoon and Oh 2014)
Abbreviations: *IDF* International Diabetes Federation, *WHO* World Health Organization, *AHA* American Heart Association, *NHLBI* National Heart, Lung, and Blood Institute, *ATP III* Adult Treatment Panel III, *KSSO* Korean Society for the Study of Obesity

Korea, and Taiwan, a province of China. In this chapter, we will focus on the prevalence and trends of children and adult general and central obesity perspectives. The purpose of this chapter is to provide basic information on the magnitude and trends of the obesity problem in East Asian countries for children and adult, respectively.

2.1 General Obesity Versus Abdominal Obesity for Adults

In accompaniment with the rapid economic development of East Asian countries over the last several decades, behavioral shifts have accelerated at a historically unprecedented pace and scale in East Asia by the adoption of "western lifestyle," diet, and physical activity patterns. Correspondingly, the epidemic of obesity in both children and adults has become a serious issue due to the dramatic number of affected individuals within the population.

In China, the most important source of data on the estimate of obesity prevalence for both adult and children is the China Health and Nutrition Survey (CHNS), an ongoing open cohort and an international collaborative project between the Carolina Population Center at the University of North Carolina at Chapel Hill and the National Institute of Nutrition and Food Safety at the Chinese Center for Disease Control and Prevention. The CHNS is a large-scale, national cross-sectional survey designed for exploring how the health and nutritional status of the Chinese population has been affected by social and economic changes. A multistage, random cluster process was used to draw samples from nine provinces (Liaoning, Heilongjiang, Jiangsu, Shandong, Henan, Hubei, Hunan, Guangxi, and Guizhou). Similar to Mainland China, the Nutrition and Health Survey in Taiwan (NAHSIT) is the most commonly used data information from national survey for estimating the prevalence of general and central obesity in Taiwan. Another national representative source of data information is the National Health Research Institute Survey (NHRIS).

The Korea National Health and Nutrition Examination Survey (KNHANES) is the most important source of data on the prevalence of general and central obesity in Korea. For children, the National Growth Survey is another source of data to estimate the trend of obesity prevalence.

In Japan, the most used data for estimating the trend of obesity in adult and children is the Japan National Nutrition Survey. Table 2 shows the prevalence and trend of general and central obesity in adults among China, Taiwan, Korea, and Japan using national representative surveys. Table 3 shows the prevalence and trend of general and central obesity in children among China, Taiwan, Korea, and Japan using national representative surveys.

3 Metabolic Health and Obesity in East Asia

The risk of developing obesity-related complications is generally well correlated with the degree of obesity; however, not all obese individuals are uniformly affected. Even in the same BMI category, a subgroup of obese individuals with normal cardio-metabolic characteristics has been designated as "metabolically healthy obese (MHO)," compared with "metabolically unhealthy obese (MUO)" (Kim et al. 2014a; Primeau et al. 2010; Karelis et al. 2004). In the same context, a subgroup of normal weight individuals who are vulnerable to cardio-metabolic abnormalities due to their adverse body composition has been identified as "metabolically obese normal weight (MONW) or normal weight obesity (NWO)," compared with their metabolically normal counterparts with the same category of BMI representing "metabolically healthy normal weight (MHNW)" (Kim et al. 2014b; Choi et al. 2013a; Lee et al. 2011b; Yajnik and Yudkin 2004; Ruderman et al. 1981).

3.1 Epidemiological and Clinical Implications of MONW Phenotype

It is important to recognize the MONW individuals in East Asian populations who are more liable to increased visceral fat and insulin resistance than

Table 2 Prevalence and trend of general obesity and abdominal obesity for adults among East Asian countries

	Survey year	Sample	Age range	Definition criteria	Prevalence of overweight	Prevalence of obesity
General obesity						
Taiwan						
	1993–1996 (Lin et al. 2003)	NAHSIT	≥20	OW, 25 < BMI < 30; obese, BMI > 30	21.10 %	4.00 %
	2000–2001 (Chu 2005)	NHRIS	≥20	OW, BMI > = 24; obese, BMI > = 27	28.9 % (M), 18.7 % (F)	15.9 % (M), 10.7 % (F)
	2005–2008 (Yeh et al. 2011)	NAHSIT	≥18	OW, BMI > = 24; obese, BMI > = 27	31.87 % (M), 19.75 % (F)	18.90 % (M), 17.13 % (F)
	2013 (Ng et al. 2014)		≥18	OW, BMI 25–30; obese, BMI > = 30	33.8 % (M), 30.9 % (F)	4.3 % (M), 6.4 % (F)
China						
	1993 (Xi et al. 2012)	CHNS	≥18	OW, BMI 25–27.49; obese, > = 27.5	Overall: 9.4 %; 8 % (M); 10.7 % (F)	Overall: 4 %; 2.9 %(M); 5.0 % (F)
	1997 (Xi et al. 2012)	CHNS	≥18	OW, BMI 25–27.49; obese, > = 27.5	Overall: 11.3 %; 10.4 %(M); 12.1 %(F)	Overall: 6.2 %; 5.5 % (M); 6.7 % (F)
	2000 (Xi et al. 2012)	CHNS	≥18	OW, BMI 25–27.49; obese, > = 27.5	Overall: 13.8 %; 13.7 %(M); 13.9 % (F)	Overall: 8.0 %; 7.2 % (M); 8.6 % (F)
	2004 (Xi et al. 2012)	CHNS	≥18	OW, BMI 25–27.49; obese, > = 27.5	Overall: 14.9 %; 15.0 % (M); 14.9 % (F)	Overall: 8.7 %; 8.2 % (M); 9.2 % (F)
	2006 (Xi et al. 2012)	CHNS	≥18	OW, BMI 25–27.49; obese: > = 27.5	Overall: 15.4; 16.5 % (M); 14.4 % (F)	Overall: 9.2 %; 9.4 % (M); 9.0 % (F)
	2009 (Xi et al. 2012)	CHNS	≥18	OW, BMI 25–27.49; obese, > = 27.5	Overall: 15.7 %; 17.1 % (M); 14.4 % (F)	Overall: 10.7 %; 11.4 % (M); 10.1 % (F)
	2013 (Ng et al. 2014)		≥18	OW: BMI 25–30; Obese: BMI > = 30	28.3 % (M); 27.4 % (F)	3.8 % (M); 4.9 % (F)
South Korea						
	2001	K-NHANES	≥20	BMI > = 25		Overall: 30.6 %, 32.4 % (M); 29.4 % (F)
	1998 (Kang et al. 2014)	K-NHANES	≥20	OW, BMI > = 23; obese, BMI > = 25	50.8 % (M); 47.3 % (F)	26.0 % (M); 26.5 % (F)
	2001 (Kang et al. 2014)	K-NHANES	≥20	OW, BMI > = 23; obese, BMI > = 25	57.4 % (M); 51.9 % (F)	32.4 % (M); 29.3 % (F)
	2005 (Kang et al. 2014)	K-NHANES	≥20	OW, BMI > = 23; obese BMI > = 25	62.5 % (M); 50.0 % (F)	35.1 % (M); 28.0 % (F)
	2007–2009 (Kang et al. 2014)	K-NHANES	≥20	OW, BMI > = 23; obese, BMI > = 25	62.6 % (M); 48.9 % (F)	36.3 % (M); 27.6 % (F)
	2013 (Ng et al. 2014)		≥18	OW, BMI 25–30; obese, BMI > = 30	36.9 % (M); 27.2 % (F)	6.8 % (M); 5.8 % (F)
Japan						
	1976–1980 (Yoshiike et al. 2002)	JNNS	≥20	Preobese, 25–29.9; obese, BMI > = 30	14.5 % (M); 15.7 % (F)	0.84 % (M); 2.33 % (F)
	1991–1995 (Yoshiike et al. 2002)	JNNS	≥20	Preobese, 25–29.9; obese, BMI > = 30	20.5 % (M); 14.7 % (F)	2.01 % (M); 2.30 % (F)
	2013 (Ng et al. 2014)		≥18	OW, BMI25–30; obese, BMI > = 30	28.9 % (M); 17.6 % (F)	4.5 % (M); 3.3 % (F)

(*continued*)

Table 2 (continued)

	Survey year	Sample	Age range	Definition criteria	Prevalence of overweight	Prevalence of obesity
Abdominal obesity						
China						
					Prevalence of central obesity	
	1993 (Xi et al. 2012)	CHNS	≥18	WC > = 90 cm (M) and > = 80 cm (F)	Overall: 18.6 %; 8.5 % (M); 27.8 % (F)	
	1997 (Xi et al. 2012)	CHNS	≥18	WC > = 90 cm (M) and > = 80 cm (F)	Overall: 22.6 %; 13.8 % (M); 30.8 % (F)	
	2000 (Xi et al. 2012)	CHNS	≥18	WC > = 90 cm (M) and > = 80 cm (F)	Overall: 28.8 %; 19.5 % (M); 37.1 % (F)	
	2004 (Xi et al. 2012)	CHNS	≥18	WC > = 90 cm (M) and > = 80 cm (F)	Overall: 31.4 %; 21.6 % (M); 40.3 % (F)	
	2006 (Xi et al. 2012)	CHNS	≥18	WC > = 90 cm (M) and > = 80 cm (F)	Overall: 32.8 %; 23.2 % (M); 41.4 % (F)	
	2009 (Xi et al. 2012)	CHNS	≥18	WC > = 90 cm (M) and > = 80 cm (F)	Overall: 37.4 %; 27.8 (M); 45.9 % (F)	
South Korea						
	1998 (Oh 2011)	K-NHANES	≥20	WC > = 90 cm (M) and > = 85 cm (F)	Overall: 22.4 %; 20.6 % (M); 24.1 % (F)	
	2005 (Oh 2011)	K-NHANES	≥20	WC > = 90 cm (M) and > = 85 cm (F)	Overall: 23.9 %; 24.0 % (M); 23.8 % (F)	
	2007–2009 (Oh 2011)	K-NHANES	≥20	WC > = 90 cm (M) and > = 85 cm (F)	Overall: 24.1 %, 24.8 % (M); 23.5 % (F)	

Note: *NAHSIT* Nutrition and Health Surveys in Taiwan, *NHRIS* National Health Research Institute Survey, *CHNS* China Health and Nutrition Surveys, *KNHANES* Korea National Health and Nutrition Examination Survey, *JNNS* Japan National Nutrition Survey, *OW* overweight, *WC* waist circumference

any other race or ethnicity with the same level of BMI (Nazare et al. 2012). The prevalence of MONW phenotype varies from 10 % to 40 % according to the definition of metabolic obesity and populations used in each study (Table 4). Multiple studies have reported that the MONW phenotype is associated with increased risk of cardio-metabolic morbidity and mortality in East Asian population. Lee et al. demonstrated that MONW phenotype was independently associated with abnormal lipid profiles such as high total cholesterol and triglycerides in both men and women (Lee et al. 2011b). Kim et al. evaluated 2,078 normal weight ($18.5 \leq$ BMI < 25 kg/m^2) subjects and analyzed the data from atherosclerosis using coronary computed tomography angiography and pulse wave velocity (Kim et al. 2015). They found that NWO phenotype defined by highest tertile of gender-specific body fat percentage by sex (men $\geq$ 25.4 % and women $\geq$ 31.4 %) was independently associated with the presence of soft plaques, meaning that NWO individuals may have a higher risk of subclinical atherosclerosis compared with MHNW individuals. Yoo et al. also demonstrated that MONW phenotype, defined by the presence of metabolic syndrome in

Table 3 Prevalence and trend of general obesity of children among East Asian countries

	Survey year	Sample	Age range	Overweight and obesity criteria	Prevalence of overweight	Prevalence of obese
Taiwan						
	1980–1982 (Lin et al. 1985)	NS	12–15	OW: 110 ± 120 % of age and sex-specific mean body weight; obese is >120 % of mean body weight	13.0 %(B); 11.3 %(G)	12.4 %(B); 10.1 %(G)
	1986–1988 (Kao et al. 1991)	NS	12–15	OW: 110 ± 120 % of age and sex-specific mean body weight; obese is >120 % of mean body weight	10.9 %(B); 13.1 %(G)	14.8 %(B); 11.1 %(G)
	1994–1996 (Chu 2001)	TCHS	12–15	Overweight is defined as body weight at 110 ± 120 % of mean body weight and obese is defined as >120 % of mean body weight at same age and gender stratum	11.6 %(B); 10.2 %(G)	16.4 %(B); 11.1 %(G)
	2001–2002 (Chu and Pan 2007)	NAHSIT	6–12	> = 85th BMI; > = 95th of BMI	Overall: 15.0 %; 15.5 % (B) and 14.4 % (G)	Overall: 12.0 %; 14.7 % (B) and 9.1 % (G)
China						
	1993 (Liang et al. 2012)	CHNS	6–17	IOTF		6.10 %
	1997 (Liang et al. 2012)	CHNS	6–17	IOTF		7.00 %
	2000 (Liang et al. 2012)	CHNS	6–17	IOTF		7.40 %
	2004 (Liang et al. 2012)	CHNS	6–17	IOTF		10.10 %
	2006 (Liang et al. 2012)	CHNS	6–17	IOTF		10.30 %
	2009 (Liang et al. 2012)	CHNS	6–17	IOTF		13.10 %
	2010 (Sun et al. 2014)	CNSSCH	7–18	100–119.9 % of standard weight for height by age and sex; > = 120 % of standard weight for height	Overall: 19.2 %; 23.4 % (B); 14.5 % (G)	Overall: 8.1 %; 10.9 % (B);5.1 % (G)
Korea						
	1997 (Oh et al. 2008)	NGS	2–18	BMI ≥ 85th; BMI ≥ 95th	Overall: 13.0 %; 12.4 % (B); 13.8 % (G)	Overall: 5.8 %; 6.1 %(B); 5.5 %(G)
	2005 (Oh et al. 2008)	NGS	2–18	BMI ≥ 85th; BMI ≥ 95th	Overall: 19.0 %; 19.7 % (B); 18.2 % (G)	Overall: 9.7 %; 11.3 % (B);8.0 %(G)
	2001 (Khang and Park 2011)	KNHANES	2–9	IOTF	21.1 %(B); 16.9 %(G)	5.5 %(B); 3.8 %(G)
	2005 (Khang and Park 2011)	KNHANES	2–9	IOTF	15.6 %(B); 17.3 %(G)	3.2 %(B); 3.8 %(G)
	2007 (Khang and Park 2011)	KNHANES	2–9	IOTF	24.4 % (B);15.7 % (G)	10.5 % (B);1.9 %(G)

(*continued*)

Table 3 (continued)

	Survey year	Sample	Age range	Overweight and obesity criteria	Prevalence of overweight	Prevalence of obese
	1998 (Khang and Park 2011)	KNHANES	10–19	IOTF	16.2 %(B);13.8 %(G)	2.0 %(B),1.0 %(G)
	2001 (Khang and Park 2011)	KNHANES	10–19	IOTF	27.8 %(B); 16.7 %(G)	5.8 %(B);1.6 %(G)
	2005 (Khang and Park 2011)	KNHANES	10–19	IOTF	27.3 %(B);16.9 %(G)	5.6 %(B);2.8 %(G)
	2007 (Khang and Park 2011)	KNHANES	10–19	IOTF	29.4 %(B);16.4 %(G)	6.0 %(B);1.0 %(G)
Japan						
	1976–1980 (Matsushita et al. 2004)	NNS-J	6–8	IOTF	7.9 %(B); 8.7 %(G)	1.8 %(B); 1.8 %(G)
			9–11	IOTF	10.7 %(B); 9.3 %(G)	1.6 %(B); 1.3 %(G)
			12–14	IOTF	9.2 %(B); 8.6 %(G)	1.0 %(B); 0.5 %(G)
	1981–1985 (Matsushita et al. 2004)	NNS-J	6–8	IOTF	9.1 %(B); 10.8 %(G)	2.1 %(B); 1.9 %(G)
			9–11	IOTF	11.9 %(B); 10.3 %(G)	2.1 %(B); 0.9 %(G)
			12–14	IOTF	12.6 %(B); 9.6 %(G)	2.1 %(B); 0.5 %(G)
	1986–1990 (Matsushita et al. 2004)	NNS-J	6–8	IOTF	12.5 %(B); 13.2 %(G)	3.8 %(B); 2.8 % (G)
			9–11	IOTF	15.4 %(B); 12.8 %(G)	3.3 %(B); 1.2 %(G)
			12–14	IOTF	12.2 %(B); 10.0 %(G)	2.1 %(B); 1.2 %(G)
	1991–1995 (Matsushita et al. 2004)	NNS-J	6–8	IOTF	13.9 %(B); 14.7 %(G)	3.7 %(B); 3.1 %(G)
			9–11	IOTF	19.1 %(B); 14.8 %(G)	4.1 %(B); 2.0 %(G)
			12–14	IOTF	14.6 %(B); 9.0 %(G)	2.5 %(B); 1.6 %(G)
	1996–2000 (Matsushita et al. 2004)	NNS-J	6–8	IOTF	15.3 %(B); 14.6 %(G)	4.6 %(B); 4.6 %(G)
			9–11	IOTF	18.4 %(B); 17.2 %(G)	4.0 %(B); 3.0 %(G)
			12–14	IOTF	14.9 %(B); 11.2 %(G)	2.7 %(B); 1.0 %(G)

Note: *CNSSCH* Chinese National Survey on Students Constitution and Health, *IOTF* the International Obesity Task Force: BMI > = age-sex-specific BMI cutoff that corresponds to a BMI of 30 kg/m^2 at age 18, *NNS-J* Japan National Nutrition Survey, *NGS* National Growth Survey, *NS* National Survey, *TCHS* Taipei Children Heart Study, *NHS* Nutrition and Health Survey, *CHNS* China Health and Nutrition Survey

Table 4 Prevalence of metabolically obese normal weight (MONW) phenotype in East Asia

Study	Country	Nationally representative sample	Population characteristic	Definition	Prevalence among normal weight population
(Lee 2009)	South Korea	Yes	5,267 participants (2,227 men, 3,040 women) (≥20 years)	BMI < 25 kg/m^2 with metabolic syndrome, defined by NCEP-ATP III guideline (2002)	12.7 % (15.6 % in men, 10.7 % in women)
(Lee et al. 2011a)	South Korea	No	8,987 nondiabetic subjects (3,632 men and 5,355 women) (≥40 years)	18.5 ≤ BMI < 23 kg/m^2 with a HOMA-IR in the highest quartile	Men (14.2 %), women (12.9 %)
(Choi et al. 2013a)	South Korea	Yes	1,736 nondiabetic women (1,197 premenopausal women and 539 postmenopausal women) (≥19 years)	18.5 ≤ BMI < 25 kg/m^2 with (HOMA-IR) in the highest quartile	18.7 % for premenopausal women and 19.2 % for postmenopausal women
(Kim et al. 2014b)	South Korea	Yes	5,313 men and 6,904 women (≥20 years)	18.5 ≤ BMI < 23 kg/m^2 greater than 26 % body fat in men and greater than 36 % body fat in women	36 % for men, 29 % for women
(Lee et al. 2015b)	South Korea	Yes	17,029 nondiabetic subjects (7,185 men and 9,844 women) (≥20 years)	18.5 ≤ BMI < 23 kg/m^2 with HOMA-IR in the highest quartile	10.54 % for men and 13.26 % for women
(Yeh et al. 2005)	Taiwan	Yes	2,143 participants (1,020 men and 1,123 women) (≥20 years)	BMI < 24 kg/m^2, high waist circumference (≥80 cm for women and ≥90 cm for men)	1.7 % for men and 4.0 % for women among total population
(Tsou 2012)	Taiwan	No	1,180 participants (≥65 years)	18.5 ≤ BMI < 24 kg/m^2 with metabolic syndrome defined by NCEP-ATP III guideline (2002), Wildman criterion	16.3 %
(Heianza et al. 2014a)	Japan	No	8,090 nondiabetic subjects (5,884 men and 2,206 women) (aged 24–80 years)	BMI < 25 kg/m^2 with two or more of metabolic syndrome components defined by IDF	21.1 % among total population
(Heianza et al. 2014b)	Japan	No	27,478 nondiabetic subjects (17,730 men and 9,748 women)	BMI < 25 kg/m^2 with two or more of metabolic syndrome components defined by IDF	14.9 % among total population
(Du et al. 2015a)	China	Yes	3,552 participants (≥18 years)	18.5 ≤ BMI < 23 kg/m^2, Wildman criterion	47.9 %

Abbreviations: *HOMA-IR* homeostasis model assessment of insulin resistance, *NCEP-ATP III* (2002) the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII 2002), *IDF* International Diabetes Federation (Alberti et al. 2006); Wildman criterion (Wildman et al. 2008)

the category of 18.5 ≤ BMI < 25 kg/m^2, was independently associated with carotid atherosclerosis compared to MHNW phenotype in the 1,012 health examinees (Yoo et al. 2014). Choi et al. conducted a prospective cohort study with 10-year follow-up in 2,317 elderly people aged over 60 years in which MONW individuals were designated as a BMI < 23 kg/m^2 with metabolic syndrome determined by modified NCEP-ATP III criteria (Choi et al. 2013b). They found that all-cause and CVD mortality were significantly higher in MONW individuals compared to overweight or obese individuals.

No consensus has been made in defining MONW phenotype. Thus, several studies have explored the novel criteria for identifying NWO phenotype and related risk factors in East Asia. Kim et al. investigated the optimal cutoffs of percentage body fat (BF) to identify the NWO phenotype with the presence of at least one cardiovascular risk factor as the outcome, using data from the Korea NHANES (Kim et al. 2014b). They suggested that 26 % BF in men and 36 % BF in women would be the best cutoff for defining NWO individuals. Lee et al. proposed a novel criterion for defining MONW phenotype using the TyG index, calculated as ln[fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2] (Lee et al. 2014, 2015a). They determined the cutoff value of TyG index using 7,541 nondiabetic nationally representative normal weight (18.5 ≤ BMI < 25 kg/m^2) subjects in Korea and found that TyG index predicts incident diabetes using 3,185 participants from a prospective community-based cohort study (Lee et al. 2015a). Du et al. assessed the capability of lipid accumulation product (LAP) and visceral adiposity index (VAI) to determine MONW phenotype using data from the nationwide China Health and Nutrition Survey and found that both LAP and VAI were highly associated with MONW phenotype independent of the different several MONW criteria (Du et al. 2015a).

A number of studies have provided the evidence of risk factors for MONW phenotype. In a study of a representative Korean population, MONW phenotype was associated with older age, lower education, moderate alcohol consumption, and moderate-intensity exercise (Lee 2009). In addition, Choi et al. found that the MONW characteristics vary before and after menopause, indicating that young age, rural residence, higher BMI, high systolic blood pressure, low HDL-C, high white blood cell count, and lack of regular exercise were associated with the MONW phenotype in premenopausal women, whereas only high alanine aminotransferase was associated in postmenopausal women (Choi et al. 2013a). For the association between MONW phenotype and dietary patterns, Choi et al. showed that a reduced intake of carbohydrates and carbohydrate snacks is inversely associated with a MONW phenotype, especially in women, in which a MONW phenotype was defined as a 18.5 ≤ BMI < 25 kg/m^2 with metabolic syndrome based on the International Diabetes Federation consensus (Choi et al. 2012). Yoo et al. demonstrated that higher serum ferritin levels are associated with MONW phenotype, defined by modified NCEP-ATP III criteria, in a representative Korean normal weight (18.5 ≤ BMI < 25 kg/m^2) young adults aged 19–39 (Yoo et al. 2012). In a recent Korea NHANES study of 1,813 normal weight (18.5 ≤ BMI < 25 kg/m^2) adults, the findings revealed that lower serum zinc levels are associated with MONW phenotype defined by the highest quartile on HOMA-IR (Yang et al. 2015).

3.2 Epidemiological and Clinical Implications of MHO Phenotype

Since there is no standard universal definition of metabolic health, large variations have been observed in the prevalence of MHO phenotype ranging from 10 % to 57 % according to the definition of metabolic obesity and populations examined in each study (Table 5). In addition, much debate remains around whether MHO phenotype is definitely healthy (Kramer et al. 2013).

Chen et al. investigated the association between metabolic health and the presence of chronic kidney disease (Chen et al. 2014). They demonstrated that MUO, but not MHO phenotype, is associated with an increased risk of

Table 5 Prevalence of metabolically healthy obese (MHO) phenotype in East Asia

Study	Country	Nationally representative sample	Population characteristic	Definition	Prevalence among obese population
(Lee 2009)	South Korea	Yes	5,267 participants (2,227 men, 3,040 women) (≥20 years)	BMI ≥ 25 kg/m^2 without metabolic syndrome defined by NCEP-ATP III guideline (2002)	47.9 % (44.3 % in men, 51.0 % in women)
(Lee et al. 2011a)	South Korea	No	8,987 nondiabetic subjects (3,632 men and 5,355 women) (≥40 years)	BMI ≥ 25 kg/m^2 with a HOMA-IR in the lowest quartile	Men (10.7 %), women (14.5 %)
(Choi et al. 2013b)	South Korea	No	2,317 participants (2,227 men, 3,040 women) (≥60 years)	BMI ≥ 25 kg/m^2 without metabolic syndrome defined by NCEP-ATP III guideline (2002)	57.6 %
(Lee et al. 2013)	South Korea	No	2,352 participants (aged 40–69 years)	BMI ≥ 25 kg/m^2 with none of metabolic syndrome components defined by NCEP-ATP III guideline (2002)	18.1 %
(Chen et al. 2014)	China	No	2,324 subjects (≥18 years)	BMI ≥ 24 kg/m^2 with no insulin resistance or any metabolic syndrome components except abdominal obesity	11.8 % among total population
(Du et al. 2015b)	China	Yes	7,765 participants (≥18 years)	BMI ≥ 27.5 kg/m^2 with none or one of metabolic syndrome components defined by NCEP-ATP III guideline (2002)	10.7 %
(Heianza et al. 2014a)	Japan	No	8,090 nondiabetic subjects (5,884 men and 2,206 women) (aged 24–80 years)	BMI ≥ 25 kg/m^2 with none or one of metabolic syndrome components defined by IDF	44.1 %
(Heianza et al. 2014b)	Japan	No	27,478 nondiabetic subjects (17,730 men and 9,748 women)	BMI ≥ 25 kg/m^2 with none or one of metabolic syndrome components defined by IDF	11.0 %
(Hwang et al. 2012)	Taiwan	Yes	1,547 participants (629 men and 918 women) (aged 18–59 years)	BMI ≥ 25 kg/m^2 without metabolic syndrome defined by modified Grundy (2005)	28.5 % (24.2 % for men and 34.8 % for women)

Abbreviations: *HOMA-IR* homeostasis model assessment of insulin resistance, *NCEP-ATP III* (2002) the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII 2002), *IDF* International Diabetes Federation (Alberti et al. 2006); Grundy et al. (2005); Wildman criterion (Wildman et al. 2008)

chronic kidney disease compared to normal weight individuals. However, a number of studies have shown that MHO phenotype may be at increased risk of CVD in East Asia. Chang et al. assessed the coronary artery calcium (CAC) scores in MHO individuals in apparently healthy 14,828 adults in which metabolic health was determined as not having any metabolic

syndrome component and having a HOMA-IR <2.5. They found that MHO individuals had a higher prevalence of subclinical coronary atherosclerosis compared with MHNW individuals (Chang et al. 2014). Jung et al. also found that MHO phenotype is associated with the prevalent subclinical coronary atherosclerotic burden defined by >50 % stenosis, plaque, and CAC scores, compared with MHNW individuals in 4,009 health examinees in which MHO was determined as BMI $\geq$ 25 kg/m^2 with Wildman criteria (Jung et al. 2014). Lee et al. examined the association between MHO phenotype and the risk of hypertension in the 8-year follow-up community-based prospective cohort study. They demonstrated that MHO individuals had higher risk of incident hypertension, compared with MHNW individuals (Lee et al. 2013). Heianza et al. studied the risk of incident diabetes across various metabolic phenotypes and found that metabolically healthy overweight phenotype was associated with a higher risk of developing diabetes than MHNW phenotype (Heianza et al. 2015).

The transition to an unhealthy metabolic phenotype contributes to adverse health outcomes. Heianza et al. evaluated stability and changes in metabolic health status in a prospective cohort study using nondiabetic Japanese population (Heianza et al. 2014b). They found that persistent MUO status was a considerable increase risk of incident diabetes, and transition from MHO to MUO status was also associated with incident diabetes compared to maintaining MHNW phenotype.

4 Cross-References

- ▶ Epidemiology of Obesity in the United States
- ▶ Metabolic Syndrome in South Asians
- ▶ Obesity in Middle East
- ▶ Obesity in Sub-Saharan Africa

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Part II

Genetic Factors

Evolution of Obesity

8

John R. Speakman

Contents

Abstract

Obesity is the result of a gene by environment interaction. A genetic legacy from our evolutionary past interacts with our modern environment to make some people obese. Why we have a genetic predisposition to obesity is problematical, because obesity has many negative consequences. How could natural selection favor the spread of such a disadvantageous trait? From an evolutionary perspective, three different types of explanation have been proposed to resolve this anomaly. The first is that obesity was once adaptive, in our evolutionary past. For example, it may have been necessary to support the development of large brains, or it may have enabled us to survive (or sustain fecundity) through periods of famine. People carrying so-called thrifty genes that enabled the efficient storage of energy as fat between famines would be at a selective advantage. In the modern world, however, people who have inherited these genes deposit fat in preparation for a famine that never comes, and the result is widespread obesity. The key problem with these adaptive scenarios is to understand why, if obesity was historically so advantageous, many people did not inherit these alleles and in modern society remain slim. The second type of explanation is that most mutations in the genes that predispose us to obesity are neutral and have been drifting over evolutionary time – so-called drifty genes, leading some individuals to be obesity prone and others

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obesity resistant. The third type of explanation is that obesity is neither adaptive nor neutral and may never even have existed in our evolutionary past, but it is favored today as a maladaptive by-product of positive selection on some other trait. Examples of this type of explanation are the suggestion that obesity results from variation in brown adipose tissue thermogenesis, or the idea that we over consume energy to satisfy our needs for protein (the protein leverage hypothesis). This chapter reviews the evidence for and against these different scenarios, concluding that adaptive scenarios are unlikely, but the other ideas may provide possible evolutionary contexts in which to understand the modern obesity phenomenon.

Keywords

Obesity • Evolution • Adaptation • Natural selection • Thrifty genotype • Drifty genes • Genetic drift • Brown adipose tissue • Protein leverage hypothesis

1 Introduction

The obesity epidemic is a recent phenomenon (▶ Chap. 1, "Overview of Metabolic Syndrome" on "Epidemiology"). In as little as 50 years, there has been a progressive rise in the worldwide prevalence of obesity. A trend that started in the Western world (Flegal et al. 1998) has rapidly spread to developing countries; until today, the only places yet to experience the epidemic are a few areas in sub-Saharan Africa. This change in the fatness of individuals over such a short timescale cannot reflect a change in the genetic makeup of the populations involved (Power and Schulkin 2009). Most of the recent changes must therefore be driven by environmental factors (▶ Chap. 15, "Diet and Obesity (Macronutrients, Micronutrients, Nutritional Biochemistry)" on "Environmental Factors"). Yet, even among the most obese countries, there remain large populations of individuals who remain lean (e.g., Ogden et al. 2006; Flegal et al. 2010). These individual differences in obesity susceptibility mostly reflect genetic factors (Allison et al. 1996; Ginsburg et al. 1998; Segal and Allison 2002; ▶ Chap. 9, "Genetics of Obesity" on "Genetic Factors"). The obesity epidemic is therefore a consequence of a gene by environment interaction (Speakman 2004; Levin 2010; Speakman et al. 2011). Some people have a genetic predisposition to deposit fat, reflecting their evolutionary history, which results in obesity when exposed to the modern environment.

However, this interpretation of why we become obese has a major problem. We know that obesity is a predisposing factor for several serious noncommunicable diseases (▶ Chap. 35, "Metabolic Syndrome, GERD, Barrett's Esophagus" on "Diseases Associated with Obesity"). The fact that a large contribution to obesity is genetic yet obesity leads to an increase in the risk of developing these serious diseases is an issue, because the theory of evolution suggests that natural selection will only favor individuals that exhibit phenotypic traits that lead to increases in fitness (survival or fecundity). How is it possible for natural selection to have favored the spread of genes for obesity – a phenotype that has a negative impact on survival? This might be explained if obesity led to increases in fecundity that offset the survival disadvantage, but in fact obese people also have reduced fecundity (Zaadstra et al. 1993; but see Rakesh and Syam 2015), making the anomaly even worse. How did the predisposition to obesity evolve? What were the key events in our evolutionary history that led us to the current situation?

2 Why Do Animals and Humans Have Adipose Tissue?

The first law of thermodynamics states that energy can be neither created nor destroyed, but only transformed, and the second law states that there is an overall direction in the transformation, such that disorder (entropy) increases. Living organisms must obey these fundamental physical laws, and they have major consequences. Being low entropy systems, living things need to continuously fight against the

impetus for entropy to increase. Complex organic molecules like proteins, lipids, DNA, and RNA become damaged and corrupted and must be continuously recycled and rebuilt to maintain their function. Doing this requires the continuous transformation of large amounts of energy. Hence, even when an organism is outwardly doing nothing, it still uses up large amounts of energy to maintain its low entropy state. However, living organisms must also grow, move around to find mates and food, defend themselves against attack by pathogens, and reproduce: processes which all require energy. The requirement for energy by living beings is continuous. Although energy sustains many different life processes, in animals, it can be obtained only by feeding, and feeding is discontinuous. Since energy cannot be created or destroyed, this means that animals need to have some mechanism(s) to store energy so that the episodic supply can be matched to the continuous requirement. The key storage mechanisms that allow us to get from one meal to the next are glucose and particularly glycogen in the liver and skeletal muscle. A useful analogy for this system is a regular bank account (Speakman 2014). Money is periodically deposited into the account (similar to food intake) where it is stored temporarily (like glucose and glycogen stores) and is depleted by continuous spending (energy expenditure). The presence of the bank account acts as an essential buffer between discontinuous income and continuous spending.

There are, however, numerous situations where animals struggle to get enough food to meet the demands. In these instances, animals need a more long-term storage mechanism than glucose and glycogen stores, and this is generally provided by body fat. Returning to the analogy of a bank account – body fat is like a savings account. During periods when food is abundantly available, animals can deposit energy into their body fat (savings account), so that it is available for periods in the future when demand will exceed supply (Johnson et al. 2013). So adipose tissue exists primarily as a buffer that is used to supply energy during periods when food supply is insufficient to meet energy demands.

3 Why Do We Get Obese?

Given this background to why adipose tissue exists, there have been three different types of evolutionary explanation for why in modern society we fill up these fat stores to tremendous levels (Table 1: also reviewed in Speakman 2013a, 2014). First, there is the adaptive viewpoint. This suggests that obesity was adaptive in the past, but in the changed environment of the modern world, the positive consequences of being obese have been replaced by negative impacts. Second, there is the neutral viewpoint. This suggests that obesity has not been subject to strong selection in the past, but rather the genetic predisposition has arisen by neutral evolutionary processes like genetic drift. Finally there is the maladaptive viewpoint. This suggests that obesity has never been advantageous and that historically people were never obese (except some rare genetic mutations). However, the modern propensity to become obese is a by-product of positive selection on some other advantageous trait. Because evolution is by definition a genetic process, evolutionary explanations seek to explain where the genetic variation that causes a predisposition to obesity comes from. There is another set of ideas that are related to evolutionary explanations but do not concern genetic changes – for example, the "thrifty phenotype" hypothesis (Hales and Barker 1992; Wells 2007; Prentice et al. 2005), the "thrifty epigenotype" hypothesis (Stoger 2008), and the oxymoronic "nongenetic evolution" hypothesis (Archer 2015) (Table 1). This chapter does not concern these non-evolutionary ideas, but a treatment of some of them can be found elsewhere in this volume (► Chap. 13, "Fetal Metabolic Programming," Aitkin).

4 Adaptive Interpretations of Obesity

The primary adaptive viewpoint is that during our evolution accumulation of fat tissue provided a fitness advantage and was therefore positively selected by natural selection. This positive

Table 1 A summary of the main "evolutionary" and "quasi-evolutionary" ideas about the origins of obesity. Evolutionary ideas pertain to the genetic variation in susceptibility to obesity, while "quasi-evolutionary" arguments include trans-generational effects that are nongenetic. The "thrifty epigenome" model is a hybrid where genetic effects are fixed by epigenetic effects. The present chapter only concerns the evolutionary theories

Evolutionary theories		
1 Adaptive scenarios		
Hypothesis	**Main feature**	**References**
Thrifty gene hypothesis	Famine survival	Neel 1962 + many others
	Famine fecundity	Prentice 2001, Prentice et al. (2005)
Loss of uricase	Efficiency of fructose use	Johnson et al. 2013
Brain development	Fat required to support large brain	Power and Shulkin 2009
Fitness first	Obesity paradox	Rakesh and Syam 2015
2. Neutral scenarios		
Drifty gene hypothesis	Release from predation	Speakman 2007, 2008
3. Maladaptive scenarios		
Protein leverage hypothesis	Regulation of protein intake	Simpson and Raubenheimer 2005
Thermogenic variation	Variation in BAT activity	Rothwell and Stock 1979
		Himms-Hagen 1979
		Selleyah et al. 2013
Quasi-evolutionary theories		
Hypothesis	**Main feature**	**References**
Thrifty phenotype	Fetal programming	Hales and Barker 1992
Thrifty epigenotype	Epigenetic consolidation of genotype	Stoger 2008
Nongenetic evolution	Trans-generational maternal effects	Archer 2015

selection in the past is why some individuals have a predisposition to become obese today in spite of its negative effects. Humans are not the only animals to become obese (Johnson et al. 2013). There are several other groups of mammals and birds that deposit large amounts of body fat at levels equivalent to human obesity, for example, deposition of fat in some mammals prior to the hibernation (e.g., Krulin and Sealander 1972; Ward and Armitage 1981; Boswell et al. 1994; Kunz et al. 1998; Speakman and Rowland 1999; Martin 2008) and the deposition of fat in some birds prior to migration (e.g., Moore and Kerlinger 1987; Klaasen and Biebach 1994; Moriguchi et al. 2010; Repenning and Fontana 2011). Several other animals show cycles in fat storage in relation to the annual cycle even though they do not engage in migration or hibernation – including voles (Krol et al. 2005; Li and Wang 2005; Krol and Speakman 2007) and hamsters (Bartness and Wade 1984; Wade and Bartness 1984) – mostly to facilitate breeding. These animal examples of obesity have in common the fact that deposition of fat is a preparatory response for a future shortfall in energy supply or an increase in demand (Johnson et al. 2013). For the hibernating animal, it will be unable to feed during winter, and for the migrating animal, it will also have no access to food when crossing barriers such as large deserts or oceans. Although humans neither seasonally hibernate nor migrate, a number of authors have made direct comparisons between these processes in wild animals and obesity in humans (Johnson et al. 2013). This is because humans must often deal with shortfalls of energy supply during periods of famine. Famine reports go back almost as long as people have been able to write (McCance 1975; Harrison 1988; Elia 2000). The argument was therefore made that human obesity in our ancient past probably served the function of facilitating survival through famines (Neel 1962), like fat storage in hibernators facilitates survival through hibernation. Famines would have provided a strong selection on genes that favored the deposition of fat during periods between famines. Individuals with alleles that favored efficient

fat deposition would survive subsequent famines, while individuals with alleles that were inefficient at fat storage would not (Neel 1962). This idea, called the "thrifty gene hypothesis" was first published more than 50 years ago (more in the context of selection for genes predisposing to diabetes than obesity which was presumed to underpin the efficiency of fat storage) (Neel 1962). It has since been reiterated in various forms specifically with respect to obesity (Eaton et al. 1988; Lev-Ran 1999, 2001; Prentice 2001, 2005a, b, 2006; Campbell and Cajigal 2001; Chakravarthy and Booth 2004; Eknoyan 2006; Watnick 2006; Wells 2006; Prentice et al. 2008; O'Rourke 2014).

In detail, the hypothesis is as follows. When humans were experiencing periodic famines, thrifty alleles were advantageous because individuals carrying them would become fat between famines, and this fat would allow them to survive the next famine. They would pass their versions of the thrifty genes to their offspring, who would then also have a survival advantage in subsequent famines. In contrast, individuals not carrying such alleles would not prepare for the next famine by depositing as much fat, and would die, along with their unthrifty alleles. Because food supplies were presumed to be always low, even between famines, the levels of obesity attained, even in those individuals who carried the thrifty alleles, were probably quite modest, and so individuals never became fat enough to experience the detrimental impacts of obesity on health. What changed since the 1950s was that the food supply in Europe and North America increased dramatically due to enormous increases in agricultural production. This elevation in food supply has gradually spread through the rest of the world. The consequence is people in modern society who carry the thrifty alleles more efficiently eat the abundant food and deposit enormous amounts of fat. Obese people are like boy scouts: always prepared. In this way, the alleles that were once advantageous have been *rendered detrimental by progress* (Neel 1962).

Advocates of the thrifty gene idea agree on some fundamental details. First, that famines are frequent. Estimates vary, but values of once every 10 years or so are often cited after Keys et al. 1950. Second, famines cause massive mortality (figures of 15–30 % mortality are commonly quoted). However, they differ in some important aspects. One area of discrepancy is how far back in our history humans have been exposed to periodic famine. Some have suggested that famine has been an "ever present" feature of our history (Chakravarthy and Booth 2004; Prentice 2005a). There is a problem, however, with this suggestion. If the "thrifty alleles" provided a strong selective advantage to survive famines and famines have been with us for this period of time, then these alleles would have spread to fixation in the entire population (Speakman 2006a, b, 2007). We would all have the thrifty alleles, and in modern society we would all be obese. Yet, even in the most obese societies, there remains a population of lean people comprising about 20 % of the population (Ogden et al. 2006; Flegal et al. 2010). If famine provided a strong selective force for the spread of thrifty alleles, it is relevant to ask how come so many people managed to avoid inheriting them (Speakman 2006a, b, 2007).

We can illustrate this issue in a more quantitative manner. If a thrifty allele existed that promoted greater fat storage such that individuals carrying two versions of that allele survived 3 % better and those who carry one version would survive 1.5 % better, then a random mutation to create the thrifty allele would spread from being in just one individual to the entire population of the ancient world in about 600 famine events. Using the most conservative estimate of famine frequency, of once per 150 years, this is about 90,000 years or about 1/500th the time since *Australopithecus*. Any mutation therefore that produced a thrifty allele within the first 99.8 % of hominin history with this effect on mortality would therefore have gone to fixation. We would therefore all have inherited these alleles, and we would all be obese (Speakman 2006a, b).

This calculation reveals a large difference between the "obesity" phenomena observed in animals and the obesity epidemic in humans. In animals, when a species prepares for hibernation, migration, or breeding, the entire population becomes obese. The reasons are clear (Speakman

and O'Rahilly 2012). If a bird migrates across an area of ocean and does not deposit enough fat for the journey, it plunges into the ocean short of its destination and the genes that caused it to not deposit enough fat are purged from the population. Selection is intense, and consequently all the animals become obese. If the same intense selection processes had operated in humans, as suggested by advocates of adaptive interpretations of obesity like the thrifty gene hypothesis (Prentice 2001b, 2005), then we too would all become obese when the environmental conditions proved favorable for us to do so. We do not.

Another school of thought, however, is that famine has not been a feature of our entire history but is linked to the development of agriculture (Prentice et al. 2008). Benyshek and Watson (2006) suggested that hunter-gatherer lifestyles are resilient to food shortages because individuals can be mobile, and when food becomes short in one area, they can seek food elsewhere or modify their diet to exploit whatever is abundant. In contrast, agricultural-based societies are dependent on fixed crops, and if these fail due, for example, to adverse weather conditions, food supply can immediately become a problem (see also Berbesque et al. 2014). Because mutations happening in the last 12,000 years would not have had chance to spread through the entire population, this shorter timescale for the process of selection might then explain why in modern society some of us become obese, but others remain lean.

The problem with this scenario, however, is opposite to the problem with the "ever present" idea. Humans developed agriculture only within the last 12,000 years (Diamond 1995), which would be only about 80 famine events with significant mortality. To be selected a mutation causing a thrifty allele would consequently have to provide an enormous survival advantage to generate the current prevalence of obesity. Calculations suggest the per-allele survival benefit would need to be around 10 %. Although it is often suggested that mortality in famines is very high and therefore a per-allele mortality effect of this magnitude could be theoretically feasible, such large mortality effects of famines are generally confounded by the problem of emigration, and true mortality is probably considerably lower. An additional problem is that for a mutation to be selected, all of this mortality would need to depend on differences in fat content attributable to a single genetic mutation. This also makes the critical assumption that the reason people die in famines is because they starve to death, and thus individuals with greater fat reserves would on average be expected to survive longer than individuals with lower fat reserves. Although there are some famines where it is clear that starvation has been the major cause of death (e.g., Hionidou 2002), for most famines this is not the case, and the major causes of death are generally disease related (Harrison 1988; Toole and Waldman 1988; Mokyr and Grada 1999; Adamets 2002). This does not necessarily completely refute the idea that body fatness is a key factor influencing famine survival. The spread of disease among famine victims is probably contributed to by individuals having compromised immune systems. A key player in the relationship between energy status and immune status is leptin (Lord et al. 1998; Matarese 2000; Faggioni et al. 2001). Low levels of leptin may underpin the immunodeficiency of malnutrition. Because circulating leptin levels are directly related to adipose tissue stores, it is conceivable that leaner people would have more compromised immune systems and hence be more susceptible to disease during famines.

One way to evaluate the role of body fatness in famine survival is to examine patterns of famine mortality with respect to major demographic variables such as age and sex and compare these to the expectation based on known effects of sex and age on body fat storage and utilization (Speakman 2013b). Females have greater body fat stores and lower metabolic rates compared with men of equivalent body weight and stature. In theory therefore, females should survive famines longer than males if body fatness plays a major role in survival (Henry 1990; Macintyre 2002). With respect to age, older individuals have declining metabolic rate, but they tend to preserve their fat stores until they are quite old (Speakman and Westerterp 2010). Consequently, older individuals would be expected to survive famines longer

than younger adults if body fatness was the overriding consideration. Patterns of mortality during actual famines suggest that males have higher mortality than females (Macintyre 2002). However, with respect to age, the highest mortality usually occurs among the very young (less than 5 years of age, including elevated fetal losses) and elderly (increasing probability of mortality with age from the age of about 40 onwards) (Watkins and Menken 1985; Harrison 1988; Menken and Campbell 1992; Scott et al. 1995; Cai and Feng 2005). The age-related pattern of mortality in adults is the opposite of that predicted if body fatness is the most important consideration. However, the impact of sex is in agreement with the theoretical expectation. Despite this apparent correspondence in many famines, the magnitude of the female mortality advantage massively exceeds the expectation from body fatness differences (Speakman 2013b). Yet in other famines, there is no female mortality advantage at all. This points to famine mortality being a far more complex phenomenon than simple reserve exhaustion. For instance, with respect to age, older individuals that have passed reproductive age may sacrifice themselves to provide food to enable survival of their offspring. Alternatively, they may succumb to diseases more rapidly because of an age-related decline in immune function. The exaggerated effect of sex may be similarly explained by social factors – females, for example, may exchange sex for extra food or may have more access to food because they do more of the family cooking – the "proximity to the pot" phenomenon (Macintyre 2002). Overall, the data on causes of mortality during famine points to an extremely complex picture, where differences in body fatness probably play a relatively minor role in defining who lives and who dies.

Recognizing the problem with the suggestion that selection for genes that cause obesity has only been in force for the past 12,000 years, Prentice et al. (2008) suggested that the impact of body fatness during famines on fitness is not on survival probability but mostly on fertility. There is strong support for this suggestion (e.g., Razzaque 1988). For many famines, we have considerable evidence that fertility is reduced. During the Dutch hunger winter, for example, when Nazi Germany imposed a blockade on some areas of the Netherlands, there was a clear reduction in the number of births from the affected regions that could be picked up in enrolments to the army 18 years later, while adjacent regions that were not blockaded and did not suffer famine show no such reduction. The effect is profound with a decline during the famine amounting to almost 50 %. Tracing back the exact time that effects were manifest suggests that the major impact was on whether females became pregnant or not, rather than an impact on fetal or infant mortality rates (Stein et al. 1975; Stein and Susser 1975). Unlike the effect of fatness on mortality, there is also good reason to anticipate that differences in fertility would be strongly linked to differences in body fatness. This is because we know from eating disorders such as anorexia nervosa that individuals with chronically low body fat stop menstruating and become functionally infertile. Leptin appears to be a key molecule involved in the association between body fatness and reproductive capability (Ahima et al. 1997). This effect is not just restricted to females. Both male and female ob/ob mice which cannot produce functional leptin are both sterile: a phenotype that can be reversed by administration of leptin in both sexes (females, Chehab et al. 1996; males, Mounzih et al. 1997). Note however, that leptin is also responsive to chronic food shortage as well as body composition (Weigle et al. 1997), and there is a school of thought that amenorrhea in anorexia nervosa is not due to low body fatness but low food intake. If this was the case, then lowered fertility need not necessarily be restricted to lean individuals. This argument may also apply to the link between fat stores and immune status elaborated above. Moreover, there is another argument why reduced fertility is unlikely to be a major selective force during famines and that is because following famines, there is usually a compensatory boom in fertility that offsets any reduction during the famine years. Individuals that fail to get pregnant during famines tend to become immediately pregnant once the famine is over. Thus if one looks at the period including only the famine years, then fertility seems to have a

major impact on demography (and hence selection), but expanding the period to include the famine and the post famine period revealing the net impact of altered fertility on demographics (and hence selection) is negligible and certainly insufficient to provide the selective advantage necessary to select genes for obesity over the period since humans invented agriculture.

These arguments about selection on genes favoring obesity were made before we had good information about the common polymorphisms that cause obesity or their effect sizes on fat storage. Without such information, it was plausible to suggest that genes might exist that have a large impact on fat storage and hence survival or fertility during famines. This view became untenable with the advent of genome-wide association studies (GWAS) which identified the main genes with common polymorphisms associated with increased obesity risk (Day and Loos 2011). These GWAS studies revolutionized our view of the genetics of obesity since the majority of identified SNPs had nothing to do with the established hunger signaling pathway, and their effect sizes were all relatively small. At present, there are about 50 genes (SNPs) suggested to be associated with BMI that that have per-allele effect sizes between 1.5 kg and 100 g (Willer et al. 2009; Speliotes et al. 2010; Okada et al. 2012; Paternoster et al. 2012; Wen et al. 2012). On this basis, it has been suggested that the genetic architecture of obesity may involve hundreds or even thousands of genes each with a very small effect (Hebebrand et al. 2010). This reality about the genetic architecture of obesity makes the proposed model by Prentice et al. (2008) that selection on these genes has only occurred over the past 12,000 years completely untenable, because SNPs causing differences in fat storage of 100–1000 g could not possibly cause differential survival or fecundity during famines of 10 %.

Setting aside the suggestion that famines are a phenomenon of the age of agriculture, if periodic food crises sufficient to cause significant mortality did affect us throughout our evolutionary history, it is possible to imagine a scenario where genes of small effect might have such a small impact on fat storage, and hence famine survival (or fecundity), that their spread in the population would be incredibly slow. Therefore, they might not progress to fixation over the duration of our evolutionary history, and we would be left today with the observed genetic architecture of many incompletely fixed genes of small effect. Speakman and Westerterp (2013) evaluated this idea by first predicting the impact of such polymorphisms of small effect on famine survival and then modeling the spread of such genes over the 4 million years of hominin evolution (assuming a 150-year frequency of famines). Using a mathematical model of body fat utilization under total starvation, combined with estimates of energy demand across the lifespan, it was shown that genes that had a per-allele effect on fat storage of 80 g would cause a mortality difference of about 0.3 %. That is 10x lower than the assumed effect that had been previously used to model the spread of thrifty genes (Speakman 2006b). Nevertheless, despite this very low impact on famine survival, a mutation causing such a difference in fat storage would move to fixation in about 6000 famine events (about 900,000 years). Thus the scenario of genetic polymorphisms moving slowly to fixation is correct, but it implies that all the mutations identified as important in GWAS studies had occurred in the last million years or so – which we know is not correct. In addition, if the selection model is correct, we would anticipate, all else being equal, that genes with greater effect size would have greater prevalence, but that is not observed in the known GWAS SNPs (Speakman and Westerterp 2013 using data from Speliotes et al. 2010).

Overall, the idea that the genetic basis of obesity is adaptive, resulting from selection in our evolutionary history which favored "thrifty" alleles, because of elevated survival or fecundity of the obese during famines, is not supported by the available data. Other adaptive scenarios could be envisioned. For example, Power and Shulkin (2009) argue that we are fat because of the need to support development of our large brains. Rakesh and Syam (2015) point to the benefits of milder levels of obesity for disease survival and fecundity. An alternative idea is that fat storage in human ancestors was promoted by the loss of the

uricase gene in the Miocene (Johnson et al. 2013), which enabled more efficient utilization of fructose to deposit fat. This fat then enabled greater survival during periods of famine. A common problem faced by such scenarios is the fact that even in the most obesogenic modern environments, many individuals do not become fat. Any proposed adaptive scenario must explain this variation. Perhaps the closest any adaptive idea comes to explaining this variation is the suggestion of Johnson et al. (2013) that we lost the uricase gene early in our evolution because of the advantages for conversion of fruit sugars to fat (i.e., everyone inherited this mutation), but this only leads to obesity in modern society in individuals with high intakes of fructose. This however does not explain the known genetic variation between individuals that predisposes to obesity (Allison et al. 1996).

5 The Neutral Viewpoint

Evolution is a complex process. We often regard natural selection as being the primary force generating genetic change. However, this is a naive viewpoint, and among evolutionary biologists, it is well recognized that natural selection is one of a number of processes including phyletic heritage, founder effects, neutral mutations, and genetic drift that underlie genetic variations between individuals in a population. We should be cautious not to interpret everything biological from the perspective of adaptation by natural selection. The emerging field of "evolutionary medicine" is rapidly learning to appreciate this fact, and there is an increasing recognition that other "nonadaptive" evolutionary processes may be important to understand the evolutionary background to many human diseases (Zinn 2010; Puzyrev and Kucher 2011; Valles 2012; Dudley et al. 2012). The "drifty gene" hypothesis is a nonadaptive explanation for the evolutionary background of the risk of developing obesity (Speakman 2007, 2008). This hypothesis starts from the observation that many wild animals can accurately regulate their body fatness. Several models are available to understand this regulation (Speakman et al. 2011), but a particularly useful idea is the suggestion that body weight is bounded by upper and lower limits or intervention points (Herman and Polivy 1984; Levitsky 2002; Speakman 2007), called the dual intervention point model (Speakman et al. 2011). If an individual varies in weight between the two limits, then nothing happens, but if its body weight decreases below the lower limit or above the upper limit, it will intervene physiologically to control its weight. Body weight is kept relatively constant (between the two limits) in the face of environmental challenges. These upper and lower limits may be selected for by different evolutionary pressures: the lower limit by the risk of starvation and the upper limit by the risk of predation.

Considerable research suggests that this fundamental balance of risks of starvation keeping body masses up (i.e., setting the lower intervention point) and risks of predation keeping body masses down (i.e., setting the upper intervention point) is a key component of body mass regulation in birds (Gosler et al. 1995; Kullberg et al. 1996; Fransson and Weber 1997; Cresswell 1998; Adriaensen et al. 1998; van der Veen 1999; Cuthill et al. 2000; Brodin 2001; Gentle and Gosler 2001; Covas et al. 2002; Zimmer et al. 2011), small mammals (Norrdahl and Korpimaki 1998; Carlsen et al. 1999, 2000; Banks et al. 2000; Sundell and Norrdahl 2002), and larger animals such as cetaceans (MacLeod et al. 2007). The "starvation-predation" trade-off has become a generalized framework for understanding the regulation of adiposity between and within species (Lima 1986; Houston et al. 1993; Witter and Cuthill 1993; Higginson et al. 2012), and laboratory studies are now starting to probe the metabolic basis of the effects of stochastic food supply and predation risk on body weight regulation (Tidhar et al. 2007; Zhang et al. 2012; Monarca et al. 2015a, b).

The drifty gene hypothesis suggests that early hominins probably also had such a regulation system. During the early period of human evolution between 6 and 2 million years ago (Pliocene), large predatory animals were far more abundant (Hart and Susman 2005). Our ancestors (*Paranthropines* and *Australopithecines*) were

also considerably smaller than modern humans, making them potential prey to a wide range of predators. At this stage of our evolution, it seems most likely that upper and lower intervention points evolved to be relatively close together, and the early hominids probably had close control over their body weights.

Several major events however happened in our evolutionary history around 2.5 million to 2.0 million years ago. The first was the evolution of social behavior. This would have allowed several individuals to band together to enhance their ability to detect predators and protect each other from their attacks. In a similar manner, some modern primates, for example, vervet monkeys, have evolved complex signaling systems to warn other members of their social groups about the approach of potential predators (Cheney and Seyfarth 1985; Baldellou and Henzi 1992). This alone may have been sufficient to dramatically reduce predation risk. A second change was the discovery of fire and weapons (Stearns 2001; Platek et al. 2002), powerful means for early *Homo* to protect themselves against predation. Social structures would have greatly augmented these capacities. Modern non-hominid apes such as chimpanzees (*Pan troglodytes*) also use weapons such as sticks to protect themselves against predators such as large snakes, and it has been concluded that bands of early hominids with even quite primitive tools could easily succeed in defending themselves in confrontations with potential predators (Treves and Naughton-Treves 1999).

The consequence was that the predation pressure that maintained the upper intervention point effectively disappeared. It has been suggested that because there was no selective pressure causing this intervention point to change, the genes that defined it were then subject to mutation and random drift (Speakman 2007) – hence, the "drifty" gene hypothesis (Speakman 2008). Genetic drift is a process that is favored by low effective population size. The suggestion that early *Homo* species had a small effective population size (around 10,000 despite a census population of around one million) (Harding et al. 1997; Eller et al. 2009) would create a genetic environment where drift effects could be common. Mutations and drift for 2 million years would generate the necessary genetic architecture, but this is insufficient to cause an obesity epidemic. By this model virtually, the same genetic architecture would also have been present 20,000 years ago (after 1,980,000 years of mutation and drift compared to 2 million years today). Why did the obesity epidemic not happen then? There have been two separate factors of importance that restricted the potential for people to achieve their drifted upper intervention points – the level of food supply and the social distribution of it (Power and Schulkin 2009). Before the Neolithic, the most important factor was probably the level of food supply. Paleolithic individuals probably could not increase their body masses sufficiently to reach their drifted upper intervention points because there was insufficient food available. At this stage, each individual or small group would be foraging entirely for their own needs. Things changed in the Neolithic with the advent of agriculture. Subsistence agriculture is not much different from hunter-gathering – in that each individual grows and harvests food for themselves and/or a small group. As yields from agricultural practice improved, however, the numbers of people needed to grow and harvest food as a percentage of the total population declined. It is at this stage that more complex human societies emerged (Diamond 1995).

Human societies are only feasible because it is possible for a subset of individuals to grow and harvest food to sustain a larger number of individuals. This wider group of individuals is then able to perform activities that would be unfeasible if they had to spend all their time growing and harvesting food. Such activities include religion, sport, politics, the arts and war, as well as building projects with stone, making pottery, iron, and bronze-ware which all require high temperatures of a kiln and mining ores. These activities were only possible when yields from crops became high enough to allow some individuals to stop raising crops and do other things. However, a crucial additional element was the societal control of food supply, so that food produced by one section of society can be distributed to those that

do not produce it. This effectively requires the development of monetary and class systems, most of which have their origins in the wake of Neolithic agriculture. This central control of food supply is important because people can only attain their drifted upper intervention points if there is an adequate supply of food for them to do so.

In the Paleolithic, most people could not get access to these resources because there were insufficient resources available. After the Neolithic, most people could also not get access to unlimited food supplies because of the central control of food supply. Because most people would normally have body weights in the region between their upper and lower intervention points, they would not experience a physiological drive forcing them to seek out such food. An exception might be during the rare periods of famine (see above). This pattern of food access led to the development of a class-related pattern of variation in body weight. In the lower classes, where food supply was restricted, people did not move to their upper intervention points, whereas in higher levels of society, where access to food was effectively unlimited, attainment of the drifted upper intervention point became possible. Consequently at this stage, obesity was restricted to the wealthy and powerful. Not all wealthy and powerful people became obese (only those with the genetic predisposition to do so – i.e., with high drifted upper intervention points), but none of the poorer classes did. Obesity became a status symbol (Power and Shulkin 2009; Brewis 2010). Reports of obese people date from at least early Greek times. In the fifth Century BC, Hippocrates suggested some potential cures for obesity (Procope 1952). This implies two things. There would be no need for a cure for obesity if nobody suffered from it, so it must have been common enough to warrant his attention. Second, Hippocrates did not regard obesity as advantageous or desirable – but something that needed to be "cured." This provides additional evidence against the famine-based "thrifty gene" hypothesis, since obesity 2500 years ago, when famines were still supposed to be a major selective pressure, should have been viewed as advantageous if that theory was correct.

Estimates by agricultural historians of the levels of food production support the idea that most people in the past were under socially restricted food supply. In the late 1700s, for example, it has been estimated that 70 % of Britain and 90 % of France were consuming less than 12 MJ/day. If only 10 % of the population had free access to unlimited energy, then only people in this proportion of the population would be expected to reach their drifted upper intervention points. Obesity prevalence would be expected to be less than 3 %. This was the actual prevalence of obesity in the USA in 1890. It seems that the social control of food supply only started to change in Western societies after the First World War. This period (1920s) saw a wave of obesity in Western societies (Dubois 1936), but this was reversed when the Western world went back to war in the 1940s, especially in countries where food rationing was introduced. The modern obesity epidemic reflects a second wave of obesity as easy access to nutritional resources became widespread across all social levels after World War II ended. Nowadays, anyone in the West can afford to overconsume energy (Speakman 2014). For example, a person in the USA earning the minimum wage of 7.25$ per hour (2013) and working a standard 38 h week would have an annual income of about 14,300 US$. Assuming half of this was available to buy food, this person could buy annually 2865 McDonalds' happy meals (about eight per day), containing about 3700 cal, about 47 % more energy than the daily intake requirement of a man and 84 % more than the daily intake requirement of a woman. In 2013, it was estimated that earners of minimum wage had lower income than those on welfare in the majority of states in the USA. It has been frequently noted that obesity increases coincidental with the economic transition from being largely rural to largely urban. Explanations for this trend have largely concerned alterations in levels of physical activity and increased access to food resources. The current model is completely consistent with these interpretations because it suggests that only following such economic transitions are individuals able to achieve their drifted upper intervention points.

The GWAS provides some support for this model. SNPs predisposing to obesity have not been under strong positive selection (Southam et al. 2010; Koh et al. 2014), and similar lack of strong positive selection is also observed in GWAS targets linked to type 2 diabetes (Ayub et al. 2014). This absence of selection is also supported by the absence of any link between prevalence and effect size among these SNPs (Speakman and Westerterp 2013). Finally, the genes that have been identified appear to include a large proportion of centrally acting genes that are related to appetite and food intake (e.g., Fredriksson et al. 2008). It is entirely conceivable that the centrally acting genes that have been identified to date somehow define the upper intervention point. Overall, this model provides a nonadaptive explanation for why some people get obese but others do not.

6 The Maladaptive Scenario

The maladaptive viewpoint is that obesity has never been advantageous. Historically, it may have never even existed, except in some rare individuals with unusual genetic abnormalities – perhaps represented in Paleolithic sculptures such as the "Venus of Willendorf." However, the idea is that genes that ultimately predispose us to obesity become selected as a by-product of selection on some other trait that was advantageous. The best example of a "maladaptive" interpretation of the evolution of obesity is the suggestion that it is caused by individual variability in the capacity of brown adipose tissue to burn off excess caloric intake (Sellayah et al. 2014).

Brown adipose tissue is found uniquely in mammals (▶ Chap. 21, "Adipose Structure (White, Brown, Beige)," Vidal-puig et al.). Contrasting white fat which contains a single large fat droplet, brown adipocytes typically contain large multilocular lipid droplets and abundant mitochondria. These mitochondria contain a unique protein called uncoupling protein 1 (UCP-1) which resides on the inner membrane. UCP-1 acts as a pore via which protons in the intermembrane space can return to the mitochondrial matrix. However, unlike protons traveling from the intermembrane space to the matrix via ATP synthase, the protons moving via UCP-1 are not coupled to the formation of ATP (hence, the name "uncoupling protein"). The chemiosmotic potential energy carried by the protons traveling via UCP-1 is therefore released directly as heat, which is the primary function of BAT – to generate heat for thermoregulation. Unsurprisingly, then BAT is found abundantly in small mammals and in the neonates of larger mammals (including humans), which have an unfavorable surface-to-volume ratio for heat loss. The weight of BAT, and hence its capacity to generate heat, varies in relation to thermoregulatory demands. During winter, the amount of BAT and UCP-1 increases (Feist and Feist 1986; Feist and Rosenmann 1976; McDevitt and Speakman 1994). During summer, BAT and UCP-1 are lower (Feist and Feist 1986; Wunder et al. 1977; McDevitt and Speakman 1996).

During the late 1970s, it was suggested that BAT might have an additional function: to "burn off" excess calorie intake (Rothwell and Stock 1979; Himms-Hagen 1979). This idea fell out of favor because it was commonly believed that adult humans do not have significant deposits of BAT. However, active BAT was discovered in adult humans in 2007 (Nedergaard et al. 2007), and since that time the idea that variability in BAT function might result in the variable susceptibility to obesity has reemerged (Sellayah et al. 2014). This has been supported by observations that the amount and activity of BAT is inversely related to obesity (Cypress et al. 2009; van Marken-Lichtenbelt et al. 2009) and that there is an age-related reduction in BAT activity, correlated with the age-related increase in body fatness (Cypress et al. 2009; Yoneshiro et al. 2011). Moreover, the seasonal changes and responses to cold exposure in animals are also observed in humans (Saito et al. 2009), suggesting important functional activity. Experimental studies in rodents have established that transplanting extra BAT tissue into an individual can protect both against diet-induced (Stanford et al. 2013; Liu et al. 2013) and genetic obesity (Liu et al. 2015).

The "maladaptive" scenario for the evolution of obesity is therefore as follows. Individuals are

presumed to vary in their brown adipose tissue thermogenesis as a result of their variation in evolutionary exposure to cold (Sellayah et al. 2014), which necessitated the use of BAT for thermogenesis. Some individuals might have high levels of active BAT, while others might have lower levels, either because their exposure to cold was lower or because they avoided cold exposure by other mechanisms such as development of clothing and the use of fire. Consequently, high levels of BAT would be one of a number of alternative adaptive strategies for thermoregulation. Because of this diversity of potential strategies, a genetic predisposition to develop high and active levels of BAT would only be present in some individuals and populations. This would lead to individual and population variation in the ability to recruit BAT for its secondary function: burning off excess energy intake.

A key question, however, is why individuals might have excessive intake of energy in the first place. Especially since this notion appears diametrically opposed to the fundamental assumption underlying the thrifty gene hypothesis that energy supply is almost always limited, one potential explanation for this effect is that individuals may not only eat food for energy but also for some critical nutrient. When food is of high quality, it may be that by eating enough food to meet the daily energy demands is enough to also meet demands for the critical nutrient. Any excess nutrient intake could be excreted. Two scenarios might alter this situation. Energy demands might decline. This could, for example, be precipitated by an increase in sedentary behavior in modern society (Prentice and Jebb 1995; Church et al. 2011). If individuals continued to eat food to meet their energy demands, then they would reduce their intake, but this might mean their intake of the critical nutrient was now below requirements, and they would be nutrient deficient. However, direct measurements of energy demand in humans in both Europe and North America since the 1980s do not support the idea that activity energy demands have declined (Westerterp and Speakman 2008; Swinburn et al. 2009). Nevertheless, another scenario is that the quality of the food might change and the ratio of energy to the critical nutrient might increase. Again, if individuals continued to eat to meet their energy requirements, then intake of the nutrient would become deficient. In both of these scenarios to avoid nutrient deficiency, individuals might consume more food to meet their demands for the nutrient. The result would be that their consumption of energy would then exceed their demands.

A strong candidate for the nutrient that may drive overconsumption of energy is protein. This idea is called the "protein leverage hypothesis" (Simpson and Raubenheimer 2005) and is elaborated in full detail in the book *The Nature of Nutrition* by Simpson and Raubenheimer (2010). By this hypothesis, the main driver of food intake is always the demand for protein. That is, people and animals primarily eat to satisfy their protein requirements, and energy balance comes along as a passenger. The idea has lots to commend it. Across human societies, the intake of protein, despite very diverse diets, is almost constant – consistent with this being the primary regulated nutrient. In contrast, energy intakes are widely divergent. Moreover, we know that diets which include a high ratio of protein to energy (e.g., the Atkins diet) are effective for weight loss. A review of 34 studies of dietary intake showed that dietary protein was negatively associated with energy intake (Gosby et al. 2014). Several experimental studies of diet choice in rodents also point to protein content as the factor regulating energy intake and hence body weight (e.g., Sorensen et al. 2008; Huang et al. 2013). Hence, the protein leverage theory may provide a necessary backdrop to the brown adipose tissue idea. It has also been noted that the protein leverage hypothesis may also explain why in modern society individuals increase their body mass to their upper intervention points as part of the "drifty gene" idea detailed above (Speakman 2014). Note however that other studies suggest little evidence in support of the protein leverage hypothesis in food intake records over time in the USA (Bender and Dufour 2015), but this may reflect the poverty of the food intake reports rather than the theory (Dhurandhar et al. 2015).

If humans do overconsume energy because of the requirement for protein, then the ability to

burn off the excess energy might then depend on levels of brown adipose tissue. Individuals with large BAT depots might burn off the excess and remain lean, while those with lower levels of BAT might be unable to burn off the excess consumption and become obese. By this interpretation, obesity is a maladaptive consequence of variation in adaptive selection on brown adipose tissue capacity. The environmental trigger is the change in the energy to nutrient ratio in modern food that stimulates overconsumption of energy. There is no need by this viewpoint to infer that obesity has ever provided an advantage or even that we have in our history ever been fat.

If brown adipose tissue is a key factor that influences the propensity to become fat, then one would anticipate that knocking out the UCP-1 gene in mice would lead to obesity. Enerbäck et al. (1997) knocked out UCP-1, but the result did not support the hypothesis, because the mice did not become any more obese than wild-type mice when exposed to a high-fat diet. One potential issue with this experiment was that the genetic background of these mice was a mix of two strains, one susceptible and the other not susceptible to weight gain on a high-fat diet. The experiment was repeated but with the mice now backcrossed onto a pure C57BL/6 background (a strain that is susceptible to high-fat diet-induced weight gain) (Liu et al. 2003). However, now the mice lacking UCP-1 were actually more resistant to the high-fat diet-induced obesity than the wild-type mice, but the protective effect was abolished when the mice were raised at 27 °C. This confusion was further compounded when the same mice were studied at 30 °C, at which temperature the KO mice became fat even on a chow diet, and this effect was multiplied with high-fat feeding (Feldmann et al. 2009). This is very confusing because at 30 °C, one would anticipate that UCP-1 would not be active in the mice that had it, and hence they should not differ from the KO animals. So the impact of knocking out the UCP-1 gene ranges from being protective from obesity at 20 °C to neutral at 27 °C to highly susceptible at 30 °C. These data for the UCP-1 KO mouse raise some interesting questions about the hypothetical role of BAT in the development of obesity in humans. In particular in some circumstances, not having functional BAT is not an impediment to burning off excess intake (i.e., the UCP1 KO mice at 20 °C). It is unclear then why humans could not also burn off excess intake by other methods – for example, physical activity or shivering.

A second major problem with this BAT idea is that the obesity genes identified so far from the GWAS studies (Willer et al. 2009; Speliotes et al. 2010) are not associated with brown adipose tissue function but instead appear mostly linked to development or expressed in the brain and linked to individual variation in food intake (e.g., the gene FTO: Cecil et al. 2008; Speakman 2015). This lack of a link to the genetics suggests that evolutionary variability in thermoregulatory requirements probably did not drive individual variations in BAT thermogenic capacity (but see Takenaka et al. (2012) for a perspective on the evolution of human thermogenic capacity relative to the great apes). Finally, there are other potential explanations for why there might be an association between BAT depot size and obesity (Cypress et al. 2009; van Marken-Lichtenbelt et al. 2009). Adipose tissue acts as an insulator, and thermoregulatory demands in the obese are reduced because of shift downwards in the thermoneutral zone (Kingma et al. 2012). Severely obese people may be under heat stress because of their reduced capacity to dissipate heat at ambient temperatures where lean people are in the thermoneutral zone. In these circumstances, the requirement for thermoregulatory heat production would be reduced, and hence it is potentially the case that the association between BAT activity and adiposity comes about because obesity reduces the need for BAT and not because variation in BAT causes variation in the capacity to burn off excess intake.

7 Conclusion

Many ideas have been presented that try to explain the evolutionary background of the genetic contribution to the obesity epidemic. These can be divided into three basic types of idea. Adaptive interpretations suggest that fat has been

advantageous during our evolutionary history. Theories include the thrifty gene hypothesis and the idea that high body fat was necessary to support our brain development. These ideas generally struggle to explain the diverse in obesity levels observed in modern society. Neutral interpretations emphasize that the propensity to become obese does not have any advantage but is a by-product of mutation and genetic drift in some key control features. The dominant idea is the drifty gene hypothesis. Finally, obesity may be a maladaptive consequence of positive selection on some other systems. Examples of this type of explanation are the brown adipose tissue hypothesis and the protein leverage hypothesis.

8 Cross-References

- Adipose Structure (White, Brown, Beige)
- Body Composition Assessment
- Endocrine Disorders Associated With Obesity
- Epidemiology of Obesity in the United States
- Fetal Metabolic Programming
- Genetics of Cardiovascular Risk in Obesity
- Genetics of Lipid Disorders
- Genetics of Obesity
- Genetics of Type 2 Diabetes
- Kidney Disease in Obesity and Metabolic Syndrome
- Linking Obesity, Metabolism, and Cancer
- Metabolic Syndrome, GERD, Barrett's Esophagus
- Metabolic Syndrome in South Asians
- Nonalcoholic Fatty Liver Disease
- Obesity and Cardiac Disease
- Obesity in Middle East
- Obesity in Sub-Saharan Africa
- Obesity, Metabolic Dysfunction, and Dementia
- Obstructive Sleep Apnea and Other Respiratory Disorders in Obesity
- Overview of Metabolic Syndrome
- Reproductive Disorders and Obesity in Males and Females and Focus on the Polycystic Ovary Syndrome
- Sarcopenic Obesity
- Type 2 Diabetes: Etiology, Epidemiology, Pathogenesis, Treatment

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Genetics of Obesity

9

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Abstract

All definitions of the metabolic syndrome include some form of obesity as one of the possible features. Body mass index (BMI) has a known genetic component, currently estimated to account for about 70 % of the population variance in weight status for non-syndromal obesity. Much research effort has been expended in trying to identify the specific genes which contain polymorphisms that account for individual differences in BMI. The largest genome-wide association study (GWAS) to date confirmed and identified almost 100 genes where variation contributes to BMI in individuals of European ancestry. This GWAS validated numerous variants which give insights into the pathophysiology of obesity centering on altered glucose and lipid metabolism and differences in adipocyte formation. The most novel contribution was identifying numerous genes expressed in the brain, which likely have behavioral consequences. This fits well with contemporary work showing that eating behaviors are a key, heritable contribution to common obesity. Future work will expand this putative gene list and continue to give insights into the etiology of common obesity which may one day contribute to individualized risk profiles and treatment options.

Keywords

Genetics • GWAS • Obesity • BMI • Common obesity • Syndromic obesity • Monogenic obesity • Polygenic obesity • Missing heritability • Meta-analysis • Review

1 Introduction

Although several clinical definitions of the metabolic syndrome exist, all agree that excess body weight is an important component. For the World Health Organization (WHO), central obesity (waist/hip ratio >0.9 in men and >0.85 in women and/or BMI >30 kg/m^2) is not a necessary component, but forms one of four features, of which two must be present (Alberti and Zimmet 1998). These features are similar to those of the European Group for the Study of Insulin Resistance (Alberti et al. 2005) and of the National Cholesterol Education Program Adult Treatment Panel III, although the latter defines five features, of which any three must be present (Lorenzo et al. 2007). The International Diabetes Federation (IDF) includes central obesity as a core (necessary) component, in addition to which any two of four other metabolic features must also be present, although recent moves have been made to move the IDF definition as more in line with others (Alberti et al. 2009). As one of the defining features, it is clear that the etiology of obesity will give important mechanistic and predictive insights into the metabolic syndrome. Although readily available highly caloric and palatable food (the so-called "obesogenic" environment) has been blamed for the rise of obesity in the general population, it is clear that there are individual differences in susceptibility to this environment, which is attributable in part to genetic differences between individuals.

This chapter focuses on the genetic etiology of obesity discussing the most recent findings on genes which influence BMI. We will argue that now is an exciting time in the quest to understand the genetic underpinnings of body weight, since the most recent large-scale genetic study, published in 2015, not only confirmed the role of variants involved in metabolism but highlighted the role of genes expressed in the brain in the pathogenesis of obesity – suggesting a strong link with behavior. We will detail these findings, delineating the functions (where known) of genes associating with obesity. Further, we will discuss important research directions needed not only to identify a fuller complement of genes associated with BMI, but further how to use these results in preventing or treating the accumulation of excess body weight.

2 Three Forms of Obesity with Differing Etiologies

A distinction is often made between three types of obesity: monogenic, syndromic, and polygenic forms of obesity. In monogenic obesity,

differences within a single gene result in severe and pervasive obesity in the absence of cognitive changes or nonfood-related behavioral changes. Syndromic obesity also results in severe obesity, but the obesity arises as part of a more complex disorder which includes severe intellectual disability, dysmorphic features, and/or morphological changes in organ development. Polygenic obesity, sometimes called common obesity, has a complex etiology involving many genes of small effect which act in addition to, and interact with, environmental contributors to obesity.

3 Monogenic Forms of Obesity

Due to the high penetrance of monogenic forms of obesity and the increased statistical power that arises from its relatively homogenous genetic etiology, monogenic forms of obesity have been well characterized. One of the earliest models came through the development of the ob/ob mouse strain at the Jackson Laboratory in 1950 (Ingalls et al. 1950). Ob/ob mice lack the OB protein and have body weights approximately three times higher than wild type mice. In addition to obesity, ob/ob mice show reduced physical activity, hyperphagia, and have impaired glucose tolerance and hyperglycemia to the point of diabetes. Injection of the recombinant OB protein into ob/ob mice results in increases in activity levels and basal metabolic rate and a reduction in food intake, suggesting the OB protein regulates body weight via both metabolic and behavioral means (Pelleymounter et al. 1995).

The position of the OB gene was later localized (Zhang et al. 1994) and the OB protein and gene named *leptin* (*LEP*) after the Greek "leptos" meaning "thin." Deficiencies in the *LEP* gene akin to the ob/ob mice mutations which lead to a complete lack of circulating leptin are extremely rare in humans (Dubern and Clement 2012). Patients are characterized by severe early-onset obesity with hyperphagia alongside additional endocrine abnormalities (Ozata et al. 1999). As in ob/ob mice hyperinsulinemia with diabetes is observed (Ozata et al. 1999). Obesity arising from leptin deficiency is one of the few forms of obesity with effective therapeutic options. Daily lifelong injections of leptin result in a reduction in fat mass attributed mostly to treating the hyperphagic aspect of leptin deficiency (Farooqi et al. 2002).

Ob/ob mice lack the leptin protein, and db/db mice lack the leptin receptor. Although db/db mice have a similar phenotype to ob/ob mice, db/db mice are not responsive to leptin therapy. Mutations in the leptin receptor gene (*LEPR*) directly resulting in a severe obesity are as rare as those resulting in a lack of circulating leptin, affecting only 3 % of obese patients (Farooqi et al. 2007; Dubern and Clement 2012). Affected individuals produce leptin, but the receptor binds to the leptin, preventing its uptake, leading to extreme serum leptin levels. Similar to leptin-deficient patients, those with *LEPR* mutation-dependent obesity exhibit severe hyperphagia and endocrine abnormalities. As in mice, no treatment for this form of monogenic obesity has yet been found.

Other monogenic forms of human obesity result in less severe obesity and, unlike those arising from homozygous mutations in *LEP/LEPR* as described above, are not fully penetrant (Farooqi et al. 2006; Stutzmann et al. 2008). Melanocortin 4 receptor (*MC4R*) mutations are the most common, seen in over 0.05 % of the population (Govaerts et al. 2005). Although less well characterized than leptin deficiency, MC4R deficiency is present in greater numbers, being the primary cause of obesity in 1–6 % of obese individuals. *MC4R* mutations present different phenotypes across the lifespan; prepuberty, the extent of functional impairment in MC4R signaling, correlates positively with adiposity and hyperphagic behaviors, but this association disappears postpuberty. Alongside the hyperphagia reduction, feelings of satiety increase and the adiposity and hyperinsulinemia reduce.

Other genes associated with forms of monogenic obesity include proopiomelanocortin (*POMC*) and prohormone convertase 1 (*PCSK1*), which are involved in the leptin–melanocortin signaling pathway. The primary mechanism of action is not metabolic but rather behavioral as leptin acts to inhibit food intake leading to obesity from excess food caloric intake in these cases (Zhou and Rui 2013).

Monogenic forms of obesity were initially thought to provide the starting block to examine causes of common (polygenic) obesity – it was thought that mutations with less deleterious effects (a reduction in circulating leptin, for example, rather than its absence) may explain a great proportion of the heritable variance on BMI. However, as discussed later, this does not appear to be the case with common obesity involving far more genes and far more environmental interactions than previously thought.

4 Syndromic Obesity

At least 20 syndromes characterized by extremely lowered intellectual ability and obesity, as well as marked changes in behavior, are caused by discrete genetic mutations or chromosomal abnormalities. The most frequent of these syndromes affecting 1 in 25,000 births is Prader–Willi syndrome (Whittington et al. 2001), an autosomal-dominant disorder that is characterized by obesity arising from hyperphagia. Prader–Willi syndrome arises from a deletion at 15q11.2–q12, most often inherited from the paternal allele. Obesity in Prader–Willi arises from a sustained increase in food intake, which appears to be from reduced satiety rather than increased hunger (Lindgren et al. 2000). Food behavior phenotypes in Prader–Willi are consistent with a number of endocrine abnormalities arising from hypothalamic impairments. For example, ghrelin stimulates hunger, and fasting levels of ghrelin are increased in both adults and children with Prader–Willi (Cummings et al. 2002). Postprandial secretion of the pancreatic polypeptide from the gastrointestinal tract, which reduces food intake, is decreased in patients with Prader–Willi, and infusions of pancreatic polypeptide reduce food intake, although this effect may be specific to females (Berntson et al. 1993). The full cause of hyperphagia in Prader–Willi syndrome remains elusive, although Prader–Willi syndrome phenotypes are consistent with a combined hypothalamic impairment, causing several endocrine abnormalities. Contributing to obesity in Prader–Willi is also a significant reduction in physical activity, the hormonal mechanisms behind which are poorly understood (Davies and Joughin 1993).

Mutations across 15 Bardet–Biedl genes have been associated with different forms of Bardet–Biedl syndrome (BBS). Although there is a strong link between BBS and obesity, one study concluded that only just over one half of patients were obese, and the functional role of mutations in the BBS network of genes is poorly characterized. The single-minded homologue 1 (*SIM1*) gene is the other well-characterized gene associated with syndromic obesity (although there are other forms of syndromic obesity, where the genetics are not identified and so not discussed here). Mice that are homozygous for a null allele of *SIM1* show brain abnormalities which cause perinatal death, whereas those with only one null *SIM1* allele show milder structural differences in the hypothalamus resulting in hyperphagia and early-onset obesity (Michaud et al. 2001). In humans, deletion of the *SIM1* region results in similar excessive food intake and early-onset obesity.

Whereas therapeutic options for Prader–Willi are available, the pervasive hyperphagia in syndromic obesity is difficult to eliminate. Behavioral therapy for syndromic obesity is minimally successful possibly due to the accompanying intellectual disabilities, and more success may be found with the restrictive diets. Better characterizing the underlying genetics of syndromic obesity remains important for understanding the patterns of eating behaviors underlying excess adiposity in these disorders; this will have implications for treatment of syndromic obesity, but also for understanding mechanistic pathways to the eating behaviors which also underpin common obesity, although the magnitude of their effects on this latter form of obesity is likely to be much smaller.

5 Common Obesity

Common, or polygenic, obesity is thought to account for the dramatic increase in obesity prevalence over the last decade (Ogden et al. 2006).

Common obesity tracks in families, but is not inherited in the predictable pattern seen in monogenic obesity. Nor is common obesity accompanied by pervasive changes in nonfood behaviors or marked cognitive changes such as intellectual disability. The complex segregation pattern of common obesity suggests that it is polygenic and influenced by many genes of small effect, none necessary nor sufficient to convey obese status on their own. This etiological model of traits is known as the "quantitative trait locus (QTL) approach," and a corollary of this model is that disorders or diseases are seen as the extreme end of the normal spectrum. Whereas monogenic forms of obesity are seen as having discrete causes and discrete consequences which are not present in those without these forms of obesity, common obesity is seen as arising from an excess of the risk factors which operate across the whole spectrum of BMI. Thus, research into the causes of common obesity often uses BMI as the outcome, rather than weight status, such as overweight ($25 \leq BMI < 30$ in adults) or obese ($BMI \geq 30$).

6 Twin Studies of BMI

6.1 Rationale

The classic twin study design uses the known amount of genetic and environmental sharing between members of twin pairs to parse the variance in a trait, for a given population, into additive genetic (A), dominant genetic (D) or common environment (C; note that C and D cannot be simultaneously estimated in the classic twin design; see Wood et al. 2010), and individual-specific environmental (E; which subsumes measurement error) influences. In child studies, the following three assumptions are made: (1) monozygotic (MZ; identical) twins share 100 % of their segregating alleles and correlate at $r = 1.00$ for genetic influences, whereas dizygotic (DZ; fraternal) twins share on average only 50 % of their segregating alleles and correlate at $r = 0.50$; (2) both MZ and DZ twins share the influences in the environment which make them more similar (C) to the same extent, and so members of a pair for both types of twin pairs correlate at $r = 1.00$; and (3) MZ and DZ twins are discordant for factors in the environment which make them phenotypically different (E) and so do not correlate for these. From this it follows that if you take a groups of twins and compare the average within-pair correlation for the MZ and DZ twin groups, MZ correlations higher than DZ correlations indicate A or D influences to a trait; MZ correlations on a trait of less than one indicate E influences, and the remaining variance is accounted for by C (denoted by MZ correlations that are less than half DZ).

6.2 Heritability of BMI

Twin studies suggest a strong heritability to BMI of around 58–84 % (Stunkard et al. 1986a; Schousboe et al. 2004) and that the relative stability of BMI as individuals age is attributable to those genetic influences exerting their effects across the lifespan, although new genetic influences are seen to emerge as individuals get older (Fabsitz et al. 1992). The findings from twin studies of a strong heritability of BMI are supported by adoption studies which show that adopted children have BMIs that more closely resemble that of their estranged biological parents (with whom they share genetics) than those of their adoptive parents (with whom they do not share genetics) (Stunkard et al. 1986b), and while focusing on exact point estimates in twin studies is ill-advised (see Wood et al. 2010), the overwhelming conclusion is that BMI is a moderately to highly heritable trait across populations defined by geography, ethnicity, gender, and age.

6.3 The Relationship of BMI to the Metabolic Syndrome

Multivariate twin studies employ cross-trait within-pair correlations to give insight into the etiology of trait covariance. That is, comparing the ratio of MZ:DZ correlations using the logic above on, for example, one twin's score on BMI with their co-twin's score on blood pressure can parse the known correlation between these two

traits into genetic and environmental influences (see Rijsdijk and Sham 2002). The overall picture is of some shared, but some etiologically distinct, pathways between components of the metabolic syndrome. For example, central abdominal fat, a stronger risk factor the metabolic syndrome that overall adiposity, is highly heritable (~92 %) and has a genetic etiology which is somewhat distinct from overall BMI (Carey et al. 1996). The relationship of obesity, diabetes, and hypertension is best explained by a common genetic factor (Carmelli et al. 1994); however, lipids have a separable etiology more influenced by the environment (Poulsen et al. 2001).

6.4 Using Twin Studies to Understand Molecular Genetic Studies and the Missing Heritability

Quantitative genetic (heritability) studies show that common obesity has a strong genetic component, and the challenge has been in identifying the genes to account for this heritability using molecular genetic methods. The failure to account for more than 5 % of the heritable variance has been termed the "missing heritability" (Manolio et al. 2009). In reviewing the molecular genetic evidence for genes which associate with BMI, it is important to learn the lessons of over a decade of GWASs, brought to light in discussion on the missing heritability, and use these to carefully select which studies provide the best evidence for variant-BMI associations.

7 Methodological Issues with Identifying the Genetic Basis of Complex Traits

As with all complex trait analysis, attributing the heritable variance in BMI to specific known genes has met with less success than expected at the start of the genome era (Manolio et al. 2009). Candidate gene studies were the mainstay of initial attempts to identify genes for BMI: carefully selected variants within genes hypothesized to have a function related to BMI were analyzed for their associations with BMI or obesity (see Bell et al. 2005 for an excellent review). However, candidate gene studies failed to elucidate the genetic basis of BMI due, principally, to two main limitations: (1) the underlying mechanisms were more complex and less known than anticipated, making the selection of genes for analysis inadequate; (2) significant findings often failed to replicate making firm conclusions about associated variants difficult to draw. On the back of these disappointments, much optimism was felt at the start of GWAS era.

In the mid-2000s, several methodological advances occurred simultaneously to provide an alternative to candidate gene studies. Firstly, the advent of DNA chip technology allowed us to sequence numerous variants (dependent on the chip technology, this could typically be between 500 K and one million in the early days, although this has been somewhat superseded now) simultaneously across the genome with little personnel effort compared to that of PCR and candidate gene studies (and eventually, with minimal cost). In addition, the International HapMap Project provided an open resource which elucidated the complex linkage disequilibrium structure of variants across the genome (Gibbs et al. 2003; Thorisson et al. 2005). What the HapMap project allowed was the imputation of up to 2.5 million variants across the genome, based on the known correlational structure of different SNPs (this has been superseded by The Human Genome Project which allows imputation of closer to 80 million variants (Siva 2008)). In effect, this allowed us to look across the whole genome (current coverage can be up to 80 %) in a hypothesis-free manner to look for those variants which showed significant associations with a complex trait. However, GWAS too suffered from flaws.

Even after a decade of GWAS, approximately 95 % of the heritable variance in all complex traits remains unaccounted for – for BMI this figure stands at ~97 % (Locke et al. 2015). The reasons for this are complex, debated, and manifold – and an in-depth discussion is beyond the scope of this chapter (but see Maher 2008; Manolio et al. 2009). Of relevance to this discussion, they

likely include the difficulties of dealing with 2.5 million + statistical tests in a single study and the trade-off between type I and type II errors this necessitates. The stringent corrections for multiple testing means we have likely missed the associations of small effect size. However, even with a Bonferroni correction, GWAS fell into the same trap as candidate gene studies: difficulties with replication. Now, many journals have demanded replication in at least one independent sample for any purported "hit" before publishing any GWA studies (see "Asking for More" (2012). Whether GWAS can have been considered to have "failed" is a matter of debate (Visscher et al. 2012); what is important are the steps scientists are taking to overcome the limitations of GWAS. For traits like BMI, which are measured in many studies and easily comparable between populations, the move has been for cohorts with the relevant phenotype and genotype data to come together within a consortium and meta-analyze their data. This neatly deals with the suspected GWAS difficulties of expected small effect sizes and the false positives that occur.

8 The GIANT GWAS

Given the difficulties of replication in GWAS, we will follow the leading scientists and focus only on those large meta-analyzed studies. The most recent example of which was from the Genetic Investigations of Anthropometric Traits (GIANT) consortium who replicated the 32 loci associated with BMI detected in their previous analysis and added 65 new loci (Locke et al. 2015). This study analyzed data from up to 339,224 individuals across 125 studies (approximately two-thirds of the participants had GWAS results, others had genotypes from Metabochip). In addition to confirming existing and identifying new genotype-BMI associations in genes with a known function in obesity metabolism (Table 1), as well as identifying genes with no known function, or for which the function in obesity is not known, the unique contribution of the GIANT GWAS was the observation that 87 % of the newly identified body mass index (BMI) variants were expressed in the central nervous system, with enrichment in the hypothalamus and pituitary gland – key sites of appetite regulation (Table 2; Locke et al. 2015).

When GWASs were first devised, they were meant to be hypothesis generating: that is, given the lack of an a priori hypothesis for each variant, the significant associations were supposed to be followed up with careful candidate gene and animal studies which delineated the functionality of new single nucleotide polymorphisms (SNPs). We will follow this model: taking the work by GIANT as the forefront of those loci known to be associated with BMI, we will follow the ideal model and combed the literature for clues into the functionality of the associated SNPs.

9 Genes with Known Metabolic Functions Which Relate to Obesity

9.1 Insulin Signaling and Glycemic Control

Insulin resistance is the hallmark of the metabolic syndrome; the reduced ability of muscle cells to react to the release of insulin and the ensuing hyperinsulinemia lead to a host of metabolic abnormalities, one of which includes increased adiposity. Insulin has numerous adiposity-promoting functions, for example, fostering the differentiation of preadipocytes to adipocytes and inhibiting lipolysis. Adipose tissues are, in themselves, insulin resistant, and the extent to which insulin resistance is a cause and not a consequence of obesity is unclear. The functionality of many BMI-associated genes in the insulin signaling pathway, or with insulin resistance, further illustrates the mechanistic links between the two traits.

FTO is one of the genes most consistently related to BMI across a number of GWAS and candidate gene studies (Dina et al. 2007; Hinney et al. 2007; Scuteri et al. 2007; Hunt et al. 2008; Speliotes et al. 2010). The association between *FTO* and BMI is not isolated to the oft-studied "adults of European ancestry" group, for example,

Table 1 Genes with known functions in metabolism related to BMI

Gene name	Common nomenclature
Adenylate cyclase 3	*ADCY3*
Apolipoprotein B receptor	*APOBR*
Apolipoprotein C-I	*APOC1*
Apolipoprotein E	*APOE*
Bardet–Biedl syndrome 4	*BBS4*
Cytochrome P450, family 27, subfamily A, polypeptide 1	*CYP27A*[a]
Double C2-like domains, alpha	*DOC2A*[a]
V-Ets avian erythroblastosis virus E26 oncogene homologue 2	*ETS2*
Ets variant 5	*ETV5*
Fas apoptotic inhibitory molecule 2	*FAIM2*
Forkhead box O	*FOXO3*
Fat mass and associated	*FTO*
Growth differentiation factor 15	*GDF-15*
Gastric inhibitory polypeptide receptor	*GIPR*
3-Hydroxy-3-methylglutaryl-coenzyme A reductase	*HMGCR*
Insulin receptor substrate 1	*IRS1*
Kruppel-like factor 7	*KLF7*
Mitogen-activated protein kinase 3	*MAPK3*
Mitochondrial carrier 2	*MTCH2*
Nuclear receptor coactivator 1	*NCOA1*
Protein kinase D1	*PRKD1*
Regulatory associated protein of MTOR, complex 1	*RPTOR*
Scavenger receptor class B, member 2	*SCARB2*
Secretogranin III	*SCG3*
SEC16 homologue B	*SEC16B*
SH2B adaptor protein 1	*SH2B1*
Sulfotransferase family, cytosolic, 1A, phenol-preferring, member 2	*SULT1A2*
Transcription factor 7-like 2	*TCF7L2*
Transcription factor AP-2 beta	*TFAP2B*
Toll-like receptor 4	*TLR4*
Translocase of outer mitochondrial membrane 40 homologue	*TOMM40*
Tubby gene	*TUB*
Subset of genes known to interact with dietary intake/physical activity on metabolism	
V-Erb-B2 avian erythroblastic leukemia viral oncogene homologue 4	*ERBB4*
Fas apoptotic inhibitory molecule 2	*FAIM2*
Gastric inhibitory polypeptide receptor	*GIPR*
Glucosamine-6-phosphate deaminase 2	*GNPDA2*
3-Hydroxy-3-methylglutaryl-coenzyme A reductase	*HMGCR*
Neuronal growth regulator 1	*NEGR1*
SEC16 homologue B	*SEC16B*
Transcription factor 7-like 2	*TCF7L2*
Transcription factor AP-2 beta	*TFAP2B*
Tu translation elongation factor mitochondrial gene	*TUFM*

[a]Expressed in the brain but not behavioral related

FTO has been associated with BMI or obesity status in Chinese (Chang et al. 2008), Korean (Lee et al. 2010), and pediatric (Dina et al. 2007; Frayling et al. 2007; Haworth et al. 2008; Sovio et al. 2011) populations. A recent review summarized that each *FTO* risk allele increases the BMI equivalent to ~0.40–0.66 BMI points such that the risk of overweight and obesity

Table 2 Genes associated with BMI which are expressed in the brain

Gene name	Common nomenclature
Known function related to obesity	
Brain-derived neurotrophic factor	*BDNF*
CAMP responsive element-binding protein 1	*CREB1*
Glutamate receptor, ionotropic, delta 1	*GRID1*
Low-density lipoprotein-related protein 1B	*LRP1B*
Melanocortin 4 receptor	*MC4R*
Neuronal growth regulator 1	*NEGR1*
Niemann–Pick disease, type C1	*NPC1*
Proopiomelanocortin	*POMC*
Zinc finger CCCH-type containing 4	*ZC3H4*
Known function not related to obesity	
ATP/GTP-binding protein-like 4	*AGBL4*
Calcitonin receptor	*CALCR*
Cerebellin 1 precursor	*CBLN1*
ELAV-like neuron-specific RNA-binding protein 4	*ELAVL4*
V-Erb-B2 avian erythroblastic leukemia viral oncogene homologue	*ERBB4*
Gamma-aminobutyric acid (GABA) A receptor, gamma 1	*GABRG1*
G protein-coupled receptor, class C, group 5, member B	*GPRC5B*[a]
Potassium channel, subfamily K, member 3	*KCNK3*
Leucine-rich repeat and fibronectin type III domain containing 2	*LRFN2*
Neurexin 3	*NRXN3*
Protocadherin 9	*PCDH9*
Polypyrimidine tract-binding protein 2	*PTBP2*
RALY RNA-binding protein-like	*RALYL*
Ras-like without CAAX 2	*RIT2*
SH3 domain binding kinase 1	*SBK1*
Syntaxin 1B	*STX1B*

[a]Specific function unknown

increases by ∼1.2 and ∼1.3 odds, respectively (Loos and Bouchard 2008). Those carrying two *FTO* risk alleles weigh 3–4 kg more than those with no risk allele (Loos and Bouchard 2008). Although the role of *FTO* in obesity appears to be mostly behavioral (see below), *FTO* appears to have truly pleiotropic effects as the risk alleles may reduce insulin response in the brain (Tschritter et al. 2007).

KLF7 encodes a protein which inhibits insulin expression and secretion in pancreatic beta cells. In addition to association between *KLF7* and obesity, *KLF7* is considered a risk gene for type 2 diabetes (Kanazawa et al. 2005; Zobel et al. 2009). *APOC1* is expressed primarily in the liver, where overexpression of *APOC1* in ob/ob mice leads to hepatic steatosis and severe hepatic insulin resistance (Muurling et al. 2004).

APOE may also exert its influence on BMI through altered insulin sensitivity; obese men with the *APOE4* genotype presented with higher levels of insulin and glucose than obese men in the other genotype groups (Elosua et al. 2003). In addition to associations between the *SH2B1* and whole body fat mass in females (Jamshidi et al. 2007; Hotta et al. 2011), the distribution of body fat and the amount of visceral adipose tissue (Hotta et al. 2011) and the amount of visceral fat area (Haupt et al. 2010), *SH2B1* variants have also been associated with type 2 diabetes independently of BMI (Sandholt et al. 2011). Circulating GDF-15 concentrations are increased with type 2 diabetes (Dostálová et al. 2009; Vila et al. 2011), and GDF-15 predicts future insulin resistance glucose control (Kempf et al. 2012). *IRS1* encodes a protein which is phosphorylated

by insulin receptor tyrosine kinase. Mutations in this gene are associated with type 2 diabetes and susceptibility to insulin resistance (Hotamisligil et al. 1996; Rung et al. 2009). *PRKD1* regulates insulin secretion; blocking PKD in vitro cells inhibited insulin secretion, but not insulin production (Sumara et al. 2009). TCF7L2 is expressed in most human tissues, including mature pancreatic β-cells and adipose tissue, with the exception of the skeletal muscle (Cauchi et al. 2006). Variants in this gene are strongly associated with type 2 diabetes (Chandak et al. 2007; Helgason et al. 2007; Herder et al. 2008) and reduce the insulin response to glucose in nondiabetic individuals (Saxena et al. 2006). Toll-like receptor 4 (TLR4) activation was associated with insulin resistance in adipocytes (Song et al. 2006), which suggested that activation of TLR4 in adipocyte might be implicated in the onset of insulin resistance in obesity and type 2 diabetes. *TLR4* knockout mice are insulin resistance in diet-induced obesity (Kim et al. 2007). *TUB* mutations in mouse models are the cause of maturity-onset obesity and insulin resistance and are not directly supported by human functional studies but mirror a C. elegans model (Mukhopadhyay et al. 2005).

Inflammation is considered to be a causal link between insulin resistance and obesity. Several genes associating with BMI also are associated with pro-inflammatory statues, for example, *FTO* mediates the expression of inflammatory genes upregulated in adipose tissue. Together, these studies support those from twin studies which suggest a shared etiology between insulin resistance and adiposity, supporting a causal connection.

9.2 The Adipocyte Cycle

Adipocytes, energy storage cells, were originally thought to be inert or nonfunctional. However, more recent research has revealed active roles for adipocytes in fat mass regulation and nutrient homeostasis, in addition to other homeostatic processes (Trayhurn 2005; Rosen and Spiegelman 2006). Functional studies across a variety of species show that *KLF7* inhibits preadipocyte differentiation (Kawamura et al. 2006; Zhang et al. 2013). *APOC1* is associated not only with total adipose cells but also average adipocyte size (Jong et al. 2001). *ETS2* encodes transcription factors which are regulated during early adipogenesis and are essential for the normal progression of the adipocyte differentiation program in vitro (Birsoy et al. 2011). *MTCH2* is highly expressed in human white adipose tissue (WAT) alongside *NEGR1* which is involved in adipocyte differentiation (Bernhard et al. 2013).

As the activity of adipocyte cells in fat regulation is a fairly new discovery a promising avenue of research is to fully delineate the genes involved and their roles in obesity.

9.3 Lipid and Fatty Acid Metabolism

Studies using *GIPR* null mice established the importance of GIPR signaling in regulating lipid metabolism (Song et al. 2007; Kim et al. 2011). *HMGCR* (also commonly called *HMG-CoA*) is the rate-limiting enzyme for cholesterol biosynthesis (Dietschy et al. 1993). This enzyme is suppressed by cholesterol derived from low-density lipoprotein (LDL) catabolism via the LDL receptor. APOE binds with high affinity to the low-density lipoprotein (LDL) receptor and facilitates catabolism (Mahley 1988). *SCARB2* mediates selective uptake of cholesteryl esters from HDL particle (Eckhardt et al. 2004), and while the role of *TOMM40* in lipid metabolism is not known, studies associate *TOMM40* variants with triglyceride levels (Aulchenko et al. 2009). In *C. elegans*, loss of *tub-1*, the worm orthologue of *TUB*, increases in the storage of triglycerides (Mukhopadhyay et al. 2005). *FOXO3* gene expressions can reduce LDL-cholesterol levels through regulation of the *PCSK9* gene. *FTO* mediated the downregulation of some genes involved in fatty acid catabolism which might explain, in part, the increased adiposity (Fawcett and Barroso 2010).

9.4 Endocrine System Functions

Obesity leads to altered metabolism of hormones; for example, increased serum estrogen levels have been associated with obesity (Glatt et al. 2001). Obesity increases the serum concentration of the steroid hormones estradiol (17-β-estradiol), estrone, and also estrone sulfate, which are all substrates of *SULT1A2* (Mahabir et al. 2006; Emaus et al. 2008). A plausible mechanism of association with BMI is through genes that influence sex hormone secretion and response. The association of *SULT1A2* on body weight has been posited to be mediated by the regulation of sex hormones (Harris et al. 2000). The absence of *NCOA1*, a coactivator for steroid and nuclear hormone receptors, causes obesity in knockout mice (Picard et al. 2002; Maquoi et al. 2005).

The role of leptin in obesity through food intake alterations is known via monogenic studies. *ERK1* protected leptin-deficient mice from insulin resistance which indicates that deregulation of the *ERK1* pathway could be an important component in insulin-associated obesity, although the ensuing changes to BMI have yet to be demonstrated (Jager et al. 2011). *SH2B1* is associated with serum leptin levels in females, as well as the broad spectrum of obesity measures outlined above (Jamshidi et al. 2007; Hotta et al. 2011).

Further elucidating the associations of hormone-related genes involved in obesity is likely to need a two-pronged approach. One angle will need to map out the roles from genes to obesity via biological pathways, but this should be complemented by an approach which better understand the role of hormonal perturbations in obesity, via, for example, effects on food intake behaviors (Klump et al. 2011; Cao et al. 2014).

9.5 Gene Interactions with Energy Intake and Expenditure

One hypothesized mechanism for the missing heritability is gene–environment interactions for which, in the case of obesity, may be most likely to operate through interactions between genetic variants and dietary intake or physical activity. We have recently reviewed the evidence for gene–diet interactions in metabolic health and concluded that while there is a compelling rationale for the existence of these, there is little empirical evidence (Frazier-Wood 2015). Since this arises from a number of methodological concerns including the difficulty in selecting genes for analysis versus the power needed for genome-wide interaction studies (GWIS), we argued that it is not to say that gene–diet interactions do not exist, rather techniques for identifying them need to be developed and refined. In terms of those variants identified as associating with BMI, there is some evidence they may exert their effects through interactions with physical activity or dietary intake (Table 1). For example, the G allele in *HMGCR* showed a greater response in lower triacylglycerol levels with a diet reduced in saturated fat intake and increased in fiber intake (Freitas et al. 2010). *ADCY3* null mice are more susceptible to obesity induced by high-fat feeding (Wang et al. 2009). The expression of *FAIM2* gene may be affected by nutritional state (Boender et al. 2012). Overall, a recent study also reported that a number of "obesity susceptibility genes" (*FAIM2*, *FLJ35779*, *FTO*, *LRRN6C*, *RBJ*, and *SEC16B*) interact with sugar-sweetened beverage intake to increase BMI (Qi et al. 2012). *TUFM* is upregulated on a high-fat diet in rats (Gutierrez-Aguilar et al. 2012) and *CYP27A*, one of the key genes involved in vitamin D metabolism pathway (Prosser and Jones 2004). However, vitamin D is synthesized as well as ingested, and candidate gene association studies showed that the vitamin D pathway genes are unlikely to have a major role in obesity-related traits in the general population (Dorjgochoo et al. 2012; Vimaleswaran et al. 2013) urging caution in interpreting these findings in relation to BMI. Gene–diet interaction: Kallio and colleagues recently suggested that diets rich in whole-grain cereals and foods with a low glycemic index may protect against T2D through the regulation of several genes in adipose tissue (Kallio et al. 2007). After 12 weeks of the rye–pasta diet, they found a decrease in TCF7L2 expression. A randomized controlled trial showed

that *TFAP2B*-rs987237 genotype AA was associated with 1.0 kg greater mass reduction on a low-fat diet than other variants and G homozygotes with 2.6 kg greater loss on the high-fat diet (Stocks et al. 2012).

Physical activity may also interact with genetic variants to influence BMI. In diet-induced obese rats, low-intensity endurance training and well-balanced diet activate the *NRG1-ERBB4* pathway in the skeletal muscle (Ennequin et al. 2015), while at the other end of the physical activity spectrum, high levels of leisure screen time (a measure of physical inactivity) exacerbate the influence of *GNPDA2* on BMI, although this finding has been limited to African-American population (Graff et al. 2013).

Together, these studies emphasize the difficulties and lack of firm conclusions in identifying gene–diet or gene–activity interactions in health, not just BMI. It is doubtless an important avenue to pursue, but will take collaborative efforts and careful consideration to dietary differences between groups to achieve (Frazier-Wood 2015).

10 Genetic Insights into the Behavioral Causes of Obesity

10.1 Obesogenic Behaviors

In the recent GIANT GWAS, nearly nine out of every ten newly identified variants associating with BMI were expressed in the brain (Locke et al. 2015). Although the study was not able to isolate all individual areas where BMI-associated variants were expressed, there was enrichment for those areas involved in appetite regulation. These gene findings are meaningful in the light of recent work which has examined not so much food intake as a precursor of BMI but a full complement of appetitive behaviors, such as satiety responsiveness, eating in the absence of hunger, emotional overeating, slowness in eating, the inability to delay the gratifying reinforcement of food, and enjoyment of food which have been associated with BMI in numerous populations (Hughes et al. 2015; Fisher and Birch 2002; Butte et al. 2007; Carnell and Wardle 2008; Carnell and Wardle 2009; Seeyave et al. 2009). Supporting the notion that these obesogenic eating behaviors may lie on the pathways from genes to obesity, these behaviors have been shown to be moderately heritable (~40–70 %) (Butte et al. 2006; Fisher et al. 2007; Carnell et al. 2008). Further enrichment for BMI-related variant expression was seen in the hippocampus and limbic system, tissues that have a role in learning, cognition, emotion, and memory. Our own work has been built on work showing that self-regulation, a construct closely linked to executive function involving the initiating and inhibition of behaviors, is associated with weight status, to show that approximately 30 % of the genes involved in some cognitive tasks are shared with BMI (Frazier-Wood et al. 2014).

10.2 Insights from Monogenic Obesity

Leptin therapy exerts its BMI-reducing effect in leptin-deficient obesity by inducing a slower rate of eating and diminished duration of eating of every meal (Farooqi et al. 2002). Leptin treatment is also able to regulate motivation to eat during mealtimes (Williamson and Stewart 2005). Individuals with *POMC* monogenic conditions respond well to hypocaloric dietary or multidisciplinary (exercise, behavior, nutrition therapy) behavioral interventions (Santoro et al. 2006). Thus, it seems clear that monogenic forms of obesity are reduced through behavioral interventions, implicating behavior in the pathogenesis.

10.3 Behavioral Genes and Obesity

FTO is the best known BMI variant and *mainly* exerts its effects through food intake behaviors, as evidenced by associations with increased food intake, but not reduced basal metabolic rate (Speakman et al. 2008). *FTO* variants are associated with self-reported hunger and satiety in

adults (den Hoed et al. 2009) and diminished satiety in children as measured by the tendency to eat after reporting being full (also called eating in the absence of hunger; (Wardle et al. 2008)). Specifically, *FTO* variants may be associated with eating more highly palatable foods (which are usually more energy dense) presented immediately after an ad libitum meal (Wardle et al. 2009).

POMC encodes a protein which is synthesized mainly in cells of the anterior pituitary (brain). *POMC* was identified as a causal variant in cases of severe early-onset obesity influencing the leptin–melanocortin pathway (Krude et al. 1998), with which *MC4R* gene variants also interact (Vaisse et al. 1998; Yeo et al. 1998). *POMC* is implicated in nutrient intake (Cai et al. 2004), as well as leptin levels (Hixson et al. 1999) and physical activity (Simonen et al. 2003). *MC4R* is specifically associated with higher dietary fat intake (Qi et al. 2008) and emotional overeating (Yilmaz et al. 2015). *CREB1* is a transcription factor mostly expressed in the brain, which can drive the expression of numerous genes (Blendy et al. 1996; Cha-Molstad et al. 2004), and postulated to play a key role downstream of the *MC4R* in the paraventricular nucleus (Sarkar et al. 2002). Like *MC4R*, *ZC3H4* was positively associated with emotional and uncontrolled (binge) eating in both men and women (Cornelis et al. 2014).

BDNF is associated with depression and in turn associated with BMI changes, although the direction of association is not always consistent. *BDNF* is associated with anorexia nervosa and bulimia (Friedel et al. 2005; Gratacòs et al. 2007) suggesting a link to altered eating behaviors, although these disorders have a very complex psychological etiology and may or may not inform us on the etiology of common obesity. *GRID1* regulates appetite although the specific eating behaviors affected are not well delineated (Justice et al. 2013).

Genes that may account for the association between cognition and BMI are less well identified. The BMI-associated alleles of *LRP1B* have been inversely associated with cognitive restraint (also called inhibition) behaviors (Cornelis et al. 2014). A fruitful avenue of future research will be to examine whether genes associate with BMI via their direct effects on changes in behavior which manifest in both food- and nonfood-related behaviors.

11 Synthesis and Conclusions

Clearly, obesity has a strong genetic influence, although this does not in any way indicate that environmental, or behavioral, interventions will not be effective treatments. Over 97 % of the heritable variance in BMI has yet to be accounted for by variants in names of genes, and further identification of BMI-raising variants will give important insights into the molecular pathways to obesity – be they metabolic or behavioral. Understanding this will help us devise not only targeted interventions but also prevention efforts. The prevalence of obesity in US adults may be leveling off, but it still remains the main contributor to the primary causes of preventable death (heart disease and cancer). Genetic research offers promise for reducing this health burden via better delineated etiological pathways to disease.

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12 Cross-References

- ▶ Brain Regulation of Feeding and Energy Homeostasis
- ▶ Carbohydrate, Fat, and Protein Metabolism in Obesity
- ▶ Dyslipidemia in Obesity
- ▶ Genetics of Cardiovascular Risk in Obesity
- ▶ Genetics of Lipid Disorders
- ▶ Genetics of Type 2 Diabetes
- ▶ Insulin Resistance in Obesity

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Genetics of Type 2 Diabetes

10

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Abstract

The promise of high-throughput genomics has started to deliver novel insights in the genetic etiology of type 2 diabetes and its related traits. In particular, genome-wide association studies have revealed new biological underpinnings to metabolic traits, with particular focus being on the strongest loci *TCF7L2* and *FTO*. However, many challenges still lie ahead as much of the "missing heritability" of such traits remains to be elucidated, with only a minority of the genetic component to type 2 diabetes being characterized to date. Undeterred, investigators are aiming to use what has been found to already attempt risk prediction models, while lab-based researchers are trying to elucidate functional mechanism. However, the latter has a number of challenges as these well-established signals still require full characterization of the causal tissue, the causal variant, and often the actual causal gene. However, once advances are made of these fronts, the future looks bright with respect to the development of novel therapeutics and diagnostics for type 2 diabetes and its related traits.

Keywords

Gene • Diabetes • Obesity • Metabolic syndrome • Insulin • Islet

1 Introduction

Type 2 diabetes (T2D) is a member of the complex traits that are both common and known to have a genetic component. The reason it is considered complex is that there are two primary processes underpinning the disorder, namely, contributions from defects in insulin resistance and insulin secretion. It is widely believed that discrete genetic factors play a role in these two mechanisms, which in turn influence T2D susceptibility. Insulin resistance is widely influenced by obesity, where a separate genetic etiology has also been implicated. However, teasing out the genetic factors contributing to the pathogenesis of T2D, where there is also such a marked environmental influence on risk, has proved challenging. So much so, that before the era of genome-wide association studies (GWAS), the disease was referred to as the "geneticist's nightmare," and the prospect of discovering the underlying genetic factors in this polygenic trait was equated to discovering the "Holy Grail."

Before one embarks on a genetic hunt for variants contributing to the pathogenesis of a disease, one has to convince oneself that there is indeed a genetic component to the trait. In the context of T2D, there is evidence from concordance observations when contrasting monozygotic twins with dizygotic twins while segregation analyses in families have led to the conclusion that the sibling risk for T2D is approximately 3.5-fold (Rich 1990). As such, investigators have been motivated to seek out the genetic contributors to this common disease blighting many societies.

2 Candidate Gene and Family-Based Studies

In the relative dark ages before GWAS (i.e., prior to 2005), the only approach to assess genes and their putative role in complex traits was the candidate gene approach. Although a number of genes were robustly implicated in T2D during that period, this approach was heavily blighted by the "winner's curse" (Lohmueller et al. 2003), where an investigator would select their favorite gene based on an already known obvious role in the pathogenesis of the trait but would only formally report the study if an association with a variant reached the significance bar of $P = 0.05$. As such, there was an inherent bias in what ended up getting reported, and thus, very many of these loci were not replicated by peer investigative groups.

The handful of genes that did hold up in the candidate gene era include peroxisome proliferator-activated receptor gamma (*PPARG*), calpain 10 (*CAPN10*), and "potassium inwardly rectifying channel, subfamily J, member 11" (*KCNJ11*) (Altshuler et al. 2000; Gloyn et al. 2003; Horikawa et al. 2000).

The first opportunity to carry out a more hypothesis-free approach was with the advent of genome-wide linkage studies. These were enabled by panels of hundreds of microsatellites in complete linkage equilibrium, and thus, if a region of the genome was shared within and across families with a given trait, it could be detected by this approach. When it came to complex traits including T2D, regions of significant linkage were indeed detected (Reynisdottir et al. 2003), but the resolution of the approach was very crude, resulting in an average region of approximately 10–20 Mb, meaning that many hundreds of genes were harbored in such a wide location, i.e., the short list of genes was still very long. Trying to drill down on the linked region using follow-up association testing with additional microsatellites and/or with SNPs proved challenging. Although relatively successful for syndromic disorders, this approach did not yield many robust novel genes for complex diseases, largely due to the fact that the principal drivers of linkage signals are rare variants with high risk while it is now widely considered that the modest effect "common variant, common disease" hypothesis is more likely to underpin complex traits. As such, if a variant is common, it is unlikely that it will have very high impact as the selective pressure against it is so high. Thus, the "age of enlightenment" came about in 2005, when GWAS was able to detect such variants.

3 Genome-Wide Association Studies (GWAS)

In order to allow for genome-wide assessment of association, technological advances were required to move away from simple single gene assessments. The outcomes from the HapMap Project (The International HapMap Project 2003; A haplotype map of the human genome 2005) proved feasible to leverage for this endeavor as it was observed that SNPs "travel" in blocks, i.e., regions of linkage disequilibrium (LD) occur in discrete "LD blocks." It became clear that a given LD block harbors a lot of redundancy with respect to information content, where there is a limited amount of haplotype diversity and which thus can be captured by small subset of the variants in the LD block, and the rest can be subsequently inferred or "imputed" (Stephens et al. 2001).

As such, rather than having to genotype the millions of common SNPs in the genome (minor allele frequency >5 %) in order to assess the genome for association with complex traits, one can leverage hand-picked "tag SNPs" that capture all common variation and can be boiled down to just hundreds of thousands of SNPs. As a consequence, this number of SNPs can be arrayed on a single chip, thus facilitating high-throughput genotyping in a cost-effect manner.

By typically genotyping thousands of patients and thousands of controls with such arrays, the discovery of novel loci associated with common diseases has been facilitated, including for T2D (see below). Indeed, now many hundreds of variants have been reported for various common diseases, but unlike the candidate gene era in the relative "dark ages," these variants are generally highly replicatable and coincide with genes that suggest novel biology underpinning such traits. Indeed, for the first time in complex trait genetics research, there is strong consensus among investigators on the robustness of vast majority of these observations. The NIH maintains a queriable record of these reports that can be found at http://www.genome.gov/gwastudies.

The resulting data can be presented in a simple graph, where the x-axis represents the geographical order down each chromosome in turn while the y-axis reveals the strength of the association via a *P*-value. One requires a large number of cases and controls in order to overcome the inevitable correction for multiple testing given the large number of SNPs being tested; after all, every 20th SNP will yield a *P*-value of 0.05 by chance, so this cannot be considered the appropriate bar for significance in this setting; rather, it has been calculated that there is a finite level of common diversity in the genome, so a specific bar for significance at the genome-wide level is $P = 5 \times 10^{-8}$. If that level of significance is achieved, there is a strong likelihood that this signal will replicate, a step which is indeed expected from a GWAS observation before it is considered

publishable. These signals appear as spikes in these graphs, thus rendering them as plots resembling the New York skyline; indeed, they are referred to as "Manhattan plots", and what researchers are looking for are these "Empire State Building"-type signals.

When one turns to the specific signals resulting from GWAS efforts of T2D, the first such report was in 2007 (Sladek et al. 2007). In that study, a number of loci achieved genome-wide significance, with the strongest "Empire State Building" signal being across the gene encoding transcription factor 7-like 2 (*TCF7L2*, formerly known as *TCF4*) (Sladek et al. 2007). Indeed, the author of this review first published this association a year before through a rare success story of an association follow-up effort to a linkage signal (Grant et al. 2006) which has gone on to be replicated in a diversity of cohorts, ranging from Europe to Asia to Africa (Cauchi et al. 2007), and is now considered the strongest genetic association with T2D in most ethnicities (Zeggini and McCarthy 2007; Weedon 2007). Findings related to functional studies of *TCF7L2* and T2D are described below to exemplify the challenges with such follow-up efforts.

In addition to agreeing on the *TCF7L2* signal, the first T2D GWAS reports (Sladek et al. 2007; Wellcome Trust Case Control Consortium 2007; Saxena et al. 2007; Zeggini et al. 2007; Scott et al. 2007) revealed signals within loci that harbored the following genes: "hematopoietically expressed homeobox" (*HHEX*), "solute carrier family 30 (zinc transporter), member 8" (*SLC30A8*), "CDK5 regulatory subunit associated protein 1-like 1" (*CDKAL1*), "insulin-like growth factor 2 mRNA-binding protein 2" (*IGF2BP2*), "cyclin-dependent kinase inhibitor 2A/B" (*CDKN2A/B*), and an intragenic region on 11p12. However, GWAS efforts in East Asians, where the haplotypic structure is substantially different from Europeans, revealed a different set of signals, with "KQT-like subfamily, member 1" (*KCNQ1*) being the gene harboring the strongest association (Unoki et al. 2008; Yasuda et al. 2008). Furthermore, strong association with common variants within the gene encoding "solute carrier family 16, member 11" (*SLC16A11*) has been shown to confer risk for T2D in Mexicans (Williams et al. 2014).

When one has exhausted the mining of the initial GWAS efforts in a given cohort, and in order to get the most of the large financial investment, investigators combine their datasets in order to find additional "Chrysler" and "Woolworth Building"-type signals. The first such "meta-analysis" of T2D GWAS efforts in cohorts of European ancestry (Zeggini et al. 2008) revealed six additional loci corresponding to the following genes: "ADAM metallopeptidase with thrombospondin type 1 motif, 9" (*ADAMTS9*), "tetraspanin 8"/"leucine-rich repeat-containing G protein-coupled receptor 5" (*TSPAN8-LGR5*), "cell division cycle 123 homolog"/"calcium/calmodulin-dependent protein kinase ID" (*CDC123-CAMK1D*), *NOTCH2*, "thyroid adenoma associated" (*THADA*), and "juxtaposed with another zinc finger gene 1" (*JAZF1*).

Larger and larger subsequent meta-analyses through the combination of more and more datasets revealed additional common variants but with diminishingly small effects (Zeggini et al. 2008; Morris et al. 2012; Steinthorsdottir et al. 2007; Voight et al. 2010; Rung et al. 2009; Gudmundsson et al. 2007; Dupuis et al. 2010; DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium; Cho et al. 2011; Kooner et al. 2011; DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium 2014; Bouatia-Naji et al. 2009; Lyssenko et al. 2009; Ng et al. 2014), with the latest and largest trans-ethnic meta-analysis derived from European, East Asian, South Asian, Mexican, and Mexican American cohorts, made up of 26,488 cases and 83,964 controls, revealing genome-wide significant signals across the following genes: transmembrane protein 154 (*TMEM154*), signal sequence receptor, alpha/ras responsive element binding protein 1 (*SSR1-RREB1*), Fas-associated factor 1 (*FAF1*), POU class 5 homeobox 1/transcription factor 19 (*POU5F1-TCF19*), ADP-ribosylation factor-like 15 (*ARL15*), and M-phase phosphoprotein 9 (*MPHOSPH9*) (DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium 2014).

Although in excess of 80 loci have now been established for T2D, it appears that only approximately 20 % of the "missing heritability" (Manolio et al. 2009) for the disease has been found; thus, the bulk of the genetic etiology of this disease still remains to be characterized.

4 T2D Risk Prediction

Undeterred by the fact that only a minority of the missing heritability has been predicted to be uncovered for T2D, investigators have already aimed to look at the predictive power of the robust variants established to date, especially if one is to consider the cumulative risk.

When the first "low-hanging fruit" variants had been uncovered, it was initially suggested that they did not add sufficient predictive power to other nongenetic predictors already known. For instance, a study of 18 variants did show that the risk of T2D was increased by 12 % per risk allele (Meigs et al. 2008) and that risk was increased by 2.6-fold when contrasting subjects who had the lowest genotype risk score with those who had the highest. However, this risk score model did not aid in prediction when one considered familial history of diabetes and/or other known risk factors. A parallel study published in the same issue of the *New England Journal of Medicine* made a similar conclusion, with only marginal improvement in predictive power when contrasted with clinical risk factors alone (Lyssenko et al. 2008).

However, as more and more loci have been established to be associated over time, there is a general opinion that the risk predictive power is improving. A study of 40 SNPs suggested that the predicted risk of developing T2D was better in younger people (de Miguel-Yanes et al. 2011). Subsequent studies have suggested a degree of predictive power if harnessing in excess of 30 variants, particularly if combined with clinical risk factors (Hivert et al. 2011; Andersson et al. 2013; Talmud et al. 2015). But as long as the bulk of the missing heritability remains elusive, the predictive power of such collections of variants remains far from optimal and hinders diagnostic attempts, including direct to consumer testing efforts.

5 Sequencing Efforts: Missense Variants

The prevailing view is that much of the missing heritability is beyond the detection bandwidth of GWAS, where the still-to-be-characterized variants are not as common and do not confer very sizable risk of T2D. In order to detect such variants, one will need to collect larger and larger cohorts and carry out extensive sequencing efforts, of which the analytical challenges will be very demanding.

However, some success stories have been described, particularly when looking at specific geographic regions using sequencing technologies. The most obvious example is the common Arg684Ter missense variant within the "TBC1 domain family, member 4" (*TBC1D4*) gene uncovered in Greenland, which confers a staggering tenfold risk for homozygotes, but its effects appear limited to that country. Although limited in its diagnostic applicability, this approach in an isolated population did uncover a bona fide novel possible generalizable therapeutic target for the disease.

Rare variants contributing to T2D have also been reported in other contexts, with Iceland proving a rich source of such events, including uncovering variants in the genes encoding cyclin D2 (*CCND2*), peptidylglycine alpha-amidating monooxygenase (*PAM*), and pancreatic and duodenal homeobox 1 (*PDX1*) (Steinthorsdottir et al. 2014). In addition, an investigative group uncovered rare loss-of-function variants in the "solute carrier family 30" (*SLC30A8*) gene that actually confers protection from T2D, suggesting a rich possibility for intervention opportunities (Flannick et al. 2014). Furthermore, a rare variant in the HNF1 homeobox A (*HNF1A*) gene has been found specifically in Latinos (Estrada et al. 2014).

Collectively, these newly sequencing-identified variants do not explain much more of the missing heritability of T2D than what was found solely with GWAS, and the remaining such variants are going to be increasingly difficult to uncover. But as analytical and technical breakthroughs occur, then the portfolio of rare,

impactful, and not-so-impactful missense variants should be detected on a more regular basis. However, rare variants with modest effects in noncoding regions will prove far more challenging to fully elucidate.

6 GWAS Outcomes for Obesity

T2D and increased body mass index (BMI) are very well known to be heavily correlated. And as for other complex traits, many loci have been implicated in conferring risk for obesity. However, the first such locus suggested by this approach, insulin-induced gene 2 (*INSIG2*), failed to be widely replicated by others (Loos et al. 2007; Dina et al. 2007; Rosskopf et al. 2007; Lyon et al. 2007; Hotta et al. 2008).

However, now 97 loci have been robustly established by GWAS as a consequence of larger and larger meta-analyses (Loos et al. 2008; Willer et al. 2009; Thorleifsson et al. 2009; Speliotes et al. 2010; Okada et al. 2012; Monda et al. 2013; Wen et al. 2012; Locke et al. 2015; Okada et al. 2012; Wen et al. 2012). In fact the "Empire State Building" signal on chromosome 16 for obesity/increased BMI was initially uncovered in a GWAS of T2D (Frayling et al. 2007), but the authors of the study observed that the association was ablated when corrected for BMI. Another study published around the same time also implicated the same locus as a consequence of a study of population markers (Dina et al. 2007). This signal resides within the "fat mass and obesity associated" (*FTO*) gene and accounts for only approximately 1 % of the predicted genetic component to obesity.

Indeed, subjects homozygous for the *FTO* BMI-increasing allele have been found to weigh on average 3 kg more than subjects carrying the other allele (Church et al. 2010). Interestingly, children homozygous for the BMI-decreasing allele of *FTO* eat significantly less than those carrying the BMI-increasing allele, pointing to a possible mechanism where the BMI-decreasing allele protects against overeating due to neurological signaling for satiety (Cecil et al. 2008; Wardle et al. 2008).

7 Functional Follow-Up of GWAS-Implicated Loci

The fact that the loci uncovered from GWAS do not explain the entire genetic architecture of complex traits has not deterred researchers from starting to look at the functional role of the signals already reported. After all, even though each locus does not explain a big proportion of the genetic component of common traits, these highly reproducible signals could represent generalizable targets for novel therapeutic intervention opportunities.

The loci that have received the most attention in this context have been the "Empire State Building" signals that have come up in T2D and obesity. As such, this section is going to highlight what has been found with efforts on *TCF7L2* and *FTO* loci to exemplify the sort of approaches that can be used to translate these findings.

The main challenge is that when a signal is observed in a given GWAS, all that one really is observing is a signal that is overrepresented in the DNA of a set of patients as compared to a set of controls, so one has very little clue on what the causal variant or causal tissue is with respect to where the site of action is. Furthermore, there is even doubt if the actual causal gene has been identified. These issues are tackled below as we go through the functional studies outlined.

8 Causal Variant

Before one can go about resolving the function of a GWAS-implicated locus, the best place to start is to determine what precisely the tag SNPs are capturing. As mentioned above, it is very unlikely the actual causal variant was physically present on the genotyping array; rather an SNP in LD with the causal variant has "traveled" through the generations with it. Elucidating the actual causal lesion at the multitude of GWAS loci has proved very challenging, and to date only a handful of loci in the complex trait area have been resolved (Maller et al. 2012).

However, given that the *TCF7L2* locus for T2D was reported nearly a decade ago, it has received widespread attention and thus represents one of the

few loci where the causal variant is presumed to have been identified. By leveraging the fact that different ethnicities have different haplotypic structures, and assuming the same locus contributes to a trait across multiple races, one can fine map down the number of variants that the causal variant must be. These are known as "credible sets" and allow investigators to have a manageable short list of variants to work with (Maller et al. 2012).

Following on from refinement studies in Africans and resequencing efforts in African Americans (Helgason et al. 2007; Palmer et al. 2011), Bayesian modeling strongly supported the previous reports by implicating rs7903146 within the third intron as being the causal variant at this locus (Maller et al. 2012). Of particular note is that the risk T allele of rs7903146 is common in populations of European and African ancestry but not in East Asians, which is consistent with the fact that the association is present in that population but is often too difficult to detect at the variant that is somewhat more rare in that ethnicity (Chang et al. 2007; Ng et al. 2007, 2008; Ren et al. 2008; Yu et al. 2010; Zheng et al. 2012).

The same approach has now implicated short lists of variants for other GWAS-implicated T2D and obesity loci (Locke et al. 2015; Maller et al. 2012).

9 Causal Tissue

9.1 TCF7L2

Although there is wide consensus that the causal susceptibility variant at the *TCF7L2* locus is the T allele of rs7903146, it is still very unclear in which tissue(s) it exerts its effect. But with the causal lesion now determined, that gives this locus a head start over its contemporary loci which have not received the same amount of attention. Given that the variant resides in an intronic region, many researchers have investigated it from a regulatory point of view by studying aspects of allele-specific expression, splicing, and chromatin state (Gaulton et al. 2010). Many studies have been carried out to understand the mechanism by which TCF7L2 plays a regulatory role in T2D pathogenesis. With the fact that T2D is a metabolic disease, the primary tissues that have received most attention have been the pancreatic islet (Lyssenko et al. 2007), liver (Boj et al. 2012), adipose (Kaminska et al. 2012), and the intestinal endocrine L cell (Yi et al. 2005). This work is outlined below.

10 Pancreatic Islet

As the *TCF7L2* locus association is stronger in cohorts with leaner T2D cases (Palmer et al. 2011), the prevailing view is that the lesion is involved in insulin secretion as opposed to insulin resistance. It is therefore not surprising that the majority of studies published to date have focused on the pancreatic islet, with many key studies suggesting that the risk variant influences beta-cell function and thus subsequent progression to diabetes (Florez et al. 2006; Le Bacquer et al. 2012).

Leveraging small interfering RNA in human islets to deplete levels of TCF7L2 has led to an observation of reduced β-cell proliferation plus elevated β-cell apoptosis. In addition, glucose-stimulated insulin secretion has been shown to be impacted by the loss of TCF7L2 in islets derived from either mice or humans, while conversely when *TCF7L2* was overexpressed in this setting, the islets turned out to be resistant to glucose and cytokine-induced apoptosis (Shu et al. 2008). Furthermore, using a dominant-negative *TCF7L2* model in rodent INS-1 cells led to the repression of proliferation, leading to the conclusion that TCF7L2 is involved in the maintenance of beta-cell mass (Liu and Habener 2008).

There have been some reports that *TCF7L2* mRNA levels in human pancreatic islets are elevated as the number of T2D risk alleles increases and that the overexpression of *TCF7L2* in the same tissue leads to reduced insulin secretion (Cauchi and Froguel 2008; Lyssenko et al. 2007), but some other reports have not observed such an effect (Elbein et al. 2007). However, one key study did show that the risk allele of rs7903146 was more abundant in the open

chromatin fraction of pancreatic islets using formaldehyde-assisted isolation of DNA combined with sequencing (FAIRE-seq), suggesting that the role of this variant is related to an allele-specific effect on transcriptional activity, promoter usage, and/or splicing (Gaulton et al. 2010).

Despite the abundance of interesting mRNA expression results, the main debate concerning TCF7L2 in beta cells is the distinct paucity of TCF7L2 protein levels in the beta cell. Indeed, an immunohistochemical staining effort in adult mouse pancreatic islets failed to detect the TCF7L2 protein at all (Yi et al. 2005), and comparable results were seen in human beta cells (Zhao et al. 2010). Furthermore, the generation of a conditional *TCF7L2* knockout mouse model (Boj et al. 2012; da Silva Xavier et al. 2012; Savic et al. 2011) revealed that deleting the gene from β cells had no impact on embryonic development of the endocrine pancreas, β-cell proliferation, or expression of the key genes operating in that tissue. As such, there is still scope to look in other tissues.

11 Liver

When one turns to the liver-specific deletion in the *TCF7L2* knockout mouse model, hepatic lipid metabolism did turn out to be impaired (Boj et al. 2012), suggesting that the gene's function impacts postnatal metabolic adaptation rather than during the development of the embryo. Connected to this, it became clear that key genes related to glycogen metabolism were significantly reduced in *TCF7L2* knockout rodent newborn livers in contrast with their wild-type littermates, including glycogen synthase 2 (*GYS2*). Genes related to gluconeogenesis were also impacted, such as phosphoenolpyruvate carboxykinase 1(*PCK1*) and glucose-6-phosphate, catalytic subunit (*G6PC*) (Boj et al. 2012).

12 Gastrointestinal Tract

The gastrointestinal tract remains a popular area to investigate the role of *TCF7L2* function in the context of T2D. After all, the full knockout mouse turns out to be embryonic lethal as a consequence of a defect in the proliferation of crypt stem cells in the small intestine (Korinek et al. 1998, 1998).

Those studying this tissue area are motivated by the hypothesis that *TCF7L2* plays a pivotal role in glucose homeostasis via the insulinotropic hormone glucagon-like peptide 1 (GLP-1), which is known to be produced in the enteroendocrine L cells of the small intestine (Hansson et al. 2010). It is also well known that *TCF7L2* occupies the promoter of the proglucagon gene, a crucial precursor to GLP-1, and is involved in its transcriptional control based on work in intestinal GLUTag cells. In this setting, the dominant-negative mutant for *TCF7L2* depletes proglucagon mRNA levels (Yi et al. 2005), thus dramatically impacting GLP-1 levels in the intestinal tract (Yi et al. 2005).

Furthermore, immunohistochemistry with a TCF7L2-specific monoclonal antibody in human cells revealed a very restricted expression pattern that was limited to normal intestinal and mammary epithelium, together with the related carcinomas observed in the same tissues (Barker et al. 1999).

And finally, it has been known for over 15 years that missense mutations in *TCF7L2* (formerly TCF4) cause colorectal cancer (Duval et al. 2000), thus further implicating the role of this gene in the intestinal tract – see more details below.

13 Adipose Tissue

Despite there being less motivation to investigate a role for TCF7L2 in insulin resistance, there have been reports showing that *TCF7L2* expression levels are reduced in subcutaneous adipose tissue from patients with T2D (Cauchi et al. 2006). In addition, tissue-specific alternative splicing of *TCF7L2* has been reported, in particular in the adipose setting (Kaminska et al. 2012; Prokunina-Olsson et al. 2009, 2009), suggesting that the coordinated expression of this gene in this tissue is physiologically relevant and meaningful to metabolic control.

14 Connection to Cancer

As mentioned above, prior to its reported association with T2D, *TCF7L2* was already well established as a colorectal cancer susceptibility gene (Duval et al. 1999, 2000). This is partly due to the fact that TCF7L2 plays a role in regulating the expression of key genes involved in the control of the G1 to S phase transition in the cell cycle, including cyclin D1 and c-Myc (Baker et al. 2000; Tetsu and McCormick 1999). Furthermore, extensive resequencing of genomic DNA from colorectal adenocarcinomas has revealed recurrent *TCF7L2* gene fusions with its neighboring gene, *VTI1A*, thus contributing to the pathogenesis of this cancer (Bass et al. 2011).

However, the cancer *TCF7L2* plot thickens further. When one conducts a GWAS in most of the common cancers, the "Empire State Building" signal is located in a gene desert on chromosome 8q24 (Amundadottir et al. 2006; Yeager et al. 2007; Haiman et al. 2007a; Gudmundsson et al. 2007; Witte 2007; Haiman et al. 2007b; Zanke et al. 2007; Tomlinson et al. 2007). Subsequent follow-up of this multi-cancer locus revealed that the mechanism was through an extreme upstream TCF7L2 occupancy site that was involved in the transcriptional control of the *MYC* gene (Pomerantz et al. 2009; Tuupanen et al. 2009; Sur et al. 2012).

Going beyond *TCF7L2*, an interesting pattern is beginning to emerge, where many of the strongest associated GWAS-implicated T2D risk alleles protect against prostate cancer (Frayling et al. 2008), including *THADA*, *JAZF1*, and *TCF2* (also known as *HNF1B*) (Zeggini et al. 2008; Gudmundsson et al. 2007; Echwald et al. 1997).

As such, the link between T2D and cancer at the GWAS level is very clear and is a potential clue on the functional mechanism of many of these key loci in metabolism. However, irrespective of the actual causal tissue (and indeed it may be all of the above as opposed to being restricted to just one), TCF7L2 is now extensively considered a "master regulator" of the canonical Wnt signaling pathway, where it plays a crucial role in multiple development processes (He 2003; Es et al. 2003; He et al. 1998; Kinzler and Vogelstein 1996). Indeed, the mining of ChIP-seq data derived from multiple tissue-derived cell lines reveals that the list of genes bound by TCF7L2 is consistently and significantly enriched for both endocrine-related pathways and GWAS-implicated loci for various cardio-metabolic traits (Zhao et al. 2010; Johnson et al. 2014; Norton et al. 2011).

14.1 FTO

The *FTO* gene has received extensive attention, including being the subject of a *science* paper when it was characterized as encoding a "2-oxoglutarate-dependent nucleic acid demethylase" (Gerken et al. 2007). The areas of the body where it is most expressed, namely, in key areas of the brain that influence appetite (Lein et al. 2007; Gerken et al. 2007) make a lot of sense with respect to the role in the pathogenesis of obesity from an increased energy intake perspective (Cecil et al. 2008).

The mouse model lacking the *Fto* gene showed increased energy expenditure and was leaner, suggesting that targeting *FTO* could protect against obesity (Church et al. 2009, 2010; Fischer et al. 2009). Conversely, the *Fto* ubiquitously overexpressing mouse reveals an increase in body and fat mass, primarily related to increased food intake (Church et al. 2010).

Putting all this data together suggests that FTO operates in a neuropsychiatric manner via the hypothalamus impacting appetite control. These data caused a lot of excitement as FTO was increasingly looking like a generalizable target for therapeutic intervention for obesity. Then investigators looked at the locus and drilled further on what could be the actual causal gene at this genomic region.

15 Causal Gene

GWAS has now delivered a large number of genomic signals that are associated with a myriad of common diseases and complex traits. Many of these loci have been widely validated and are thus

considered robust observations by the community. However, these reports only represent a genomic signal and not necessarily, as often presumed, the localization of a culprit gene. This is due to the fact that gene expression can be controlled locally or via large genomic distances; indeed, most regulatory elements do not control the nearest genes and can reside tens or hundreds of kb away.

One clear example of this in highlighting how ignoring this basic concept in molecular biology can lead to misdirected research efforts is the strong associated signal with common obesity and *FTO*. Hundreds of scientific papers have been published studying the role of FTO in the context of obesity and/or BMI determination; however, a paper published in *Nature* in March 2014 revealed that this signal was actually an enhancer for the neighboring *IRX3* gene (Smemo et al. 2014) leveraging chromatin conformation capture (3C)-based techniques. Such approaches can aid in the identification of causal genes at such loci by identifying genomic regions that are in physical contact with the locus of interest. Once the causal genes are actually identified with greater confidence, development can take place for therapeutic and diagnostic purposes.

16 Genetics of Early Life: Implications for T2D in Later Life

It is well established that many of the risk factors for common diseases of middle and old age often have their origins in childhood. If one can determine the genetic basis to these observations, then possible early stage interventions could be developed.

For instance, a link between low birth weight and the development of metabolic disease in adulthood has been established (Whincup et al. 2008). Genetic variation at the locus harboring the glucokinase (*GCK*) gene, which encodes a protein involved in pancreatic glucose sensing and has been implicated by GWAS analyses of T2D-related traits, has been shown to have differing effects on birth weight depending on whether it is carried by the mother or the fetus (Hattersley et al. 1998). This exemplifies the importance of endogenous fetal insulin-secreting capacity in order to determine antenatal growth, which is also known as the "fetal insulin hypothesis" (Hattersley and Tooke 1999).

Taking this concept one step further, a study consisting of in excess of 15,000 subjects and over 8,000 mothers showed that each maternal risk-conferring rs7903146 allele within *TCF7L2* increased birth weight while the combined effect of three to four maternal risk-conferring alleles of *TCF7L2* and *GCK* showed an even more marked impact (Freathy et al. 2007); however, the *TCF7L2* interaction with birth weight is not universally agreed upon (Mook-Kanamori et al. 2009; Pulizzi et al. 2009), possibly due to statistical power differences between study designs.

Such reports have led to subsequent studies looking at other T2D GWAS loci in the context of birth weight, with positive reports for loci including *CDKAL1*, *HHEX-IDE*, *CDKN2A/B*, *JAZF1*, and *IGFBP2* (Pulizzi et al. 2009; van Hoek et al. 2009; Freathy et al. 2009; Zhao et al. 2009; Morgan et al. 2010). However, the full significance of these observations requires additional follow-up to fully understand the mechanism of action.

A meta-analysis of six European ancestry cohorts with GWAS data for birth weight identified variants associated with lower birth weight (Freathy et al. 2010), with a subsequent larger meta-analysis from the same consortium revealing additional loci (Horikoshi et al. 2013). Of particular note were the adenylate cyclase 5 (*ADCY5*) and *CDKAL1* loci, as they are already established for T2D; however, it appears that their primary role is in much earlier life.

Another influence of childhood on adulthood is in the context of obesity. Indeed, approximately 70 % of children who are obese during adolescence go on to become obese adults (Nicklas et al. 2001; Whitaker et al. 1997; Parsons et al. 1999) and are thus at much higher risk of disease in later life, including T2D. It has therefore been important to uncover the genetic determinants of childhood obesity as it would not only have implications for pediatric health but also for diseases of old age. Furthermore, it is also highly likely that it is easier to distill out genetic loci

contributing to obesity in the pediatric setting where the influence of environmental confounders is lessened.

Cross-sectional cohort studies have consistently reported an age-dependent effect of high-risk *FTO* variants on BMI. The first reports revealed that there was no influence on fetal growth or birth weight, while the effect on BMI became most pronounced by the age of 7 years old (Frayling et al. 2007). Indeed, a subsequent study found a negative association between the key *FTO* variant and BMI before the age of two years old and only took effect after that time point (Hardy et al. 2010). Furthermore, there is a growing picture that very few of the risk alleles first detected in the adult GWAS analyses of BMI have an influence on birth weight (Andersson et al. 2010), which is in contrast to risk variants reported for T2D (Manco and Dallapiccola 2012).

The Early Growth Genetics Consortium went on to conduct the largest GWAS for childhood obesity reported to date (Bradfield et al. 2012) and observed many of the detected loci in adults but with a much lower sample number, supporting the notion that the pediatric setting is a more sensitive setting to uncover obesity genes. The study also uncovered two novel loci, homeobox B5 (*HOXB5*) and olfactomedin 4 (*OLFM4*).

17 LADA: A Major Confounder in Genetic Studies of T2D

With the hunt for more and more subtle effect size variants in T2D-related traits, there is an increasing risk that artifacts will be detected and inappropriate assignment of loci to the disease. After all, the *TCF7L2* locus confers a relative risk of 1.4 while the more recent loci are closer to 1.1. As sample sizes increase in ever bigger meta-analyses, the likelihood that comorbidities are driving some new signals is ever more likely, especially when hunting for loci that yield sub 1.1 odds ratios.

A clear example of this is the fact that among any given group of random T2D patients, there will be in fact antibody-positive subjects present at a frequency of 8–10 % (Grant et al. 2010; Basile et al. 2014). There is good recent evidence to believe that subjects, often referred to as "latent autoimmune diabetes in adults" (LADA) cases will be driving some of the more recent signals reported in massive meta-analyses of T2D GWAS. Indeed, the well-established autoimmune loci harboring the GLIS family zinc finger 3 (*GLIS3*) and "zinc finger, MIZ-type containing 1" (*ZMIZ1*) genes have been reported to be associated with T2D (Andersen et al. 2014). Added to that, the most recent GWAS meta-analysis of T2D in African Americans reported two loci (Ng et al. 2014), *HLA-B* and *INS-IGF2*, both of which are well-known type 1 diabetes loci.

18 Summary

Although there have been huge advances in elucidating the genetics of T2D-related traits, much is still to be uncovered. Apart from the missing heritability that remains to be characterized, there remain challenges when it comes to determining the causal tissue, the causal variant, and even the causal gene for many of the established GWAS loci. Once advances are made in these key areas, a better understanding of the genetic etiology of T2D will be in place, and new therapeutic and diagnostic opportunities should present themselves.

19 Cross-References

- ▶ Epidemiology of Obesity in the United States
- ▶ Genetics of Cardiovascular Risk in Obesity
- ▶ Genetics of Obesity
- ▶ Metabolic Syndrome in South Asians
- ▶ Obesity in East Asia
- ▶ Obesity in Latin America
- ▶ Obesity in Sub-Saharan Africa
- ▶ Overview of Metabolic Syndrome

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Genetics of Lipid Disorders

11

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Contents

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Abstract

This chapter focuses on the genetics of common lipid disorders, collectively referred to as "dyslipidemia," a component of the metabolic syndrome (MetSyn). We begin by providing a brief background on the lipids discussed in this chapter. Then, we discuss specific variants in key candidate genes and their role in related pathways that have been associated with individual lipid levels and dyslipidemia in larger-scale studies. In addition, we comment on associations observed in genome-wide association studies (GWAS) and sequencing studies. We also discuss how the use of more sophisticated statistical methods (e.g., genetic risk scores and pathway modeling) are helping to better understand the collective effects of multiple variants in multiple genes on these lipid traits. We conclude by providing perspectives for future directions.

Keywords

Obesity • Metabolic syndrome • Dyslipidemia • Genetics • Cholesterol • Triglycerides

1 Introduction

Dyslipidemia is characterized by an aggregation of lipoprotein abnormalities including high serum triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C), and high or increased small low-density lipoprotein cholesterol (LDL-C). Lipoproteins, which contain lipids and apolipoproteins (APO), are responsible for transporting water-insoluble lipids (e.g., cholesterol and TG) in plasma from the intestines and liver, where they are absorbed and synthesized, respectively, to peripheral tissues (e.g., muscle, adipose) for utilization, processing, and/or storage (Kwan et al. 2007).

There are several subtypes of lipoproteins that have specific functions including the following (from smallest to largest): (1) chylomicrons, which transport dietary TG from the intestines to the peripheral tissue and liver; (2) very LDL (VLDL) particles, which transport TG from the liver to peripheral tissues; (3) intermediate density lipoproteins (IDL), which are produced from VLDL particle metabolism and may be taken up by the liver or further hydrolyzed to LDL; and (4) HDL, which is key in "reverse cholesterol transport" or shuttling cholesterol from peripheral cells to the liver (Kwan et al. 2007). When LDL becomes lipid-depleted, small dense LDL (sdLDL) particles are formed that have a lower affinity for the LDL receptor (LDLR), more susceptibility to oxidation and a higher affinity for macrophages, and, thus, sdLDL particles can also contribute to the atherosclerotic process (Austin et al. 1990; Littlewood and Bennett 2003). Plasma triglycerides (TG) integrate multiple TG-rich lipoprotein particles, predominantly, intestinally synthesized chylomicrons in the postprandial state and hepatically synthesized VLDL in the fasted state.

Dyslipidemia is defined within the context of the metabolic syndrome (MetSyn), which is a clustering of metabolic traits including dyslipidemia as well as hypertension (raised systolic and/or diastolic blood pressure), dysglycemia (high fasting glucose), and obesity (high body mass index (BMI) and/or waist circumference). Multiple definitions for MetSyn have been proposed by organizations including the World Health Organization (WHO) (Alberti and Zimmet 1998), European Group Insulin Resistance (EGIR) (Balkau and Charles 1999), National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (2001), International Diabetes Federation (IDF) (Alberti et al. 2005), American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) (Grundy et al. 2006), and the joint interim statement proposed by the AHA/NHLBI, IDF, and others (Alberti et al. 2009). The dyslipidemia component of MetSyn has been fairly consistently defined as having TG $\geq$150 mg/l, HDL-C $<$40 mg/dl (1.03 mmol/l, in males) or $<$50 mg/dl (1.29 mmol/l in females) or drug treatment for elevated TG or low HDL-C (2001; Alberti et al. 2005, 2009). However, the World Health Organization (WHO) (Alberti and Zimmet 1998) proposed slightly lower limits for HDL-C (male: $<$0.9 mmol/l (35 mg/dl); female: $<$1.0 mmol/l (39 mg/dl)), and the EGIR (Balkau and Charles 1999) recommended that dyslipidemia be defined by

HDL-C <1.0 mmol/l (39 mg/dl) or TG >2.0 mmol/l (177 mg/dl). Although the aforementioned guidelines exist, many authors have chosen to use cut points other than those specific in the context of MetSyn when defining dyslipidemia; therefore, in this chapter, we attempt to clarify the specific values and parameters used when referring to dyslipidemia. Furthermore, although LDL-C remains the primary target of therapy for the management of high blood cholesterol, there is currently no recommended value for LDL-C levels in the context of MetSyn. However, we note that the NCEP ATPIII guidelines for recommended drug therapy are based on LDL-C values ranging from ≥100 mg/dl to ≥190 mg/dl, depending on the presence/absence of other coronary heart disease (CHD) risk factors (Grundy et al. 2004).

Dyslipidemia is quite common in developed nations, and its prevalence is rising worldwide, which may be attributed, in part, to the rising rates of overweight and obesity (Halpern et al. 2010). According to the National Health and Nutrition Examination Survey (NHANES) III, conducted in 1988–1994 in the USA, which used the NCEP ATP III criteria, the age-adjusted prevalence of dyslipidemia defined by high TG or low HDL-C was approximately 30.0 % and 37.1 %, respectively (Ford et al. 2002). In a study using the Health Survey for England (HSE) (2003–2006) survey data and NHANES (1999–2006) data, the prevalence of low HDL-C (defined in both males and females as <40 mg/dl) was 10.0 % in England and 19.2 % in the USA (Martinson et al. 2011). Interestingly, trends in the USA and England have indicated that during the past two decades, there has been an increase in the proportion of individuals diagnosed with high cholesterol (≥240 mg/dl) that achieve therapeutic control (Roth et al. 2010). In the USA, 54.0 % of men (95 % CI, 47.6–60.4) and 49.7 % of women (95 % CI, 44.3–55.0) in 2006 compared to 10.8 % of men (95 % CI, 8.0–13.6) and 8.6 % (95 % CI, 6.7–10.6) of women in 1993 had high total serum cholesterol and were on cholesterol-lowering medication (Roth et al. 2010). In England, in 2006, 35.5 % of men (95 % CI, 32.8–38.3) and 25.7 % of women (95 % CI, 23.4–28.1) were on cholesterol-lowering medication as opposed to 0.6 % of men (95 % CI, 0.3–1.3) and 0.4 % of women (95 % CI, 0.1–0.7 %) in 1993 (Roth et al. 2010). Prevalence rates may also vary by whether or not relevant drug treatments have been considered, which should include not only cholesterol-lowering therapies (e.g., statins) but other drugs (e.g., tamoxifen, glucocorticoids) that are known to alter TG and cholesterol levels (Garg and Simha 2007).

Although the environment plays a substantive role in the manifestation of dyslipidemia, there is a strong genetic component. Heritability estimates reported for dyslipidemia typically range from 0.20 to 0.60 (Edwards et al. 1997; Goode et al. 2007; Herbeth et al. 2010; Kronenberg et al. 2002; Wang and Paigen 2005), and a recent review suggests HDL-C heritability may even extend up to 80 % (Rankinen et al. 2015). There have been many common genetic variants in the form of single nucleotide polymorphisms (SNPs) that have been associated with dyslipidemia. In this chapter, we update our previous summary of associations that have been reported between SNPs with a minor allele frequency (MAF) greater than 0.05 and HDL-C, LDL-C, and TG levels (Nock and Chandran Pillai 2012). We note that, together, common variants have been estimated to explain less than 10 % of HDL-C levels in the general population (Kronenberg et al. 2002); however, we purport that this is likely an underestimation of the genetic contribution and that more elegant statistical modeling methods that combine SNPs in a more biologically meaningful way will enable a better estimate and understanding of the collective role that genetic variants play in the manifestation of dyslipidemia and MetSyn. In the last section of this chapter, we review studies that have undertaken such more complex modeling strategies to better understand the aggregate effects of SNPs in dyslipidemia and MetSyn and provide insights to additional potential future directions.

2 Genetics of HDL-C

In Table 1, we list common SNPs associated with HDL-C that were initially tabulated in Boes et al. (2009), which reviewed studies with sample

sizes of 500 or greater, as well as other common SNPs in large studies that were identified in and since our previous review (Nock and Chandran Pillai 2012). Variants in Table 1 are organized by gene acronyms which are listed in alphabetical order. Below, we describe variants in genes based on their involvement in relevant biological pathways including HDL-C synthesis and metabolism as well as relevant transport, receptor, and ligand-binding (via apolipoproteins) mechanisms.

2.1 Variation in Genes Involved in HDL-C Synthesis and Metabolism

One of the most notable genes involved in HDL-C synthesis and metabolism is the cholesterol ester transfer protein (CETP) gene located on chromosome 16 (16q21) whose variants have been associated with HDL-C. CETP is a key plasma protein that mediates the transfer of esterified cholesterol from HDL to APOB (see section "Variation in Genes Involved in HDL-C Transport and Binding") containing particles in exchange for TG. Three common polymorphisms (Table 1: TaqIB (rs708272); −629C > A (rs1800775); Ile405Val (rs5882)) can all modestly inhibit CETP activity and have been consistently associated with higher HDL-C levels (Bernstein et al. 2003; Blankenberg et al. 2004; Boekholdt and Thompson 2003; Boekholdt et al. 2005; Borggreve et al. 2005; Eiriksdottir et al. 2001; Freeman et al. 2003; Kathiresan et al. 2008; Klerkx et al. 2003; Tai et al. 2003b; Thompson et al. 2008; Shakhtshneider et al. 2014).

Another key gene involved in HDL-C metabolism is lipoprotein lipase (LPL) located on chromosome 8 (8p22), which encodes an enzyme involved in lipolysis of TG-containing lipoproteins such as VLDL and chylomicrons (Miller and Zhan 2004) that generate free fatty acids (FFA) that can be taken up by the liver, muscle, and adipose tissues (Kwan et al. 2007). Thus, LPL may only affect HDL-C levels indirectly (Lewis and Rader 2005) but can affect LDL levels directly (see section "Genetics of LDL-C"). Several SNPs in LPL have been associated with HDL-C (Table 1) (Ahn et al. 1993; Corella et al. 2002; Holmer et al. 2000; Klos et al. 2006; Komurcu-Bayrak et al. 2007; Lee et al. 2004; Nettleton et al. 2007; Senti et al. 2001; Wittrup et al. 1999), and many of these SNPs are in strong linkage disequilibrium (LD) with each other (e.g., rs320, rs326, rs13702, rs10105606) (Boes et al. 2009; Heid et al. 2008).

The hepatic lipase (HL; LIPC) gene located on chromosome 15 (15q21) encodes a glycoprotein that is synthesized by liver cells (hepatocytes) and catalyzes the hydrolysis of TG and phospholipids (Miller et al. 2003), and following hydrolysis of TG by LPL, VLDL particles are reduced to IDL particles that may be further hydrolyzed by HL/LIPC to LDL or taken up by the liver (Kwan et al. 2007). Several HL/LIPC SNPs have been associated with HDL-C with, perhaps, the most consistent associations with rs1800588 and rs2070895 (Table 1; Andersen et al. 2003; Costanza et al. 2005; de Andrade et al. 2004; Fang and Liu 2002; Grarup et al. 2008; Iijima et al. 2008; Isaacs et al. 2004; Kathiresan et al. 2008; Ko et al. 2004; McCaskie et al. 2006; Nettleton et al. 2007; Tai et al. 2003a; Talmud et al. 2002b; Whiting et al. 2005; Yamada et al. 2007).

The endothelial lipase (EL; LIPG) gene, located on chromosome 18 (18q21.1), is an enzyme expressed in endothelial cells that, in the presence of HL/LIPC, metabolizes larger (HDL3) to smaller (HDL2) HDL-C particles and increases the catabolism of APOA-I (see section "Variation in Genes Involved in HDL-C Transport and Binding") (Jaye and Krawiec 2004). Several EL/LPIG polymorphisms have been associated with HDL-C levels (Table 1; Hutter et al. 2006; Ma et al. 2003; Mank-Seymour et al. 2004; Paradis et al. 2003; Tang et al. 2008; Yamakawa-Kobayashi et al. 2003). Only the nonsynonymous SNP, rs2000813, has been consistently associated with HDL-C levels in African-Americans (Hutter et al. 2006; Tang et al. 2008; Yamakawa-Kobayashi et al. 2003).

The lecithin-cholesterol acyltransferase (LCAT) gene, located on chromosome 16 (16q22.1), catalyzes the esterification of free cholesterol and metabolizes larger HDL-C particles to smaller HDL-C particles in the presence of cofactor APOA-I (Klos and Kullo 2007;

Table 1 Genetic polymorphisms associated with HDL-C

Gene	Polym.	rs number	MAF	Ethn.	Sample size	Results (effect size, p-value)	Reference
ABCA1	C (−297)T	rs2246298	0.25 (T)	A	1625 (GP)	p = 0.0455	(Shioji et al. 2004b)
ABCA1	G (−273)C	rs1800976	0.40 (C)	A	1626 (GP); 735 (HBP)	+1.9/+2.7 mg/dl (1/2copies); p = 0.03 +1.9/+5.0 mg/dl (1/2 copies); p = 0.03	(Shioji et al. 2004b)
ABCA1	G (−273)C	rs1800976	0.38 (T)	Tu	2332 (GP)	+0.7/+1.9 mg/dl (1/2 copies); p < 0.02	(Hodoglugil et al. 2005)
ABCA1	G378C	rs1800978	0.13 (C)	W	5040 (GP)	−1.2/−2.7 mg/dl (1/2 copies); p = 0.03	(Porchay et al. 2006)
ABCA1		rs3890182	0.13 (A)	W	5287 (GP)	−1/−3 mg/dl (1/2 copies); p = 0.003	(Kathiresan et al. 2008)
ABCA1		rs2275542		A	<1880 (GP)	p = 0.006	(Shioji et al. 2004b)
ABCA1		rs2515602	0.27	B	1943 (P)	M; p = 0.034; F; p < 0.001	(Klos et al. 2006a)
ABCA1	G596A	rs2853578	0.28 (A)	W	2468 (CVD) 834 (Co)	0.2/+2.8 mg/dl (1/2 copies); p = 0.02	(Whiting et al. 2005)
ABCA1	G2310A	rs2066718	0.03 (A)	W	9123 (P)	F: higher levels in carriers; p = 0.02	(Frikke-Schmidt et al. 2004)
ABCA1	G2706A	rs2066718	0.05 (A)	Tu	2458 (GP)	M: +2.0 mg/dl for heteroz.; p < 0.01	(Hodoglugil et al. 2005)
ABCA1	G2472A G2868A	rs2066718	0.06 (A)	Tu	2105 (GP)	F: +3.1 mg/dl for carriers; p = 0.0005	(Hodoglugil et al. 2005)
ABCA1	1883 M	rs4149313	0.12 (G)	W	9123 (P)	F: + heteroz.; p = 0.05	(Frikke-Schmidt et al. 2004)
ABCA1	32b. + 30 ABC32			W	1543 (P)	−2.2 mg/dl for carriers; p = 0.0040	(Costanza et al. 2005)
ABCA1	R1587K	rs2230808	0.24 (A)	W	9123 (P)	M: −1.5 mg/dl for heteroz.; p = 0.008	(Frikke-Schmidt et al. 2004)
ABCA1	G4759A	rs2230808	0.26 (K)	W	779 (CVD)	−1.5 mg/dl for carriers; p = 0.03	(Clee et al. 2001)
ABCA1	50b.3038 ABC50	rs41474449	.	W	1543 (P)	+1.6 mg/dl for carriers; p = 0.043	(Costanza et al. 2005)
ABCA1		rs3890182	0.12 (A)	EA	25,167	p = 4.53E-07	(Dumitrescu et al. 2011)
ADH5	A > G	rs2602836	0.44 (G)	EA AA, A	188,577 (Meta)	p = 5 × 10–9	Willer et al. (2013)
ANGPTL1	G > A	rs4650994	0.49 (A)	EA AA, A	188,577 (Meta)	p = 7 × 10–9	Willer et al. (2013)
ATG7	C > T	rs2606736	0.37(T)	EA AA, A	188,577 (Meta)	p = 5 × 10–8	Willer et al. (2013)

(*continued*)

Table 1 (continued)

Gene	Polym.	rs number	MAF	Ethn.	Sample size	Results (effect size, p-value)	Reference
APOA1	T84C (HaeIII)	rs5070	0.23 (C)	A	1637 (GP)	+1.9/+5.4 mg/dl (1/2copies); p = 0.0005	(Shioji et al. 2004a)
APOA1	MspI RFLP	rs5069	0.31 (C)	B	3831 (P)	M/F; p = n.s/0.022	(Brown et al. 2006)
APOA1		rs28927680	0.93 (G)	EA	25,167	p = 8.61E-09	(Dumitrescu et al. 2011)
APOA1		rs964184	0.86 (C)	EA	25,167	p = 6.08E-10	(Dumitrescu et al. 2011)
APOA5-A4/A1		rs964184	0.14 (G)	C	5547	−0.03 (−0.04 to −0.01); p = 0.007	(van de Woestijne et al. 2014)
APOA5	−1131 T > C	rs662799	0.06 (C)	UK	1696 (P)	−1.5 mg/dl/−5.4 mg/dl (1/2 copies); p = 0.04	(Talmud et al. 2002a)
APOA5	−1131 T > C	rs662799	0.07 (C)	W	1596 (SA PHIR)	−3.5 mg/dl per copy; p = 0.00038	(Grallert et al. 2007)
APOA5	−1131 T > C	rs662799	0.23–0.30 (C)	C, Ma	2711 (C); 707 (M)	−2.3/−5.4 mg/dl 1/2 copies; p <0.0001 −1.2 /−8.1 mg/dl1/2 copies; p <0.0001	(Lai et al. 2003)
APOA5	−1131 T > C	rs662799	0.34 (C)	A	521 Ho Co	−3.3 mg/dl per copy; p < 0.001	(Yamada et al. 2007)
APOA5	−3A > G	rs651821	0.07	W	2056 (P)	M; p = 0.30; F; p = 0.26	(Klos et al. 2006a)
APOA5	−3A > G	rs651821	0.18 (G)	C	2711 (GP)	−2.3/−5.8 mg/dl 1/2 copies; p < 0.0001	(Lai et al. 2003)
APOA5	−3A > G	rs651821	0.34 (C)	A	5207 (Ho Co, P)	−2.7 mg/dl per copy; p < 0.001	(Yamada et al. 2007)
APOA5	−3A > G	rs651821	0.36 (G)	A	2417 (Ho Co)	−3.9/−7.0 mg/dl 1/2 copies; p <0.001	(Yamada et al. 2008)
APOA5	S19W	rs3135506	0.06 (W)	UK	1660 (P)	−1.9/+1.2 mg/dl (1/2 copies); p = 0.02	(Talmud et al. 2002a)
APOA5	56C > G	rs3135506	0.06 (G)	W	2347 (P)	−2.0 mg/dl for carriers; p = 0.008	(Lai et al. 2004)
APOA5		rs2072560	0.16 (A)	C	2711 (GP)	−1.9/−3.9 mg/dl (1/2 copies); p = 0.003	(Lai et al. 2003)
APOA5	IVS3 + 476 G > A	rs2072560		Ma	707 (P)	−0.4/9.3 mg/dl (1/2 copies); p = 0.004	(Qi et al. 2007)
APOA5	V153M	rs3135507		W	2557	F: −3.5 mg/dl for carriers; p <0.01	(Hubacek 2005)
APOA5	+553	rs2075291	0.07 (T)	A	5206 Ho Co	−4.6 mg/dl per copy; p < 0.001	(Yamada et al. 2007)
APOA5	Gly185Cys	rs2075291	0.08 (T)	A	2417 Ho Co	−5.0/−11.2 mg/dl (1/2 copies); p <0.001	(Yamada et al. 2008)
APOA5	1259 T > C	rs2266788	0.18 (C)	C	2711 (GP)	−2.3/−3.1 mg/dl 1/2 copies; p < 0.0001	(Lai et al. 2003)
APOB		rs11902417	0.78 (G)	E	17723	p = 3.7 × 10–7	(Waterworth et al. 2010)
APOC3	C455T	rs2854116	0.41 (C)	In	1308 (P)	−3.1/−5.4 mg/dl (1/2 copies); p < 0.05	(Lahiry et al. 2007)
APOC3	PvuII	rs618354	0.49	A	F, 291 (GP)	F: +0.1/−4.2 mg/dl 1/2 copies;p = 0.029	(Kamboh et al. 1999)

APOC3	Sst1 RFLP	rs5128	0.09 (S2)	W	M, 1219 (P)	M: −1.8 mg/dl for carriers; p = 0.04.	(Russo et al. 2001)
APOC3	3′-utr/Sac I	rs5128	0.09 (+)	Hu	713 (P)	−5.0 mg/dl for heteroz.; p = 0.0014	(Hegele et al. 1995)
APOC3	3238C > G	rs5128	0.07 (S2)	W	906 (GP)	+1.9 mg/dl for carriers; p = 0.079	(Corella et al. 2002)
APOE	Cys112Arg	rs429358	0.16 (A)	N	3575	p = 0.001	(Povel et al. 2011)
APOE	Cys112Arg	rs429358	0.12 (A) (E4)	L	1030	1.98 (1.05–3.74); men (n = 425); high versus low	Smalinskiene et al. (2013)
BTN2A1	C > T	rs6929846		J; K	7471; 3529	CT or TT versus CC, p = 0.005; p = 0.01	Fujimaki et al. (2011)
C4orf52	G > A	rs10019888	0.18 (A)	EA AA, A	188,577 (Meta)	p = 5 × 10–8	Willer et al. (2013)
CETP	G2708A	rs12149545	0.30 (A)	W	2683 GP 556 CVD	+1.9 mg/dl per copy; p < 0.001	(McCaskie et al. 2007)
CETP	G2708A	rs12149545	0.31 (A)	W	709 (CVD)	+1.5/+3.5 mg/dl (1/2 copies); p = 0.0016	(Klerkx et al. 2003)
CETP		rs3764261	0.14 (T)	C	4192	+0.07 mg/dl; p = 4.3 × 10–14	(Liu et al. 2011)
CETP	G971A	rs4783961	0.49 (A)	W	709 (CVD)	+1.2/+1.9 mg/dl (1/2 copies); p = 0.09	(Klerkx et al. 2003)
CETP	C629A	rs1800775	0.48 (A)	W	7083 (P)	+2.7/+5.4 mg/dl (1/2 copies); p <0.001	(Borggreve et al. 2005a)
CETP	C629A	rs1800775	0.51 (A)	W	847 M; 873 F (P)	+4.2 mg/dl for homoz.; p < 0.002	(Bernstein et al. 2003)
CETP	C629A	rs1800775	0.49 (A)	W	5287 (GP)	+3/+5 mg/dl (1/2 copies); p = 2 × 10–29	(Kathiresan et al. 2008)
CETP	C629A	rs1800775	0.42 A	A	4050 (GP)	+2.2/+3.4 mg/dl 1/2 copies; p = 3.28 × 10–9	(Tai et al. 2003b)
CETP	C629A	rs1800775	0.48 (A)	W	2683 GP; 556 CVD	+2.7 mg/dl per copy; p <0.001	(McCaskie et al. 2007)
CETP	C629A	rs1800775	0.40 (A)	W	1214 (CVD); 574 (Co)	CVD: +2.0/3.5 mg/dl (1/2 copies) p = 0.02 Co: +3.3/6.1 mg/dl (1/2 copies); p = 0.05	(Blankenberg et al. 2004)
CETP	C629A	rs1800775	0.44 (A)	W	709 (CVD)	+0.8/3.9 mg/dl (1/2 copies); p < 0.0001	(Klerkx et al. 2003)
CETP	C629A	rs1800775	0.50 (A)	W	309 (MI) 757 (Co)	+1.9/6.1 mg/dl (1/2 copies); p <0.0001	(Eiriksdottir et al. 2001)
CETP	C629A	rs1800775	0.48 (A)	W	498 (CVD) 1107 (Co)	+2.9/4.4 mg/dl (1/2 copies); p < 0.001	(Freeman et al. 2003)
CETP	Taq1B	rs708272	0.40 (B2)		13,677 (Meta)	+1.2/+3.8 mg/dl (1/2 copies); p < 0.0001	(Boekholdt et al. 2005)
CETP	Taq1B	rs708272			>10,000 (Meta)	+4.6 mg/dl for homoz.; p <0.00001	(Boekholdt and Thompson 2003)

(*continued*)

Table 1 (continued)

Gene	Polym.	rs number	MAF	Ethn.	Sample size	Results (effect size, p-value)	Reference
CETP	Taq1B	rs708272	0.42 (B2)	W	7083 (P)	+2.7/5.0 mg/dl (1/2 copies); $p < 0.001$	(Borggreve et al. 2005b)
CETP	Taq1B	rs708272	0.44 (B2)	W	2916 (P)	+2.5/4.7 mg/dl (1/2 copies); $p < 0.001$	(Ordovas et al. 2000)
CETP	Taq1B	rs708272	0.43 0.26 (A)	W B	2056 1943 (P)	$p < 0.01$; $p < 0.02$	(Klos et al. 2006b)
CETP	Taq1B	rs708272	0.44 0.27 (A)	W B	8764 (P)	+2.3/5.8 mg/dl (1/2 copies); $p < 0.001$ +3.8/9.8 mg/dl (1/2 copies); $p < 0.001$	(Nettleton et al. 2007)
CETP	Taq1B	rs708272	0.41 (A)	W	1503 (P)	+2 /+5 mg/dl (1/2 copies); $p < 0.001$	(Sandhofer et al. 2008)
CETP	Taq1B	rs708272	0.33 (A)	A	4207 (GP)	+2.5/4.4 mg/dl (1/2 copies); $p = 1.25 \times$ 10–10	(Tai et al. 2003b)
CETP	Taq1B	rs708272	0.40 (A)	A	1729 (GP)	M: +1.2/3.5 mg/dl (1/2 copies); $p =$ 0.096 F: +1.9/6.2 mg/dl (1/2 copies); $p < 0.001$	(Tsujita et al. 2007)
CETP	Taq1B	rs708272	0.42 (A)	W	2683 GP; 556 CVD	+2.7 mg/dl per copy; $p < 0.001$	(McCaskie et al. 2007)
CETP	Taq1B	rs708272	0.42 (A)	W	2392 CVD; 827 Co	+1.7/3.6 mg/dl (1/2 copies); $p < 0.001$	(Whiting et al. 2005)
CETP	Taq1B	rs708272	0.40 (A)	W	1464 CVD	+2.1/3.0 mg/dl (1/2 copies); $p = 0.003$	(Carlquist & Anderson 2007)
CETP	Taq1B	rs708272	0.41 (A)	W	1200 CV; 571 (Co)	+2.6/+4.3 mg/dl (1/2 copies); $p < 0.02$	(Blankenberg et al. 2004)
CETP	Taq1B	rs708272	0.44 (A)	W	499 CVD; 1105 Co	+2.1/3.6 mg/dl (1/2 copies); $p < 0.001$	(Freeman et al. 2003)
CETP	Taq1B	rs708272	0.45 (A)	WS	851 265 Co; 586 TC	$p = 0.014$ (2 copies)	Shakhtshneider et al. (2014)
CETP	+784CCC	rs34145065	0.39 (A)	W	709 (CVD)	+1.2/3.5 mg/dl (1/2 copies); $p = 0.0009$	(Klerkx et al. 2003)
CETP	A373P	rs5880	0.05 (A)	W	8467 P; 1636 CV	5.4 mg/dl for heteroz.; $p < 0.0001$	(Agerholm-Larsen et al. 2000)
CETP	Ile405Val	rs5882			>10,000 (Meta)	+1.9 mg/dl for homoz.; $p < 0.00001$	(Boekholdt and Thompson 2003)
CETP	A +16G/ Ex.14	rs61212082	0.32 (A)	W	6421 (P)	M: +1.5/2.3 mg/dl (1/2 copies); $p =$ 0.002 F: +0.0/+2.3 mg/dl (1/2 copies); $p =$ 0.007	(Isaacs et al. 2007)

CETP		rs61212082	0.30 (A)	W	1208 (CVD) 572 (Co)	+1.4/+3.1 mg/dl (1/2 copies); p = 0.08 +0.3 /+8.4 mg/dl (1/2 copies); p = 0.003	(Blankenberg et al. 2004)
CETP		rs61212082	0.30 (A)	W	498 (CVD); 1108 (Co)	+1.2/+3.5 mg/dl (1/2 copies); p < 0.05 +1.5 /+1.5 mg/dl (1/2 copies); p < 0.05	(Freeman et al. 2003)
CETP	D442G	rs2303790b	0.03 (A)	A	3469 (He Ex)	+4.9 mg/dl for heteroz.; p < 0.001	(Zhong et al. 1996)
CETP	R451Q	rs1800777	0.04 (A)	W	8467 (P); 1636 (CVD)	5.4 mg/dl for heteroz.; p < 0.001	(Agerholm-Larsen et al. 2000)
CETP	G + 82A/Ex15	rs1800777	0.03 (A)	W	1071 CV; 532 Co	3.6/5.2 mg/dl for heteroz.; p = 0.06/0.07	(Blankenberg et al. 2004)
CETP		rs12596776	0.90 (C)	EA	25,167	p = 1.18E-05	(Dumitrescu et al. 2011)
CETP		rs9989419	0.39 (A)	EA	25,167	p = 1.71E-53	(Dumitrescu et al. 2011)
CPS1	A > C	rs1047891	0.33 (C)	EA AA, A	188,577 (Meta)	p = 5 × 10–8	Willer et al. (2013)
DAGLB	G > A	rs702485	0.45 (A)	EA AA, A	188,577 (Meta)	p = 7 × 10–12	Willer et al. (2013)
FAM13A	A > G	rs3822072	0.46 (G)	EA AA, A	188,577 (Meta)	p = 4 × 10–12	Willer et al. (2013)
FTO	A > G	rs1121980	0.43 (G)	EA AA, A	188,577 (Meta)	p = 7 × 10–9	Willer et al. (2013)
GATA2	C > A	rs7431368		S	2386 CAD; 2171 C	B = 1.67; s.e. = 0.82; p = 0.043	Muiya et al. (2014)
GSK3B	T > C	rs6805251	0.39 (C)	EA AA, A	188,577 (Meta)	p = 1 × 10–8	Willer et al. (2013)
HAS1	A > G	rs17695224	0.26 (G)	EA AA, A	188,577 (Meta)	p = 2 × 10–13	Willer et al. (2013)
HDGF-PMVK	G > T	rs12145743	0.34 (T)	EA AA, A	188,577 (Meta)	p = 2 × 10–8	Willer et al. (2013)
IKZF1	G > T	rs17695224	0.32 (T)	EA AA, A	188,577 (Meta)	p = 1 × 10–8	Willer et al. (2013)
KAT5	A > G	rs12801636	0.23 (G)	EA AA, A	188,577 (Meta)	p = 3 × 10–8	Willer et al. (2013)
LCAT	Gly230Arg			W	156 low; 160 high	Variant sig. only in low-HDL group	(Miettinen et al. 1998)

(*continued*)

Table 1 (continued)

Gene	Polym.	rs number	MAF	Ethn.	Sample size	Results (effect size, p-value)	Reference
LCAT	608C/T	rs5922	.	A	203 (CVD)	Increase in HDL; p = 0.015	(Zhang et al. 2003)
LCAT		rs5922		A	150 Str; 122 Co	Lower HDL-C in heteroz.; p < 0.05	(Zhu et al. 2006)
LCAT	P143L +511C > T			A	190 CVD; 209 (Co)	Association with low HDL-C; p < 0.01	(Zhang et al. 2004)
LCAT		rs2292318	0.12 (A)	W	1442 CVD, Co	Increases HDL-C; p = 2 × 10–5	(Pare et al. 2007)
LDLR	Exon 2	rs2228671		W	1543 (P)	+3.8 mg/dl for carriers; p = 0.0056	(Costanza et al. 2005)
LDLR	1866C > T Asn591As n	rs688 = rs57911429	0.12 (T)	A	2417 (Ho Co)	+1.5/+8.5 mg/dl (1/2 copies); p = 0.0155	(Yamada et al. 2008)
LDLR	Exon 12/HincII	rs688 = rs57911429	0.39 (+)	Hu	713 (P)	2.3/4.3 mg/dl (1/2 copies); p = 0.047	(Hegele et al. 1995)
LDLR	2052 T > C	rs5925 = rs57369606	0.17 (C)	A	2417 Ho Co	+1.2/+5.4 (1/2 copies); p = 0.043	(Yamada et al. 2008)
LIPC	T-710C	rs1077834	0.22 (C)	W	9121 (P)	+3–4 % per copy; p < 0.001	(Andersen et al. 2003)
LIPC	C-514Ta	rs1800588	0.25 (T)	Va	>24,000 (Meta)	+1.5/+3.5 mg/dl (1/2 copies); p <0.001	(Isaacs et al. 2004)
LIPC	Pos.-480 T	rs1800588	0.21 (T) 0.53 (T)	W B	8897 (P) 2909 (P)	W: +2.2/+3.8 mg/dl (1/2 copies); p <0.001 B: +1.6/+4.0 mg/dl (1/2 copies); p < 0.001	(Nettleton et al. 2007)
LIPC		rs1800588	0.21 (T)	W	6239 (P)	+1.3/+4.3 mg/dl (1/2 copies); p < 0.001	(Isaacs et al. 2007)
LIPC		rs1800588	0.38 (T)	A	2170 (P)	+2.3/+2.7 mg/dl (1/2 copies); p = 0.001	(Tai et al. 2003a)
LIPC		rs1800588	0.21 (T)	W	5287 (GP)	+1/+4 mg/dl (1/2 copies); p = 4 × 10–10	(Kathiresan et al. 2008)
LIPC		rs1800588	0.25 (T)	W	2773 (GP)	+1.5 mg/dl per copy; p = 0.04	(Talmud et al. 2002b)
LIPC		rs1800588	0.24 (T)	W	3319 CV 1385 Co	+1.0/+3.8 mg/dl (1/2 copies); p = 0.001	(Whiting et al. 2005)
LIPC		rs1800588	0.51 (T)	A	5207 Ho Co	+2.5 mg/dl per copy; p < 0.001	(Yamada et al. 2007)
LIPC		rs1800588	0.21 (T)	W	6412 (CVD)	+2.0–2.5 mg/dl per copy; p < 0.001	(McCaskie et al. 2006)
LIPC	G -250A	rs2070895	0.22 (A)	W	9121 (P)	+3–4 % per copy; p < 0.001	(Andersen et al. 2003)
LIPC		rs2070895		W	1543 (P)	+1.5 mg/dl for carriers; p = 0.020	(Costanza et al. 2005)

LIPC		rs2070895	0.32 (A)	W	514 (P)	M; p = 0.001	(de Andrade et al. 2004)
LIPC		rs2070895	0.23 (A)	W	5585 (P)	+3.9/3.9 mg/dl (1/2 copies); p = 8 × 10–10	(Grarup et al. 2008)
LIPC		rs2070895	0.51 (A)	A	5213 Ho Co	+2.7 mg/dl per copy; p < 0.001	(Yamada et al. 2007)
LIPC		rs2070895	0.39 (A)	A	716 He Ex	+2.1 mg/dl for carriers; p = 0.026	(Ko et al. 2004)
LIPC		rs12594375	0.37 (A)	A	2970 (GP)	p = 0.00003	(Iijima et al. 2008)
LIPC		rs8023503	0.38 (T)	A	2970 (GP)	p = 0.0001	(Iijima et al. 2008)
LIPC	+1075C	rs3829462	0.05 (C)	A	823	+8.0 mg/dl for heteroz.; p < 0.05	(Fang and Liu 2002)
LIPC		rs4775041	0.29C	EA	25,167	p = 1.03E-16	(Dumitrescu et al. 2011)
LIPC		rs261332	0.20 (A)	EA	25,167	p = 1.99E-13	(Dumitrescu et al. 2011)
LPC		rs261334	0.20 (T)	E	17723	p = 4.9 × 10–22	(Waterworth et al. 2010)
LIPG	−384A > C	rs3813082	0.12 (C)	A	541 (Co)	+1.3/+10.2 mg/dl (1/2 copies); p = 0.021	(Hutter et al. 2006)
LIPG		rs3813082	0.12 (C)	A	340 (kids)	+0.7/+9.8 (1/2 copies); p = 0.0086	(Yamakawa-Kobayashi et al. 2003)
LIPG	584 C/T T1111	rs2000813	0.32 (I)	W	495 (GP)	M: 1.2/+2.7 mg/dl (1/2 copies); p = 0.82 F: 0.4 /+1.9 mg/dl (1/2 copies); p = 0.09	(Paradis et al. 2003)
LIPG		rs2000813	0.24 (T)	A	541 (Co)	+0.5/+6.1 mg/dl (1/2 copies); p = 0.048	(Hutter et al. 2006)
LIPG		rs2000813	0.30 (T)	A	265 CVD 265 Co	+3.7 for carries; p = < 0.02	(Tang et al. 2008)
LIPG		rs2000813	0.29 (T)	W 90 %	372 (CVD)	+1.6/+6.0 mg/dl (1/2 copies); p = 0.035	(Ma et al. 2003)
LIPG	C + 42 T/ln 5	rs2276269	0.44 (T)	W	594 (HDL)	Decreases HDL-C; p = 0.007	(Mank-Seymour et al. 2004)
LIPG	T + 2864C/l n8	rs6507931	0.42 (C)	W	594 (HDL)	Decreases HDL-C; p = 0.004	(Mank-Seymour et al. 2004)
LIPG	2237G > A	rs3744841	0.36 (A)	A	340 (kids)	4.0 mg/dl/−4.3 mg/dl (1/2 copies); p = 0.011	(Yamakawa-Kobayashi et al. 2003)
LPL	D9N; Asp9Asn	rs1801177		–	5067 (Meta)	−3.1 mg/dl for heteroz.; p = 0.002	(Wittrup et al. 1999)
LPL	Gly188Glu			–	10,434 (Meta)	−9.7 mg/dl for heteroz.; p < 0.001	(Wittrup et al. 1999)
LPL	N291S	rs268		–	14,912 (Meta)	−4.6 mg/dl for heteroz.; p < 0.001	(Wittrup et al. 1999)

(*continued*)

Table 1 (continued)

Gene	Polym.	rs number	MAF	Ethn.	Sample size	Results (effect size, p-value)	Reference
LPL	HindIII; Int8	rs320	0.30 (H)	W	520 (P)	+5.5 mg/dl in H − H − versus H + H +; p = 0.025	(Senti et al. 2001)
LPL	HindIII; Int8	rs320	0.26 (H1)	W	1361 (P)	M: +3.5 mg/dl for heteroz.; p = 0.0018 F:+4.2 mg/dl for heteroz.; p = 0.0212	(Holmer et al. 2000)
LPL	HindIII; Int8	rs320	0.32 (H)	W	906 (GP)	+1.9 mg/dl; p = 0.003	(Corella et al. 2002)
LPL	HindIII; Int8	rs320		A	550 (NGT) 465 (DM)	NGT: +3.0 mg/dl for carriers; p < 0.05 DM: +1.0 mg/dl for carriers; p < 0.05	(Radha et al. 2006)
LPL	HindIII; Int8	rs320	0.27–0.31	NHW, H	615(W); 579(H)	p = 0.005	(Ahn et al. 1993)
LPL		rs326	0.44	B	1943 (P)	M; p = 0.013; F; p = 0.004	(Klos et al. 2006a)
LPL	S447X Ser447Ter	rs328			4388 (Meta)	+1.5 mg/dl for heteroz.; p <0.001	(Wittrup et al. 1999)
LPL	S447X Ser447Ter	rs328	0.10 (G)	W	8968 (P)	+2.8/+4.0 mg/dl (1/2 copies); p <0.001	(Nettleton et al. 2007)
LPL	S447X Ser447Ter	rs328	0.07 (G)	B	2677 (P)	+3.1/+12.6 mg/dl (1/2 copies); p < 0.001	
LPL	S447X	rs328	0.11 (X)	A	4058 (P)	+3.1 mg/dl; p < 0.001	(Lee et al. 2004)
LPL		rs328		W	1543 (P)	+2.7 mg/dl; p = 0.0017	(Costanza et al. 2005)
LPL		rs328			25,167	p = 5.6E-22	(Dumitrescu et al. 2011)
LPL		rs328	0.09 (G)	W	5287 (GP)	+3/+5 mg/dl (1/2 copies); p = 3 × 10–12	(Kathiresan et al. 2008)
LPL		rs325	0.89 (T)	E	17723	p = 7.8 × 10–25	(Waterworth et al. 2010)
MARCH8	C > A	rs970548	0.26 (A)	EA AA, A	188,577 (Meta)	p = 2 × 10–10	Willer et al. (2013)

MLXIP L		rs17145738	0.12 (T)	EA	25,167	p = 1.64E-05	(Dumitrescu et al. 2011)
MOGAT2	A > C	rs499974	0.19 (C)	EA AA, A	188,577 (Meta)	p = 1 × 10–8	Willer et al. (2013)
M-RAS		rs6782181	0.39 (G)	S	2,429 CAD 2,221 C		Alshahid et al. (2013)
M-RAS		rs253662	0.19 (G)	S	2,429 CAD 2,221 C		Alshahid et al. (2013)
OR4C46	C > T	rs11246602	0.15 (T)	EA AA, A	188,577 (Meta)	p = 2 × 10–10	Willer et al. (2013)
PIGV-NR0B2	T > C	rs12748152	0.09 (C)	EA AA, A	188,577 (Meta)	p = 1 × 10–15	Willer et al. (2013)
PON1	Q192R	rs662 = rs60480675	0.30 (G)	W	1232 (P)	W: +0.1/+2.3 mg/dl (1/2 copies); p = 0.041	Srinivasan et al. (2004)
PON1	Gln192Ar g	rs662 = rs60480675	0.67	B	554	−5.4/−6.7 mg/dl (1/2 copies); p = 0.008	Srinivasan et al. (2004)
PON1		rs662 = rs60480675	0.29 (R)	Hu	738 (P)	−3.1 mg/dl/−3.1 mg/dl (1/2 copies); p = 0.001	(Hegele et al. 1995)
PON1		rs662 = rs60480675	0.36 (R)	W-Bra	261 CVD, Co	M: +1.5/+2.7 mg/dl (1/2 copies); p = 0.035	(Rios et al. 2007)
PON1	C-107 T	rs705379	0.48 (C)	W	710 (CVD)	−3.1/−2.3 mg/dl (1/2 copies); p = 0.006	(Blatter Garin et al. 2006)
PON1	Leu55M	rs85456	0.20 (T)	M-A	741	p = 0.02	(Chang et al. 2010)
PPAR γ	C1431T	rs3856806	0.15 (T)	C	820	p < 0.01	Gu SJ et al. (2014a)
RSPO3	C > T	rs1936800	0.49 (T)	EA AA, A	188,577 (Meta)	p = 3 × 10–10	Willer et al. (2013)
SETD2	A > G	rs2290547	0.20 (G)	EA AA, A	188,577 (Meta)	p = 4 × 10–9	Willer et al. (2013)
SCARB 1	Exon 8 C > T	rs5888	0.44 (T)	W	865 (P)	+1.9/2.7 mg/dl (1/2 copies); p = 0.006	(Morabia et al. 2004)
SCARB 1	C1050T	rs5888	0.49 (T)	W	546 (CVD)	+2.3/+1.9 mg/dl (1/2 copies); p = 0.03	(Boekholdt et al. 2006)

(*continued*)

Table 1 (continued)

Gene	Polym.	rs number	MAF	Ethn.	Sample size	Results (effect size, p-value)	Reference
SNX13	T > G	rs4142995	0.38 (G)	EA AA, A	188,577 (Meta)	p = 9 × 10–12	Willer et al. (2013)
STAB1	A > G	rs13326165	0.21 (G)	EA AA, A	188,577 (Meta)	p = 9 × 10–11	Willer et al. (2013)
TMEM176A	C > T	rs17173637	0.12 (T)	EA AA, A	188,577 (Meta)	p = 2 × 10–10	Willer et al. (2013)
ZBTB42-AKT1	G > A	rs4983559	0.40 (A)	EA AA, A	188,577 (Meta)	p = 1 × 10–8	Willer et al. (2013)

Abbreviations: *MAF* minor allele frequency, *A* Asians, *AA* African-Americans, *Am* Amish, *A-I* Asian Indian, *B* Blacks, *C* Chinese, *CH* Caribbean Hispanics, *E* European, *EA* European America, *I* Inuit, *Ma* Malays, *N* Netherlands, *NHW* non-Hispanic whites, *H* Hispanics, *Hu* Hutterites, *J* Japanese, *K* Korean, *L* Lithuanian, *S* Saudi Arabian, *Tu* Turks, *UK* United Kingdom, *W-Bra* Caucasian Brazilians, *W* Whites/Caucasians, *WS* Western Siberian Caucasians, *Va* various, *Non-DM C0* non diabetic control subjects, *MI* myocardial infarction, *NGT* normal glucose tolerance, *DM* Diabetes mellitus, *Ho Sta* hospital staff, *HBP* hypertensive patients, *He Ex* health examination, *Cor Ang* coronary angiography, *hyperCH* hypercholesterolemia patients, *CVD* cardiovascular disease, *C* controls, *Ho Co* hospital-based controls, *GP* general population, *Meta* meta-analysis, *P* population based, *M* males, *F* females, + increase, − decrease, *n.s.* not significant; see text for full gene names. Adapted from Nock and Pillai (2012) and Boes et al. (2009) with permission from Elsevier

Miller and Zhan 2004). However, polymorphisms in LCAT have only been inconsistently associated with changes in HDL-C levels (Table 1; Zhu et al. 2006; Zhang et al. 2004; Pare et al. 2007; Miettinen et al. 1998; Boekholdt et al. 2006).

Paraoxonase 1 (PON1), which is located on chromosome 7 (7q21.3), inhibits the oxidation of LDL (Mackness et al. 1991) and may, therefore, only indirectly affect antioxidant properties of HDL-C. Several SNPs in PON1 have been associated with HDL-C levels including two nonsynonymous SNPs, rs662 and rs3202100, which are in strong LD; however, results have been inconsistent across studies (Table 1; Blatter Garin et al. 2006; Hegele et al. 1995; Manresa et al. 2006; Rios et al. 2007; van Aalst-Cohen et al. 2005).

2.2 Variation in Genes Involved in HDL-C Transport and Binding

Many common variants in genes involved in HDL-C transport and binding have been implicated. The scavenger receptor class B type 1 (SCARB1; SR-B1) gene located on chromosome 12 (12q24.31) is a key gene, which has been shown to participate in the uptake of HDL in animals by transferring cholesterol from the HDL-C particle and releasing the lipid-depleted HDL particle into the circulation (Acton et al. 1996; Miller et al. 2003). Polymorphisms in SCARB1 have been associated with HDL-C levels with the most notable being rs5888 (Table 1; Boekholdt et al. 2006; Costanza et al. 2005; Hsu et al. 2003; Morabia et al. 2004; Osgood et al. 2003; Roberts et al. 2007; Smalinskiene et al. 2013).

The LDL receptor (LDLR) gene located on chromosome 19 (19p13.2) participates in the uptake of LDL and chylomicron remnants by hepatocytes (Kwan et al. 2007) and may only indirectly affect HDL-C levels. However, a few polymorphisms in LDLR have been associated with HDL-C levels (Table 1; Costanza et al. 2005; Hegele et al. 1995; Yamada et al. 2008), but their impact is greater on LDL-C levels.

The ATP-binding cassette transporter A1 (ABCA1), located on chromosome 9 (9q31.1), plays a key role in "reverse cholesterol transport" by mediating the efflux of cholesterol and phospholipids from macrophages to the nascent lipid-free, APOA-1 HDL particle (Cavelier et al. 2006; Miller et al. 2003). Several polymorphisms have been fairly consistently associated with HDL-C levels, but different variants appear to drive this association in different ethnic groups (Table 1; Clee et al. 2001; Costanza et al. 2005; Frikke-Schmidt et al. 2004; Hodoglugil et al. 2005; Kathiresan et al. 2008; Klos and Kullo 2007; Porchay et al. 2006; Shioji et al. 2004b; Whiting et al. 2005).

The apolipoprotein A-1 (APOA1; APOA-I) gene, located on chromosome 11 (11q23-24), encodes a ligand required for HDL-C binding to its receptors including SCARB1 and ABCA1 and is an important cofactor in "reverse cholesterol transport" (Miller et al. 2003; Remaley et al. 2001; Rigotti et al. 1997). Polymorphisms in APOA-I have been associated with HDL-C levels, but results across studies have been inconsistent (Table 1; Brown et al. 2006; Kamboh et al. 1999; Larson et al. 2002; Shioji et al. 2004a). Apolipoprotein A-4 (APOA4; APOA-IV) gene is part of the "APOA1/C3/A4/A5 gene cluster" and a potent activator of LCAT which modulates the activation of LPL and transfer of cholesteryl esters from HDL to LDL (Kwan et al. 2007). Polymorphisms in APOA4 have not been as well studied, but rs5110 (Gln360His) and rs675 have been associated with reduced HDL-C levels (Ota et al. 2011; Qi et al. 2007).

Apolipoprotein A-5 (APOA5; APOA-V), located predominantly on TG-rich chylomicrons and VLDL, activates LPL (Hubacek 2005). A few APOA5 SNPs have been associated with HDL-C levels with rs651821 and rs662799 having the most consistent results across studies (Table 1; Grallert et al. 2007; Hubacek 2005; Klos et al. 2006; Lai et al. 2004; Qi et al. 2007; Talmud et al. 2002a; Yamada et al. 2007; Yamada et al. 2008). Recently, rs964184 in the APOA5-A4-C3-A1 cluster was associated with HDL-C in the SMART (Second Manifestations of ARTerial disease) cohort (van de Woestijne et al. 2014a).

Apolipoprotein C-3 (APOC3; APOC-III), an inhibitor of LPL and transferred to HDL during the hydrolysis of TG-rich lipoproteins (Kwan et al. 2007; Miller et al. 2003), has several SNPs

that have been identified, but associations with HDL-C levels have been inconsistent (Table 1; Arai and Hirose 2004; Brown et al. 2006; Corella et al. 2002; Hegele et al. 1995; Kamboh et al. 1999; Lahiry et al. 2007; Pallaud et al. 2001; Qi et al. 2007; Russo et al. 2001). Apolipoprotein E (APOE), a critical ligand for binding to hepatic receptors that remove VLDL and LDL particles from the circulation, has several SNPs that have been fairly consistent associated with HDL-C levels (Costanza et al. 2005; Frikke-Schmidt et al. 2000; Gronroos et al. 2008; Kataoka et al. 1996; Srinivasan et al. 1999; Volcik et al. 2006; Wilson et al. 1994; Wu et al. 2007; Smalinskiene et al. 2013).

2.3 Variation in Genes Involved in Cell Proliferation, Inflammation, and Related Pathways

The M-RAS gene located on chromosome 3 (3q22.2) encodes a member of the membrane-associated family of Ras small GTPase proteins engaged in tumor necrosis factor-alpha-stimulated lymphocyte function that appears to play a role in adhesion signaling, which is an important aspect of atherosclerotic pathways (Galkina and Ley 2007). Interestingly, a few common variants in M-RAS, most notably, rs6782181, have recently been associated with low HDL-C levels in a large study involving CAD cases and "controls" with "no significant coronary stenosis by angiography" (Alshahid et al. 2013); however, this finding does not appear to have been replicated yet in other populations.

GATA2, an endothelial transcription factor, located on chromosome 3 (3q21.3), is a multicatalytic transcription factor that plays a major role in controlling growth factor responsiveness and regulating inflammatory processes (Tsai et al. 1994). The rs7431368 SNP of the GATA2 gene has recently been associated with low HDL-C levels in a large Saudi case-control study involving 2,386 CAD cases and 2,171 angiographed controls (Muiya et al. 2014).

Peroxisome proliferator-activated receptor gamma (PPARγ) may play a key role in lipid metabolism by inducing the transcription of related genes. Recently, the rs3856808 variant in PPARγ was associated with HDL-C levels in a random sample of 820 Chinese from the prevention of multiple metabolic disorders and metabolic syndrome in the Jiangsu province cohort (Gu et al. 2014b).

The butyrophilin subfamily 2 member A1 (BTN2A1) gene, located on chromosome 6 (6p22.1), encodes proteins that help in the production of milk fat globules and regulating immune function (Ogg et al. 2004). The rs6929846 variant of BTN2A1 has been associated with HDL-C levels in large cohorts of Japanese and Korean individuals (Fujimaki et al. 2011). The combination of the rs6929846 T allele of BTN2A1 with the rs662799 C allele of APOA5 has also been associated with 35 % lower HDL-C levels in Japanese individuals (Hiramatsu et al. 2012).

2.4 Genetic Variants Associated with HDL-C Identified Through GWAS

Results from genome-wide association studies (GWAS) have confirmed associations between polymorphisms in viable candidate genes including CETP, LPL, HL/LIPIC, EL/LIPG, ABCA1, LCAT, and the APOA1/C3/A4/A5 gene cluster and HDL-C levels (Boes et al. 2009). GWAS have also identified two novel putative loci associated with HDL-C levels in a large Chinese pediatric population (Shen et al. 2013). Twenty-four novel loci, all of which had MAF >0.05 (Table 1), were recently identified in a joint GWAS and Metabochip meta-analysis in 188,577 individuals of European East Asian, South Asian, and African ancestry (Willer et al. 2013). Other novel and candidate loci from GWAS have been summarized nicely in other reviews (Teslovich et al. 2010; Rankinen et al. 2015).

3 Genetics of LDL-C

Table 1 lists genetic variants associated with LDL-C in larger-scale studies. Below, we describe variants in genes based on their involvement in

relevant biological pathways including LDL-C-related enzymes, receptors and transporters, lipoprotein, and protease mechanisms.

3.1 Genetic Variation in Enzymes, Receptors and Transporters, and LDL-C

The most marketed drugs for lowering LDL-C are statins, which inhibit hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), the rate-limiting enzyme in cholesterol synthesis that is normally suppressed (Endo 1992). The human HMGCR gene is located on chromosome 5 (5q13.3-14). Only a few common HMGCR polymorphisms have been associated with LDL-C levels including rs3846662 (Table 2) (Burkhardt et al. 2008; Hiura et al. 2010; Polisecki et al. 2008; Teslovich et al. 2010).

As mentioned above, the LDL receptor (LDLR) gene, located on chromosome 19 (19p13.2), helps to regulate the uptake of LDL and chylomicron remnants by hepatocytes (Kwan et al. 2007). Although not the focus of this review, we note that familial (monogenic) hypercholesterolemia (FH: OMIM No. 143890) is one of the most common inherited metabolic diseases due to mutations in LDLR (a frequency of approximately 1 in 500 (heterozygotes) to 1 in 1,000,000 (homozygotes)) with heterozygotes having a decreased receptors and a two to threefold increase in LDL-C levels and homozygotes having a complete loss of LDLR function and a greater than fivefold increase in LDL-C (Garg and Simha 2007). Several common polymorphisms in LDLR have also been identified and associated with more modest changes in LDL-C levels, including rs17248720, which was associated with LDL-C levels in Spanish "normolipemic" controls from the Aragon Workers Health Study (AWHS) (De Castro-Oros et al. 2014), and rs6511720, which was associated with LDL-C in a meta-analysis (Teslovich et al. 2010; Willer et al. 2008).

The ATP-binding cassette transporters G5 and G8 (ABCG5/8) gene cluster, located on chromosome 2 (2p21), regulates the efflux of cholesterol back into the intestinal lumen and, in hepatocytes, the efflux of cholesterol into bile (Graf et al. 2003). A few common variants in ABCG5/8 have been associated with LDL-C levels (Table 2); however, a recent meta-analysis failed to find an association between the ABCG5/G8 polymorphism, rs6544718, and plasma lipid levels (Jakulj et al. 2010; Teslovich et al. 2010).

3.2 Genetic Variation in Lipoproteins and LDL-C

Apolipoprotein B (APOB; main isoform: ApoB-100), located on chromosome 2 (2p23-24), is responsible for the uptake of LDL by LDLR, which clears approximately 60–80 % of the LDL in "normal" individuals with the remaining taken up by LRP or SCARB1 (Kwan et al. 2007). Common polymorphisms in APOB have been identified and associated with changes in LDL-C (Table 2; Haas et al. 2011; Teslovich et al. 2010; Waterworth et al. 2010; Willer et al. 2008).

As mentioned above, APOE, located on chromosome 19 (19q13.2), is a critical ligand for binding chylomicron remnants, VLDL, and IDL particles to hepatic receptors to remove these particles from the circulation (Kwan et al. 2007). The structural APOE gene is polymorphic with three common alleles, designated as ε2, ε3, and ε4, which encode for E2, E3, and E4 proteins, respectively. Recently, the ε2 allele has been associated with high LDL-C levels in Lithuanian women (Smalinskiene et al. 2013); however, the APOE ε4 allele has been the most consistently associated with LDL-C levels (Anoop et al. 2010; Chang et al. 2010; Eichner et al. 2002; Teslovich et al. 2010; Willer et al. 2008).

3.3 Genetic Variation in Proteases and LDL-C Levels

Proprotein convertase subtilisin-like kexin type 9 (PCSK9), located on chromosome 1 (1p32.3), is a serine protease that degrades hepatic LDLR in endosomes (Maxwell et al. 2005). Over 50 variants in PCSK9 have been shown to affect circulating levels of cholesterol; however, most of

Table 2 Genetic polymorphisms associated with LDL-C (see Table 1 legend for details)

Gene	Polym.	rs number	MAF	Ethn.	Sample size	Results (effect size, p-value)	Reference
ABCG8		rs4299376	0.30 (G)	E	95,454 (Meta)	+2.75 mg/dl; p = 2 × 10−8	(Teslovich et al. 2010)
ABCG8	A632V	rs6544718		Va	982	p = 0.02	(Jakulj et al. 2010)
ACAD11	T > G	rs17404153	0.14 (G)	EA AA, A	188,577 (Meta)	p = 2 × 10–9	Willer et al. (2013)
APOB		rs562338	0.18 (A)	Va	10,849	+4.89 mg/dl; p = 3.6 × 10−12	(Willer et al. 2008)
APOB		rs754523	0.28 (A)	Va	6,542	+2.78 mg/dl; p = 1.3 × 10–6	(Willer et al. 2008)
APOB		rs693	0.42 (G)	Va	3,222	+2.44 mg/dl; p = 0.0034	(Willer et al. 2008)
APOB	Thr98Ile	rs1367117	0.30 (A)	E	95,454 (Meta)	+4.05 mg/dl; p = 4 × 10−114	(Teslovich et al. 2010)
APOB		rs7575840	0.28 (T)	F	5054	0.131; p = 3.88 × 10–9	(Haas et al. 2011)
APOB		rs515135	0.19 (A)	Va	982	p = 2.4 × 10–20	Waterworth et al. (2010)
APOE		rs4420638	0.17 (G)	E	95,454 (Meta)	+7.14 mg/dl; p = 9 × 10–147	(Teslovich et al. 2010)
APOE	Arg176 Cys	rs7412	0.06 (T)	N-HB	683	−22.52 mg/dl; p < 0.0001	(Chang et al. 2010)
APOE	Cys130 Arg	rs429358	0.076 (T)	M-A	739	10.54 mg/dl; p < 0.0001	(Chang et al. 2010)
APOE	Cys130 Arg	rs429358	0.10 (E2)	L	1030; 605 W	E2 vs. E3 (women); 0.35 (0.22–0.57)	Smalinskiene et al. (2013)
APOE	Cys130 Arg	rs429358	0.09 (E4)	L	1030; 425 M	E4 vs. E3 (men); p < 0.05	Smalinskiene et al. (2013)
APOC1		rs4420638	0.82 (A)	Va	10,806	+6.61 mg/dl; p = 4.9 × 10–24	(Willer et al. 2008)
APOE/ C1/C4		rs10402271	0.67 (T)	Va	6,519	+2.62 mg/dl; p = 1.5 × 10−5	(Willer et al. 2008)
ANXA9-CERS2	G > A	rs267733	0.16 (A)	EA AA, A	188,577 (Meta)	p = 5 × 10–9	Willer et al. (2013)
BTN2A1		rs6929846		J	5958	T allele; p = 0.046	Horibe et al. (2014)
BRCA2	T > C	rs4942486	0.48 (C)	EA AA, A	188,577 (Meta)	p = 2 × 10–11	Willer et al. (2013)

CMTM6	T > C	rs7640978	0.09 (C)	EA AA, A	188,577 (Meta)	p = 1 × 10–8	Willer et al. (2013)
CSNK1G3	G > A	rs4520754	0.46 (A)	EA AA, A	188,577 (Meta)	p = 4 × 10–12	Willer et al. (2013)
EHBP1	G > A	rs2710642	0.45 (A)	EA AA, A	188,577 (Meta)	p = 6 × 10–9	Willer et al. (2013)
FN1	T > C	rs1250229	0.27 (C)	EA AA, A	188,577 (Meta)	p = 3 × 10–8	Willer et al. (2013)
LDLR		rs6511720	0.11 (T)	E	95,454 (Meta)	−6.99 mg/dl; p = 4 × 10–117	(Teslovich et al. 2010)
INSIG2	A > G	rs12464355	0.10 (G)	W	561 (child)	B = −0.12 ± 0.03; p = 2.7 × 10–5	Kaulfers et al. (2015)
INSIG2	C > T	rs2042492	0.27 (T)	B	497 (child)	B = 0.04 ± 0.02; p = 0.04	Kaulfers et al. (2015)
INSIG2	A > G	rs10490626	0.08 (G)	EA AA, A	188,577 (Meta)	p = 2 × 10–12	Willer et al. (2013)
LDLR		rs6511720	0.90 (T)	Va	7,442	+9.17 mg/dl; p = 3.3 × 10–19	(Willer et al. 2008)
LDLR	C3130T	rs17248720	0.16 (T)	S	525 C		(DeCastro-Oros 2014)
MIR148A	C > T	rs4722551	0.20 (T)	EA AA, A	188,577 (Meta)	p = 4 × 10–14	Willer et al. (2013)
PCSK9		rs11206510	0.81 (C)	Va	10,805	+3.04 mg/dl; p = 5.4 × 10−7	(Willer et al. 2008)
PCSK9		rs2479409	0.30 (G)	E	95,454 (Meta)	+2.01 mg/dl; p = 2 × 10–28	(Teslovich et al. 2010)
PCSK9	A443T Ala443Thr	rs28362263	0.06 (A)	B	1750	95.5 versus 106.9 mg/dl; p <0.001	(Huang et al. 2009)
PCSK9	C679X	rs28362286		B	1750	81.5 versus 106.9 mg/dl; p <0.001	(Huang et al. 2009)
PCSK9	E670G	rs505151	0.11 (G)	W	691	p = 0.001	(Chen et al. 2005)
PCSK9		rs11206510	0.81 (T)	EA	21,986 (Meta)	p = 1.44E-05	(Dumitrescu et al. 2011)
SCARB 1 C1050T rs5888 0.41 (T) L 1030 TT	C1050T	rs5888	0.41 (T)	L	1030	TT vs. CC (men); p <0.05	Smalinskiene et al. (2013)

(*continued*)

Table 2 (continued)

Gene	Polym.	rs number	MAF	Ethn.	Sample size	Results (effect size, p-value)	Reference
vs. CC (men only): $p < 0.05$ Smalinskiene et al. (2013)							
SNX5	C > A	rs2328223	0.21 (A)	EA AA, A	188,577 (Meta)	$p = 4 \times 10–9$	Willer et al. (2013)
SORT1		rs629301	0.22 (G)	E	95,454 (Meta)	−5.65 mg/dl; $p = 1 \times 10–170$	(Teslovich et al. 2010)
SOX17	A > G	rs10102164	0.21 (A)	EA AA, A	188,577 (Meta)	$p = 4 \times 10–11$	Willer et al. (2013)
SPTLC3	A > G	rs364585	0.38 (G)	EA AA, A	188,577 (Meta)	$p = 4 \times 10–10$	Willer et al. (2013)

these are relatively rare (Davignon et al. 2010). However, a few common polymorphisms in PCSK9 have been associated with LDL-C levels (Table 2) (Chen et al. 2005; Evans and Beil 2006; Huang et al. 2009; Teslovich et al. 2010; Willer et al. 2008).

3.4 Genetic Variation in Inflammatory and Immune Systems and LDL-C

As mentioned above, the BTN2A1 gene, located on chromosome 6 (6p22.1), encodes proteins that help in the production of milk fat globules and regulating immune function (Ogg et al. 2004). The rs6929846 variant of BTN2A1 has been associated with HDL-C levels in a large community-dwelling cohort of Japanese individuals (Horibe et al. 2014).

Insulin-induced gene 2 (INSIG2) located on chromosome 2 (2q14.2) plays a role in regulating lipid storage as well as blocking further cholesterol synthesis when sterols are present in the cell (Yabe et al. 2002). Recently, a common variant in INSIG2, rs12464355, has been associated with LDL-C levels in a random sample of non-Hispanic white children from the Princeton School District Study, a prospective cohort of fifth through 12th graders (Kaulfers et al. 2015). However, in this same study, rs1352083, rs13393332, and rs2042492, all in strong LD (but not rs12464355) in the INSIG2 gene, were associated with LDL-C levels in African-American children (Kaulfers et al. 2015).

3.5 GWAS, Exome Sequencing, and LDL-C

GWAS have confirmed associations between polymorphisms in viable candidate genes including APOB, APOE, LDLR, and PCSK9 and have identified novel SNPs associated with LDL-C levels with strong biological plausibility including an inhibitor of lipase (ANGPTL3) and a transcription factor activating triglyceride synthesis (MLXIPL) (Teslovich et al. 2010). GWAS have also identified four novel putative loci associated with LDL-C levels in a large Chinese pediatric population (Shen et al. 2013). Fifteen novel loci, 13 of which had MAF > 0.05 (and are listed in Table 2), were recently identified in a joint GWAS and Metabochip meta-analysis in 188,577 individuals of European East Asian, South Asian, and African ancestry (Willer et al. 2013).

Exome sequencing can help to identify rare, low-frequency variants and confirm known candidate loci. Recently, 2005 individuals (1,854 African-American, 1,153 European-American) from seven population-based cohorts were exome sequenced (with at least 20× coverage over 70 % of the exome target) and evaluated for associations with LDL-C levels (Lange et al. 2014). Interestingly, single-variant (univariate/multivariable) analyses only identified one variant near APOE that was statistically significant (rs1160983, $p = 7.6 \times 10^{-14}$) (Lange et al. 2014); however, more elegant statistical methods identified additional novel variants and confirmed associations with candidate loci.

4 Genetics of Triglycerides (TG)

Table 3 lists genetic variants associated with TG in larger-scale studies. Below, we describe variants in genes based on their involvement in relevant biological pathways including binding (via apolipoproteins) as well as relevant enzymes, receptors, and transporter mechanisms. Because plasma TG integrate multiple TG-rich lipoprotein particles, it is not surprising that there is considerable overlap between the genetic variants associated with TG levels and the genetic variants associated with HDL-C and LDL-C levels. The Global Lipids Genetics Consortium (GLGC) found that 15 of the 32 loci associated with TG levels were also jointly associated with HDL-C levels, explaining 9.6 % of the total variation in plasma TG, which corresponded to 25–30 % of the total genetic contribution to TG variability (Teslovich et al. 2010). However, most loci appear to be more strongly associated

Table 3 Genetic polymorphisms associated with TG (see Table 1 legend for details)

	Polym.	rs number	MAF	Ethn.	Sample size	Results (effect size, p-value)	Reference
AKR1C4	G > A	rs1832007	0.10 (A)	EA AA, A	188,577 (Meta)	p = 2 × 10–12	Willer et al. (2013)
ANGPTL3		rs2131925	0.32 (G)	E	96,598 (Meta)	−4.94 mg/dl; p = 9 × 10−43	Teslovich et al. (2010)
ANGPTL3		rs1748195	0.70 (G)	Va	9,559	7.12 mg/dl; p = 5.4 × 10–8	Willer et al. (2008)
APOA5		rs964184	0.13 (G)	E	96,598 (Meta)	+16.95 mg/dl; p = 7 × 10–240	(Teslovich et al. 2010)
APOA5-A4/A1		rs964184	0.14 (G)	C	5547	0.12 (0.10 − 0.15); p = 1.1 × 10–19	van de Woestijne et al. (2014)
APOA5/A4/C3/A1		rs12286037	0.94 (C)	Va	9,738	25.82 mg/dl; p = 1.6 × 10–22	Willer et al. (2008)
APOA5		rs662799	0.05 (A)	Va	3,248	16.88 mg/dl; p = 2.7 × 10–10	Willer et al. (2008)
APOA5/A4/C3/A1		rs2000571	0.17 (G)	Va	3,209	6.93 mg/dl; p = 8.7 × 10–5	Willer et al. (2008)
APOA5/A4/C3/A1		rs486394	0.28 (A)	Va	3,597	1.50 mg/dl; p = 0.0073	Willer et al. (2008)
APOE		rs439401	0.40 (C)	C	4.192	p = 2.2 × 10–5	Liu et al. (2011)
APOE		rs439401	0.64 (C)	Va	Meta	p = 5.5 × 10–30	Johansen et al. (2010)
BTN2A1	C > T	rs6929846		J	5958	T allele; p = 0.001	Horibe et al. (2014)
GATA2	C > A	rs7431368		S	2386 CAD 2171 C	B = −1.49; s.e. = 0.67; p = 0.03; p = 0.ppp	Muiya et al. (2014)
INSIG2	G > A	rs889904	0.58 (A)	B	497 (child)	B = −0.06 ± 0.03; p = 0.01	Kaulfers et al. (2015)
INSR	A > G	rs7248104	0.42 (G)	EA AA, A	188,577 (Meta)	p = 5 × 10–10	Willer et al. (2013)
LRPAP1	G > A	rs6831256	0.42 (A)	EA AA, A	188,577 (Meta)	p = 2 × 10–12	Willer et al. (2013)
LIPC/HL		rs4775041	0.67 (G)	Va	8,462	3.62 mg/dl; p = 2.9 × 10–5	Willer et al. (2008)
LIPC/HL		rs261342	0.22 (G)	Va	Meta	p = 2.0 × 10–13	Johansen et al. (2010)
LPL		rs12678919	0.12 (G)	E	96,598 (Meta)	−13.64 mg/dl; p = 2 × 10–115	Teslovich et al. (2010)
LPL		rs10503669	0.90 (A)	Va	9,711	11.57 mg/dl; p = 1.6 × 10–14	Willer et al. (2008)
LPL		rs2197089	0.58 (A)	Va	3,202	3.38 mg/dl; p = 0.0029	Willer et al. (2008)
LPL		rs6586891	0.66 (A)	Va	3,622	4.60 mg/dl; p = 5 × 10−4	Willer et al. (2008)
LPL	S447X	rs328	0.90 (C)	EA	24,258	p = 4.16E-30	Dumitrescu et al. (2011)

(*continued*)

Table 3 (continued)

	Polym.	rs number	MAF	Ethn.	Sample size	Results (effect size, p-value)	Reference
LPL	S447X	rs328	0.10 (X)	Va	43,242	−0.15 (−0.12 to −0.19) mmol/l	Sagoo et al. (2008)
LPL	D9N	rs1801177	0.03 (N)	Va	21,040	0.14 (0.08–0.20) mmol/l	Sagoo et al. (2008)
LPL	N291S	rs368	0.03 (S)	Va	27,204	0.19 (0.12–0.26) mmol/l	Sagoo et al. (2008)
LPL		rs326	0.18 (G)	C	4,192	p = 2.3 × 10−6	Liu et al. (2011)
LRP1		rs11613352	0.23 (T)	E	96,598 (Meta)	−2.70 mg/dl; p = 4 × 10−10	Teslovich et al. (2010)
MET	G > A	rs38855	0.47 (A)	EA AA, A	188,577 (Meta)	p = 1 × 10–8	Willer et al. (2013)
MPP3	C > A	rs8077889	0.22 (A)	EA AA, A	188,577 (Meta)	p = 1 × 10–8	Willer et al. (2013)
MLXIPL		rs17145738	0.12 (T)	E	96,598 (Meta)	−9.32 mg/dl; p = 6 × 10–58	Teslovich et al. (2010)
MLXIPL		rs17145738	0.84 (T)	Va	9,741	8.21 mg/dl; p = 5 × 10–8	Willer et al. (2008)
MLXIPL		rs7811265	0.81 (A)	Va	Meta	7.91 mg/dl p = 9.0 × 10−59	Johansen et al. (2011)
PDXDC1	T > C	rs3198697	0.43 (C)	EA AA, A	188,577 (Meta)	p = 2 × 10–8	Willer et al. (2013)
PEPD	G > A	rs731839	0.35 (A)	EA AA, A	188,577 (Meta)	p = 3 × 10–9	Willer et al. (2013)
PPAR γ	Pro12 Ala	rs180592	0.26 (Ala)	C	820	p <0.01	Gu SJ et al. (2014)
SULF2	A > G	rs2281279		C	1319	"G" allele; p = 0.049	Hassing et al. (2014)
VEGFA	A > C	rs998584	0.49 (C)	EA AA, A	188,577 (Meta)	p = 3 × 10–15	Willer et al. (2013)

Abbreviations: *MAF* minor allele frequency, *A* Asians, *AA* African-Americans, *Am* Amish, *A-I* Asian Indian, *B* Blacks, *C* Chinese, *CH* Caribbean Hispanics, *E* European, *EA* European America, *I* Inuit, *Ma* Malays, *N* Netherlands, *NHW* non-Hispanic whites, *H* Hispanics, *Hu* Hutterites, *J* Japanese, *K* Korean, *L* Lithuanian, *S* Saudi Arabian, *Tu* Turks, *UK* United Kingdom, *W-Bra* Caucasian Brazilians, *W* Whites/Caucasians, *WS* Western Siberian Caucasians, *Va* various, *Non-DM C0* non diabetic control subjects, *MI* myocardial infarction, *NGT* normal glucose tolerance, *DM* Diabetes mellitus, *Ho Sta* hospital staff, *HBP* hypertensive patients, *He Ex* health examination, *Cor Ang* coronary angiography, *hyperCH* hypercholesterolemia patients, *CVD* cardiovascular disease, *C* controls, *Ho Co* hospital-based controls, *GP* general population, *Meta* meta-analysis, *P* population based, *M* males, *F* females, + increase, − decrease, *n.s.* not significant; see text for full gene names. Adapted from Nock and Pillai (2012) and Boes et al. (2009) with permission from Elsevier

with one lipid phenotype, while only a few loci have similar effect sizes across lipid phenotypes. Furthermore, there is substantial genetic heterogeneity between major ethnic groups (e.g., between Caucasians and African-Americans).

4.1 Genetic Variation in Apolipoproteins and TG

As mentioned above, APOB, located on chromosome 2 (2p23–24), is the backbone of atherogenic lipoproteins. APOB polymorphisms have been

predominantly associated with LDL-C (Benn 2009), but GWAS revealed that a common SNP in APOB, rs1042034, has been associated with TG (Johansen and Hegele 2011; Teslovich et al. 2010). Further, polymorphisms in the APOA1/C3/A4/A5 gene cluster, located on chromosome 11 (11q23), have been associated with TG as well as HDL-C levels (Teslovich et al. 2010; Willer et al. 2008; van de Woestijne et al. 2014). An SNP in the APOE gene, rs439401, has been shown to be strongly associated with TG levels (Hegele et al. 1995; Johansen and Hegele 2011; Teslovich et al. 2010). The combination of the rs662799 C allele of APOA5 and the rs6929846 T allele of BTN2A1 has been associated with 41 % higher TG levels in Japanese and 24 % higher TG levels in Korean individuals (Hiramatsu et al. 2012; Aung et al. 2014). Furthermore, the BUD13/ZNF259 A-C—A-G-C-C haplotype (ZNF259 rs2075290, ZNF259 rs964184, BUD13 rs10790162, BUD13 rs17119975, BUD13 rs11556024, BUD13 rs35585096), near APOA5 on chromosome 11q23.3 and involved in cell proliferation and signal transduction, has been associated with high TG in a random sample of 1181 Chinese individuals (Aung et al. 2014).

Angiopoietin-like 3 protein (ANGPTL3) inhibits LPL catalytic activity, but this process is reversible (Shan et al. 2009; Shimizugawa et al. 2002). Polymorphisms in ANGPTL3, most notably, rs2131925, have been associated with TG levels (Johansen and Hegele 2011; Keebler et al. 2009; Lanktree et al. 2009; Teslovich et al. 2010; Willer et al. 2008). In addition, several nonsynonymous ANGPTL3 variants have been associated with TG levels (Musunuru et al. 2010) in the Dallas Heart Study, but these SNPs have not been validated yet in other populations.

4.2 Genetic Variation in Enzymes and Transcription Factors and TG

As mentioned above, LPL is an enzyme that hydrolyzes TG-rich particles in peripheral tissues (muscle, macrophages, adipose) generating FFA and glycerol for energy metabolism and storage (Goldberg 1996). Although more than 100 mutations in LPL have been identified (Murthy et al. 1996), only a few common nonsynonymous SNPs have been consistently associated with TG levels including rs1801177, rs328, and rs268 (Mailly et al. 1995; Rip et al. 2006; Sagoo et al. 2008; Teslovich et al. 2010; Willer et al. 2008). Two of these SNPs, rs1801177 and rs328, have been shown to be in strong LD in Caucasians (Sagoo et al. 2008).

The MLX interacting protein-like (MLXIPL) gene, located on located on chromosome 7 (7q11.23), encodes a transcription factor of the Myc/Max/Mad superfamily that activates, in a glucose-dependent manner, carbohydrate response element-binding protein (CREBP), which is expressed in lipogenic tissues coordinating the subsequent activation of lipogenic enzymes such as fatty acid synthase (FAS) to convert dietary carbohydrate to TG (Iizuka and Horikawa 2008). The rs1745738 polymorphism, initially identified via GWAS, has been associated with TG levels in several studies (Johansen and Hegele 2011; Teslovich et al. 2010; Wang et al. 2008; Willer et al. 2008).

As mentioned above, GATA2, an endothelial transcription factor, is a multi-catalytic transcription factor that plays a major role in controlling growth factor responsiveness and regulating inflammatory processes (Tsai et al. 1994). The rs7431368 SNP of the GATA2 gene has recently been associated with high TG levels in a large Saudi case-control study involving 2,386 CAD cases and 2,171 angiographed controls (Muiya et al. 2014).

Peroxisome proliferator-activated receptor gamma (PPARγ) may play a key role in lipid metabolism by inducing the transcription of related genes that sense and regulate lipid metabolism, and, recently, the rs180592 variant in PPARγ was associated with TG levels in a random sample of 820 Chinese from the prevention of multiple metabolic disorders and metabolic syndrome in the Jiangsu province cohort (Gu et al. 2014b). In addition, the PPARα "V" allele of rs1800206 and the "G" allele of

rs4253778 (haplotype) have been shown to be associated with high TG in a Chinese Han population (Gu et al. 2014a).

4.3 Genetic Variation in Storage and Inflammatory and Immune Systems and TG

The INSIG2 gene, located on chromosome 2 (2q14.2), plays a role in regulating lipid storage as well as blocking further cholesterol synthesis when sterols are present in the cell (Yabe et al. 2002). Recently, a common variant in INSIG2, rs889904, was associated with TG levels in African-American children (Kaulfers et al. 2015). However, none of the 13 SNPs evaluated in the INSIG2 gene were associated with the non-Hispanic white children in this study (Kaulfers et al. 2015).

The sulfatase-2 (SULF2) gene, located on chromosome 20 (20q13.12), encodes for the heparin sulfate glucosamine-6-*O*-ensosulfatase that removes 6-*O* sulfate groups (Rosen and Lemjabbar-Alaoui 2010) and is a hepatic heparan sulfate proteoglycan (HSPG) remodeling enzyme involved in TG-rich lipoprotein (TRL) remnant clearance (Foley et al. 2013; Chen and Williams 2013). Recently, the "G" allele of rs2281279 in SULF2 has been found to lower SULF2 mRNA expression in liver biopsies of "healthy" subjects (Matikainen et al. 2013), and the "G" allele of rs2281279 has been associated with TG in the Diabetes Care System cohort (Hassing et al. 2014).

Further, the BTN2A1 gene, mentioned above, located on chromosome 6 (6p22.1), encodes proteins that help in the production of milk fat globules and regulating immune function (Ogg et al. 2004). The rs6929846 variant of BTN2A1 has been associated with TG levels in a large community-dwelling cohort of Japanese individuals (Horibe et al. 2014).

4.4 GWAS and TG

GWAS have identified novel mutations and confirmed associations between polymorphisms in viable candidate genes including APOB, APOE, LPL, and MLXIPL (Teslovich et al. 2010). A recent GWAS in a large Chinese pediatric population has identified six additional novel loci associated with TG levels (Shen et al. 2013). Furthermore, eight novel loci, all of which had MAF >0.05 (Table 3), were recently identified in a joint GWAS and Metabochip meta-analysis in 188,577 individuals of European East Asian, South Asian, and African ancestry (Willer et al. 2013).

5 Genetics of Dyslipidemia

Several investigators have also evaluated many of the aforementioned genetic variants on "dyslipidemia" in addition to individual lipid phenotypes. For example, the rs6929846 variant of BTN2A1 has been associated with dyslipidemia (defined as HDL-C <1.04 mmol/l, LDL-C ≥ 3.64 mmol/l, TG ≥ 1.65 mmol/l, or on antidyslipidemic drugs), as well as high LDL (section "Genetic Variation in Inflammatory and Immune Systems and LDL-C") and high TG (section "Genetic Variation in Enzymes and Transcription Factors and TG") levels in a large community-dwelling cohort of Japanese individuals (Horibe et al. 2014). The PPARγ rs3856806 "T" allele, the PPARγ rs1805192 "Ala" allele, and the PPARα rs1800206 "V" allele have all been associated with an increased risk of dyslipidemia (defined as HDL-C <1.04 mmol/l for men, HDL-C <1.30 mmol/l for women, LDL-C ≥ 4.14 mmol/l, TG ≥ 2.26 mmol/l, or total cholesterol (TC) ≥ 6.24 mmol/l) in a Chinese Han population (Gu et al. 2014a). In addition, the PPARα "V" allele of rs1800206 and the "G" allele of rs4253778 (haplotype) have been shown to be associated with a fivefold increased risk of dyslipidemia in this Chinese Han population (Gu et al. 2014a).

The Niemann-Pick C1-like 1 (NPC1L1) gene, located on chromosome 7 (7p13), plays a role in intestinal cholesterol absorption, and decreases in LDL-C levels in response to Ezetimibe, a pharmacologic inhibitor of NPC1L1, have been observed (Cohen et al. 2006).

The rs2072183, rs217428, and rs217434 polymorphisms in NPC1L1 have been associated with dyslipidemia in several studies (Kashiwabara et al. 2014; Maeda et al. 2010; Hegele et al. 2005).

5.1 Genetics of Dyslipidemia Using More Complex Modeling Approaches

Given the polygenic nature and complexity of dyslipidemia, a better understanding of the collective integration of these genetic determinants is needed, which will undoubtedly require more elegant statistical modeling methods. As stated throughout this chapter, there is some overlap between genetic variants associated with HDL-C, LDL-C, and TG levels as well as MetSyn, since dyslipidemia is a component of MetSyn. As a result, we need to better understand the aggregate effects of multiple variants as well as how the effects of variation in one gene are modified in the presence of other genes and their variants. Below, we discuss some more advanced approaches which have attempted to better understand the effects of multiple variants on lipid levels and dyslipidemia.

5.2 Genetics of Dyslipidemia Using Genetic Risk Scores

Methods to evaluate the aggregate effects of multiple variants in genes affecting dyslipidemia and MetSyn traits have included calculation of genetic "risk scores," which add the number of "risk alleles" in a weighted or unweighted manner. For example, higher genotype risk scores (GRS), constructed by simply summing risk alleles in nine common SNPs, have been associated with decreasing HDL-C levels (Kathiresan et al. 2008). In addition, unweighted risk scores have been constructed by summing the number of "TG-raising" alleles at 32 loci and then placed in "risk bins" (categories) to show that higher risk scores were significantly associated with patients with high TG (hypertriglyceridemia, HTG) compared to controls (Johansen and Hegele 2011; Teslovich et al. 2010).

GRS constructed using a weighted sum where the weight was based on the effect size and the number of SNPs (i.e., 47 SNPs for HDL-C, 37 SNPs for LDL-C, 32 SNPs for TG) were found to be strongly associated with HDL-C, LDL-C and TG in all age groups of children and adults, ages 3–45 years, in the Cardiovascular Risk in Young Finns Study; however, the total variance explained in these lipid levels decreased slightly with increasing age (3–6 years, 11.8–26.7 %; 18 years, 11.3–18.4 %; 33–45 years, 7.4–13.1 %) (Tikkanen et al. 2011). Using the area under the (AUC) receiver operating curve (ROC) and the Venkatraman test for correlated ROCs (Venkatraman ES 1996) and integrated model discrimination improvement, which compares the mean differences between predicted probabilities (Pencina and D'Agostino 2008), they concluded that the discrimination of high TG (HTG) in adulthood increased when the TG GRS were added to a model that also contained the childhood lipid measurement (Tikkanen et al. 2011). We note that the GRS in the Tikkanen et al. (2011) study contained SNPs in many of the genes summarized in this chapter including ABCA1, ANGPTL3, APOA1-C3-A4-A5, APOB, APOE, CETP, GALNT2, LDLR, LIPC, LIPG, LPA, LPL, MLXIPL, NPC1L1, PCSK9, PLTP, and SCARB1.

Additional studies in adults have also not found improved discrimination with the addition of GRS. For example, quantiles of unweighted GRS have been evaluated in two large British cohorts (British Women's Heart and Health Study, BWHS: $n = 3414$; Whitehall II, WHII: $n = 5059$), and when comparing the highest to the lowest quintiles of LDL-C GRS (derived from 23 SNPs), they observed higher LDL-C levels (mean difference: BWHS, 0.63 (0.50–0.76); WHII, 0.85 (0.76–0.94)) and an increased odds of developing coronary heart disease (CHD) (BWHS, 1.43 (1.02–2.00); WHII, 1.31 (0.99–1.72)) (Shah et al. 2013). However, the GRS did not improve discrimination over the Framingham Risk Score, which incorporates age, gender, smoking, diabetes status, SBP, TC, and HDL-C for assessing the 10-year risk of developing CVD (Anderson et al. 1991) when using AUC ROC methods (Shah et al. 2013).

In addition, weighted GRS constructed using 13 SNPs and 30 SNPs identified through associations with CVD in GWAS were found to be associated with CVD mortality (l3 SNPs, 1.35 (1.10–1.81); 30 SNPs, 1.46 (1.08–1.16)), but neither AUC ROC analyses nor the net classification index approach indicated the addition of the GRS (both 13 and 30 SNP versions) did not significantly improve prediction capacity of CVD mortality (Cox et al. 2014). Therefore, other more elegant methods may be needed to better understand the aggregate effects of multiple SNPs and their potential ability to predict disease.

5.3 Genetics of Dyslipidemia Using Multi-locus Burden and Dimension Reduction Methods

Using exome sequencing data from 2005 individuals from seven cohort studies, genetic burden tests, which evaluate aggregate effects of rare variants with low MAF, confirmed associations with APOE, LDLR, and PCSK9 genes and identified novel variants in PNPLA5 which were subsequently replicated in an independent study of 2,084 individuals of European descent (Lange et al. 2014).

Multifactor dimensionality reduction (MDR) (Ritchie et al. 2001) and generalized multifactor dimensionality reduction (GMDR) methods (Lou et al. 2007) have been used to evaluate genetic interactions at multiple loci. Interestingly, when six SNPs in the ZNF259/BUD13 region were evaluated using single-locus analyses in a sample of 1181 Chinese individuals, only one SNP (BUD13 rs17119975) was found to be marginally associated with TG ($p = 0.064$), but GMDR analyses revealed significant associations between two loci (BUD13 rs17119975, BUD13 rs10790162) and three loci (ZNF259 rs2075290, BUD13 rs17119975, BUD13 rs10790162) interaction models using cross-validation and permutation testing procedures (Aung et al. 2014), which suggests that GMDR may provide better insight to genetic interactions that may not be obviously revealed in single-locus analyses.

5.4 Genetics of Dyslipidemia and MetSyn Using Causal Modeling and Pathway Approaches

We have used the multivariate statistical framework of structural equation modeling (SEM) to evaluate multiple genetic determinants of MetSyn and aggregate effects of individual genes by modeling MetSyn as a second-order factor supported by lower-order factor traits (e.g., dyslipidemia) together with multiple latent candidate gene constructs, which we mathematically define by multiple SNPs in each respective gene (Nock et al. 2009). Using this approach with the Framingham Heart Study (Offspring Cohort, Exam 7; Affymetrix 50 k Human Gene Panel) data, we found that the CETP gene had a very strong association with the dyslipidemia factor but was not statistically significantly associated with MetSyn directly. Furthermore, we found that the association between the CSMD1 gene and MetSyn diminished when modeled simultaneously with six other candidate genes, most notably CETP and STARD13 (Nock et al. 2009). Our approach might also help identify and explain novel signals (e.g., CSMD1) in GWAS studies (Parra et al. 2011). Furthermore, we have evaluated the latent gene construct approach in the 1000 Genomes Project exon 5 sequencing data (24,497 SNPs in 697 unrelated individuals in seven populations), and we found that the approach provides a viable framework for modeling the aggregate effects of rare and common variants in multiple genes, but more elegant methods are needed to better identify the initial list of candidate loci (Nock and Zhang 2011).

The use of other forms of "causal modeling" (edge/node; integrative genetics) has been proposed to more fully address the complexity of MetSyn by integrating potential effects of maternal nutrition and epigenetics (Lusis et al. 2008; Wu et al. 2010). Furthermore, using gene enrichment analysis and protein-protein interaction network approaches, the retinoid X receptor and farnesoid X receptor (FXR), which have multiple interactions in metabolism, cell proliferation, and oxidative stress pathways, have been identified as key players in MetSyn (Sookoian and Pirola 2011).

Various other types of pathway and network analyses have also been used to model multiple variants and identify candidate pleiotropic loci. In a secondary analysis of the GWAS data from 188,577 individuals from Willer et al. (2013) where 62 SNPs were associated with HDL-C, 30 SNPs associated with LDL-C, and 32 SNPs associated with TG (157 unique loci), which were integrated with several other data sets of other components of MetSyn (BMI, SBP, DBP, BMI, CRP) and disease phenotypes (CAD, T2DM), 87 autosomal regions with 181 SNPs in 56 genes were found to be pleiotropic (Rankinen et al. 2015). Further evaluation of these data using interactome analysis (via the Reactome FI plug-in (Croft et al. 2011; Shannon et al. 2003)) and functionally interacting networks (via the Disease Association Protein-Protein Link Evaluator software (Rosen et al. 2011)) identified a network of 18 genes that showed statistically significant direct connectivity including direct connections with a cluster of genes consistently implicated in lipid disorders (APOA1, APOB, APOC1, APOE, ABCA1, CETP, LDLR, LIPC, LPL, PCSK9, PLTP), which contributed to the authors' conclusion that they found strong evidence for pleiotropy in CAD and lipid traits (Rankinen et al. 2015).

5.5 Pharmacogenomics for Dyslipidemia and MetSyn

However, more elegant kinetic models may be required to understand the true influence of genetic variants on dyslipidemia and MetSyn phenotypes given the presence of multiple feedback loops and reversible reactions (Bakker et al. 2010; Gutierrez-Cirlos et al. 2011), and pharmacogenomics is likely to have the most impact on the future of personalized medicine for lipid disorders. For example, statins remain the cornerstone for lowering lipids; however, the individual response to statins is influenced by the patient's underling genetics. Decent progress has already been made in understanding how genetic variation in CETP, HMGRC, ABCB1, CYP3A4, PCSK9, LDLR, and solute carrier organic anion transporter family member 1B1 (SLCOB1), which transports statins from the blood to the liver, affects statin pharmacology and lipid response (Kitzmiller et al. 2013). However, a better understanding of statin pharmacogenomics utilizing relevant pathway and network analysis will undoubtedly help to improve personalized response to statins and, in turn, help reduce the burden of CAD and CVD.

6 Cross-References

- ▶ Dyslipidemia in Obesity
- ▶ Genetics of Cardiovascular Risk in Obesity
- ▶ Genetics of Obesity
- ▶ Genetics of Type 2 Diabetes
- ▶ Nonalcoholic Fatty Liver Disease
- ▶ Overview of Metabolic Syndrome

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Genetics of Cardiovascular Risk in Obesity

12

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Contents

Abstract

Genetic risk assessment for cardiovascular disease (CVD) in obese patients requires considering all the background traits beginning as early as possible. Traits for both CVD and type 2 diabetes (T2D) first appear in gestation and childhood when birth weight and childhood weight gain influence; the traits and risk factors are more reversible than when they present later. Subsequently, gains in body fat leading to obesity, ectopic lipid deposition in liver and muscle, dyslipidemia, and hypertension expressed in the β-cells, hypothalamus, adipocytes, myocytes, liver, and kidney are associated with worsening insulin resistance and β-cell failure leading to both diabetes and CVD. In addition to being a central and causative factor for the metabolic syndrome, obesity is an increasingly common trait associated with energy balance under tightly regulated genetic control. Although nonalcoholic fatty liver disease (NAFLD) has an independent genetic background, it is strongly associated with obesity and is considered as a new addition to the metabolic syndrome and is also associated with dyslipidemia and CVD. Atherogenic dyslipidemia occurring in insulin-resistant states such as obesity consists of increased triglyceride, low high-density lipoprotein (HDL) cholesterol, small dense LDL particles, and dysfunctional HDL particles. It is greatly impacted by environmental and genetic effects. Like other preceding traits, the genetic

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background for commonly encountered hypertension is independent of that for diabetes, although it remains a predictive trait for both CVD and diabetes. Increasing evidence supports a role for the renin-angiotensin system in oxidative stress, CVD, and insulin resistance. In this review, we discuss how sequential progression of obesogenic environment leads to CVD with overlapping effects on β-cell, inflammation, and endothelial dysfunction. This review also provides current update on the discovery of novel predictive genes through genome-wide association studies and how they may illuminate novel disease pathways. Ultimately, these may help identify novel risk factors/biomarkers leading to the design of more effective treatment and/or prevention strategies.

Keywords

Metabolic syndrome • Cardiovascular disease • Type 2 diabetes • Pleiotropism • Gestation • Birth weight • Childhood • Adolescence • Obesity • Dyslipidemia • Hypertension • Glucose levels • β-cell • Endothelial dysfunction

1 Introduction

Recent worldwide trends toward increasing rates of obesity have been instrumental in increasing the prevalence of both cardiovascular disease (CVD) and type 2 diabetes (T2D). Although there is some leveling off in obesity trends in the United States (Flegal et al. 2010), global trends in overweight and obesity are increasing (Stevens et al. 2012) with serious implications for health. Obesity is often unrecognized, and screening and treatments are generally inaccessible and often ineffective (Wang and Lobstein 2006) accounting for secular changes in BMI in children (Ogden et al. 2012). This leads to obesity-associated disease beginning in childhood (Weiss et al. 2004) that progresses over time (Weiss et al. 2009) with increased loss of β-cell function and insulin resistance (Gungor et al. 2005) and the metabolic syndrome (Meigs et al. 2004). Associated metabolic changes include ectopic fat deposition (Cali and Caprio 2009), fat-induced insulin resistance (Samuel et al. 2010), β-cell dysfunction (Boden and Shulman 2002), and endoplasmic reticulum stress leading to β-cell apoptosis (Cui et al. 2013; Kharroubi et al. 2004). Waist circumference or BMI are strongly associated with insulin resistance (Farin et al. 2006) and are both highly correlated; however, BMI is the obesity quantitative trait in most genetic studies because of its availability and widespread acceptance.

The Metabolic Syndrome (According to ATP III Criteria) (Carr et al. 2004)

- Central obesity (also known as visceral, male-pattern, or apple-shaped adiposity) waist-hip ratio >0.90 (male) and >0.85 (female) or body mass index >30 kg/m^2
- Raised blood pressure (BP): systolic BP >130 or diastolic BP >85 mmHg
- Reduced high-density lipoprotein (HDL) cholesterol: <40 mg/dL (1.03 mmol/L) in males and <50 mg/dL (1.29 mmol/L) in females
- Raised serum triglyceride level: >150 mg/dL (1.695 mmol/L)
- Raised fasting plasma glucose: >100 mg/dL (5.6 mmol/L)
- Insulin resistance or prediabetes

Accumulating evidence suggests that insulin resistance and associated traits, traditionally known as the "metabolic syndrome," are associated with both diabetes and CVD and the more years that an individual carries the metabolic syndrome, the greater the risk for both T2D and CVD (Meigs et al. 2004; Haffner et al. 2000). These observations suggest that there is a window of time during which metabolic syndrome, as a predictive marker, could be used for timely intervention to prevent CVD. This window may extend further back than adulthood. Antecedent traits, similar to those of the metabolic syndrome, have been identified in the fetus, child, and adolescent suggesting early stages of pathogenesis. Although the age of onset for obesity-associated risk factors has been decreasing, the likelihood of appearance

of risk factors increases with age. This has been shown in epidemiological and genetic studies, most of which have been conducted on adult populations over 18 years of age. Typically, age is included as a confounder in data analysis. Nevertheless, early onset of obesity, in childhood or adolescence, may have a greater lifetime effect than later onset of obesity. Since components of the metabolic syndrome precede CVD and T2D (Haffner et al. 2000), it is important to recognize the onset of these risk traits during gestation and their persistence through childhood to adulthood (Morrison et al. 2008; Ford et al. 2008a). However, despite this association between metabolic syndrome traits and subsequent T2D, genetic studies have found that genetic variants associated with obesity or other metabolic syndrome traits do not usually overlap with genetic variants associated with T2D, suggesting relatively independent genetic backgrounds (Grarup et al. 2014). These findings suggest that shared interaction with lifestyle- and obesity-related environmental factors is significant and appear throughout life in a distinct sequence (Fig. 1). Furthermore, the traits themselves are known to activate additional metabolic pathways.

An analogy for the indirect effects on the final clinical outcomes is comparable to a railway transport system. A train with a sequence of coaches loaded with cargo in a city of origin for travel and delivery of goods to a destination city also delivers to towns en route. For example, delivery of tractors for a rural agricultural town and boats for a coastal town may result in a significant number of empty coaches. When the effect of the load on the economy of the destination city is assessed over a 10-year period based on the depleted coaches, an economist would arrive at an erroneous conclusion. More thorough investigation would reveal that delivered goods in regions along the train route caused increased production and economy in the respective regions of the country. The resulting ocean and agricultural produce, delivered from the respective regions, result in substantially increased purchase and consumption in the destination city. The environmental contributions from five rural and coastal regions surrounding the stations en route account for highly significant boost for the destination city, meaning that the initial appearance of empty coaches gave the false impression. Similarly, genome-wide association studies (GWAS) have only explained a small proportion of the genetic variance (up to 5 %) – implying only a minor role of genetic variation in the etiology of T2D and CVD phenotypes. Therefore, like the train analogy, perhaps it would be more instructive to identify the genetic variation determining hidden traits (endophenotypes or intermediary traits) and their respective biochemical effects that may accelerate insulin resistance and β-cell failure leading to onset of T2D. This may account for large proportion of the genetic variation that is missed in studies restricted to just CVD or T2D phenotypes as an endpoint. This is supported by findings that prediction models based on clinical risk factors such as age, sex, race, parental history of CVD and T2D, BMI, mean arterial pressure, fasting glucose, triglyceride, and HDL cholesterol, predict as well as a gene score as shown in the CARDIA study (Vassy et al. 2012a). Also, demographics, family history, physical examination, and routine biomarkers were predicted in T2D in adolescents from the Bogalusa study (Vassy et al. 2012b). These findings suggest that the clinical characteristics and biomarkers representing preceding traits have a strong effect on T2D and therefore could add to or alter effects of the genotype. Similarly multiple clinical traits could be superimposed on genetic background to influence overlapping pathways leading to CVD outcomes.

In this chapter, we present current evidence for genetic determination of obesity-associated prediabetic traits such as abnormal fetal and childhood growth, nonalcoholic fatty liver disease, dyslipidemia, and hypertension during childhood and adolescence and how each of these may activate metabolic pathways that lead to prediabetes, T2D, and CVD. Evidence is presented supporting the hypothesis that quantifiable obesity-related traits precede and predict CVD and T2D despite these traits and outcomes having distinct genetic backgrounds. Figure 2 summarizes major known variants associated with each of these antecedent phenotypes.

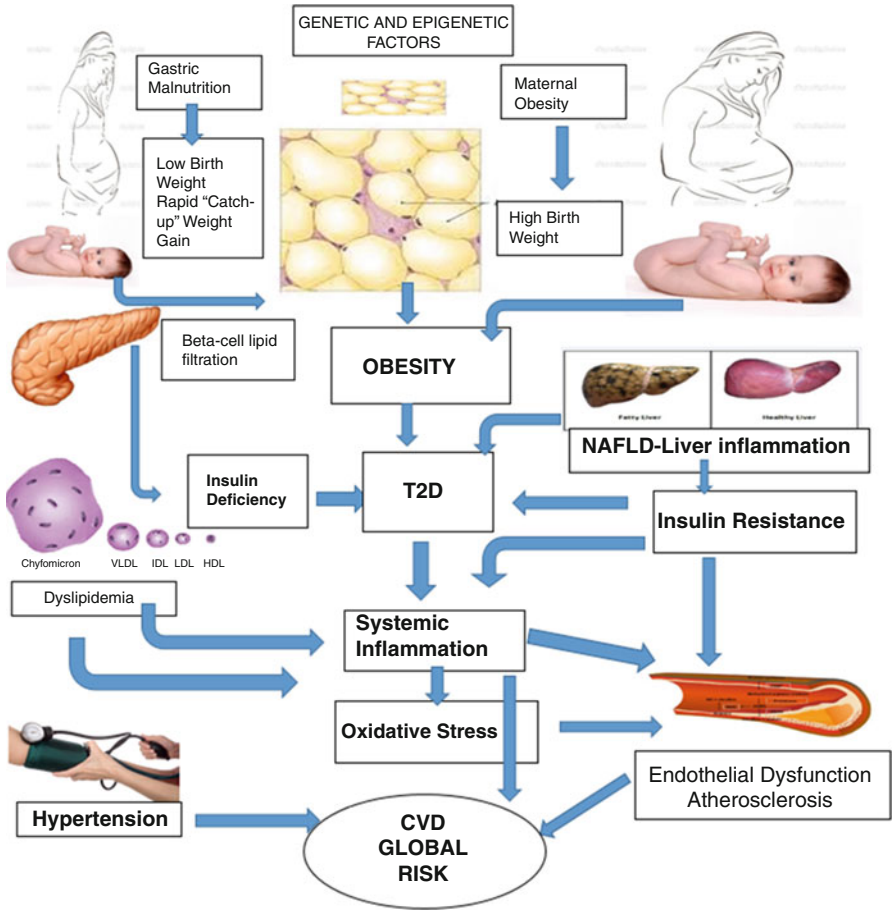

Fig. 1 A sequence of obesity-driven phenotypes interacting with genetic and epigenetic effects leading to CVD. The sequence of events begins in the fetus with maternal gestational nutrition and interaction with genetic endowment, affecting growth of the baby. Maternal malnutrition or fetal growth restriction causes small babies, and maternal overnutrition or hyperglycemia with gestational diabetes results in large babies. During childhood, exposure to nutritional excess results in obesity associated with rapid catch-up fat deposition and weight gain in small babies. The onset of obesity, dyslipidemia, and nonalcoholic fatty liver disease (*NAFLD*) occurs in children and adults and affects the β-cell resulting in insulin deficiency. Muscle and liver fat storage and hypertension are associated with insulin resistance, but the biochemical relationships are complex and bidirectional. Both insulin resistance and β-cell failure lead to T2D and to factors affecting the arterial wall such as inflammation and endothelial dysfunction ultimately leading to CVD which may be compounded by primary genetic susceptibility

2 Genetic Determinants of Obesity

Hypothalamic control of appetite has been associated with uncommon forms of monogenic obesity. However, despite being uncommon, these have provided insight into mechanisms for the development of obesity in the general population (Farooqi and O'Rahilly 2007). Studies on monogenic obesity cases and their families have led to definition of metabolic pathways using animal models, in particular the leptin-melanocortin pathway involved in satiation (Farooqi and O'Rahilly 2005). *MC4R* encoding the melanocortin-4 receptor is the commonest of the clinically occurring single-gene defects associated with severe obesity (Farooqi et al. 2003). Apart from these specific defects, genetic polymorphisms within these known genes are also involved in polygenic

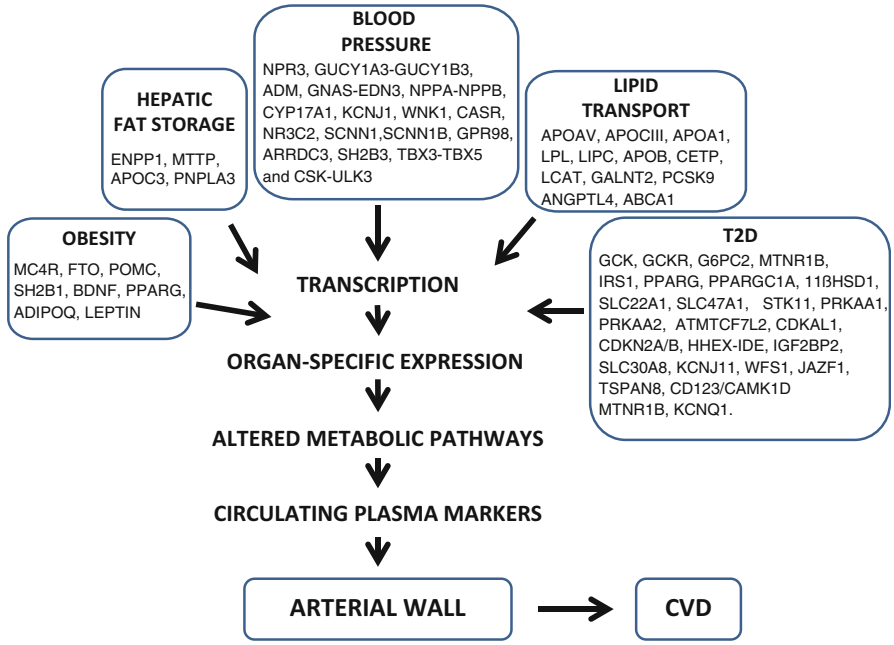

Fig. 2 Genetic variants undergo transcription, organ-specific expression, and alter metabolic pathways. The resulting plasma markers act on the arterial wall to cause cardiovascular disease. The effects of the variants can be interactive with each other (gene-gene) and the effects of altered metabolic pathways, which are additive

inheritance of obesity in the general population. Moreover, ~60 % of the BMI variance within a general population is accounted for by genetic variance (Stunkard et al. 1990). A large GWAS study on BMI conducted on 123,865 individuals using 2.8 million single nucleotide polymorphisms (SNPs) and follow-up in significant numbers revealed 14 known obesity susceptibility loci and identified 18 new loci (Speliotes et al. 2010). Some of the variants near loci, such as *MC4R*, *POMC*, *SH2B1*, and *BDNF*, were known hypothalamic regulators of energy balance. Another BMI locus detected by GWAS was near *GIPR*. The *GIPR* gene encodes for an incretin receptor present on β-cells and is regulated by intestinal incretions (Speliotes et al. 2010). These observations support a predisposition to T2D with pleiotropic effects in the hypothalamus and β-cell.

An intronic variant (rs9939609) in the *FTO* (fat mass and obesity-associated) gene was found to be associated with T2D GWAS, but the association was abolished when adjusting for BMI suggesting that the *FTO* variant influences T2D via its effect on obesity, a powerful diabetes-determining factor (Frayling et al. 2007). The association of *FTO* with obesity has been well replicated in longitudinal studies in childhood (Hallman et al. 2011; Liu et al. 2011). Additionally, a Dutch study reported association of *FTO* with higher BMI, fat mass index, and leptin concentrations during puberty but declining at ages 13–14 years, a finding thought to be consistent with hormonal effects at pubertal onset (Rutters et al. 2011). The association of severe obesity with *FTO* has been studied using a haplotype approach. Using linkage disequilibrium (LD) block structure of a region surrounding the candidate *FTO* rs9939609 SNP, a haplotype composed of a three-SNP combination was shown to be associated with severe obesity. The calculation of a risk score based on the *FTO* haplotype yielded an attributable risk of 34 % for severe obesity suggesting that the approach has clinical use for examining risk in predisposed families (Gonzalez et al. 2011).

Abundance of *FTO* mRNA transcripts has been reported in mouse hypothalamic nuclei encoding 2-oxoglutarate-dependent nucleic acid demethylase that supports a regulatory role in

energy balance, appetite, and sympathetic outflow to the circulatory system (Gerken et al. 2007). The mouse model studies further validated the role of *FTO* in controlling food intake, energy homeostasis, and energy expenditure (Church et al. 2009). Based on the findings in African and European American youth, the genetic effects on obesity occur early and affect the rate of weight gain (Liu et al. 2011). Consistent with these findings, another study reported that the high-fat intake and low physical activity modify the association between the *FTO* genotype and obesity (Sonestedt et al. 2009). Quantitative traits (QTs) of obesity such as BMI and waist circumference were associated with *FTO* as was seen in Europeans, but the association with T2D is only partly accounted for by BMI (Rees et al. 2011) suggesting that *FTO* has pleiotropic effects. Phenotypic interactions of the *FTO* variant (rs9939609) appear to be diabetogenic and have been explored in a recent large-scale meta-analyses study conducted on 96,551 individuals from East and South Asia confirming the association with T2D independent of obesity (Li et al. n.d.).

3 Hyperglycemia Precedes T2D and CVD

The risk factors preceding T2D vary in sequence and in the number of components reflecting both individual and population differences in inheritance and environments. However, detectable changes in glucose-insulin metabolism precede T2D and have been studied as QTs in genetic studies and as targets for reversal or prevention of T2D onset. Therefore, there has been interest not only in searching for genetic association but also in finding the glucose levels which accurately reflect T2D and risk for T2D. Consequently, The American Diabetes Association Expert Committee established the impaired fasting glucose range as 100–125 mg/dl and impaired glucose tolerance levels after ingestion of a glucose load as 140–199 mg/dl (*The Expert Committee of the Diagnosis and Classification of Diabetes Mellitus* 2000). These cut points were selected to facilitate early diagnosis of risk and have subsequently been of great significance since the defined prediabetic state is reversible by lifestyle (Knowler et al. 2002), suggesting that differences in lifestyle could affect outcomes in association studies.

Approximately 60 % of people who develop diabetes have either IGT (impaired glucose tolerance) or IFG (impaired fasting glucose) about 5 years before T2D onset, with 40 % having normal glucose tolerance (Unwin et al. 2002). Some studies suggest that IGT is more strongly associated with hypertension and dyslipidemia with worse cardiovascular outcomes (Unwin et al. 2002). Also, it is known that progression of IGT to T2D is potentially reversible with lifestyle (Knowler et al. 2002). However, insulin-mediated glucose disappearance becomes impaired in cases with IFG and IGT, who also have increased cardiovascular risk (Basu et al. 2013; Bock et al. 2007). The rs553668 of the *ADRA2A* gene predicts worsening of fasting glucose values in a prediabetic cohort (Bo et al. 2012). Variants associated with fasting glucose levels discovered through GWAS such as *GCK*, *GCKR*, *G6PC2*, *MTNR1B*, and *DGKB-TMEM195* (Takeuchi et al. n.d.) in the normoglycemic population do not always influence risk for T2D (in contrast to *TCF7L2* and *SLC30A8*), but their effect appears confined to fasting glucose homeostasis (Reiling et al. 2009; Chen et al. 2008). The data support recognition of early hyperglycemic phenotypes derived from regulatory polymorphisms on the genes affecting interacting pathways leading to T2D. Meta-analysis of 21 GWAS identified nine new loci influencing fasting blood glucose (*ADCY5*, *MADD*, *ADRA2A*, *CRY2*, *FADS1*, *GLIS3*, *SLC2A2*, *PROX1*, and *C2CD4B*), but of these, only *ADCY5* and *PROX1* were associated with T2D. These data suggest that although there is overlap, the genetic background for fasting glucose is different from that of T2D (Dupuis et al. 2010). Similarly, the 2-h glucose levels, after a standard oral glucose load, can be defined as a separate trait to T2D with overlap in the associated variants. Meta-analysis identified new loci, *GIPR* and *UPS13C*, uniquely influencing 2-h glucose (Saxena et al. 2010) supporting the hypothesis that there are separate glucose-related

QTs representing specific modes of carbohydrate metabolism (Bonnefond et al. 2010).

There is a prevailing hypothesis that excess weight gain precedes type 1 diabetes (T1D) and accounts for the increased prevalence over the past decade (Wilkin 2009); furthermore, T1D patients who become obese have increased risk for CVD. One possible mechanism for this is that hypersecretion of insulin during states of insulin resistance, a consequence of excess weight gain, is antigenic, triggering or contributing to an unregulated immune response when predisposed by genetic variants coding for aberrant T-cell responses and T-cell-mediated β-cell destruction. Dietary factors have also been implicated, including the timing of introduction of solid foods and cow's milk to the infant's diet (Kostraba et al. 1993). Like T2D, T1D is associated with CVD and is a major cause of death among T1D individuals (Secrest et al. 2010).

Increased prevalence of T2D in adolescents over the past two decades has coincided with an increase in adults with descending age of onset for both obesity and T2D (Pinhas-Hamiel et al. 1996). Resistance to insulin action occurs in the liver, fat cell, and muscle, and respective pathways may contribute to T2D (Samuel et al. 2010). Furthermore, longitudinal studies indicate association of insulin resistance and obesity in youth with gender and ethnic-specific tracking of BMI and lipids to middle-age adulthood (Juhola et al. 2011). Not only is the metabolic syndrome a predictor of T2D (Ford et al. 2008a, b) but also the syndrome traits or QTs are associated with insulin resistance (Salazar et al. 2011). Also, the prevalence of the metabolic syndrome increases with progression from normal glucose tolerance to IGT to onset of T2D when it often exceeds 60 % depending on the definition and study population (Isomaa et al. 2001; Xiang et al. 2012). Based on population studies and animal models, it has been proposed that T2D has a progressive pathogenesis beginning with insulin resistance and advancing to β-cell failure (Doria et al. 2008) and that it may involve several genes, sometimes with significant interaction (Bruning et al. 1997). For example, using knockout models for both *IRS-1* and the insulin receptor, it was shown that neither model alone had much effect on diabetes onset, but the combined effect resulted in more than 50 % developing diabetes at young ages (Bruning et al. 1997).

Glucose cut points for the diagnosis of diabetes have been based on arbitrary glucose thresholds. Based on evidence for a bimodal distribution, the National Diabetes Data Group in the United States initially used the glucose levels that best distinguished overlapping populations (Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group 1979). Two decades later, it was observed that the levels appeared too high since cases below the cut points developed retinopathy; consequently, the American Diabetes Association Expert Committee decreased the thresholds based on cross-sectional association between glucose levels and the development of retinopathy (Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997). Accordingly, a fasting glucose greater than or equal to 126 mg/dl and 2 h post-glucose load level $\geq$200 mg/dl have become cut points for diabetes. Also, HbA1c is increasingly being introduced as supportive diagnostic evidence for T2D (Saudek et al. 2008) in addition to its use in defining prediabetes. Since it does not require fasting conditions and has become generally available as a standardized assay with less interindividual biologic variability than glucose, it has a potential for diagnostic use in clinics and for screening. However, conditions that influence hemoglobin production or disposal influence the levels and when used alone can lead to missed diagnoses even when using a relatively high cut point of 6.5 % (Herman and Fajans 2010).

Since the diagnosis of T2D has been based on glucose thresholds defining overt diabetes, it is possible that variants determining β-cell function interact with secondary metabolic derangements since subjects are assessed at a point when the β-cells are likely to be undergoing failure or cell death. This is supported by observations that the majority of GWAS variants associated with T2D such as *TCF7L2*, *CDKAL1*, *CDKN2A/B*, *HHEX-IDE*, *IGF2BP2*, *SLC30A8*, *KCNJ11*, *WFS1*, *JAZF1*, *TSPAN8*, *CD123/CAMK1D*, and *MTNR1B* (Table 1) are implicated in β-cell functions such as glucose-stimulated insulin secretion,

Table 1 Established genetic determinants of the traits preceding type 2 diabetes and cardiovascular disease

Trait	Gene	Chromosome	Entrez gene ID	Role
Fetal growth	*INS*	11 p15.5	3630	Signaling hormone increases permeability to monosaccharides, amino acids, and fatty acids
	INSR	19 p13.3	3643	Signaling hormone receptor tyrosine kinase
	IPF1/ PDX1	13q12.1	3651	Activates insulin, glucokinase, and glucose transporter T2D gene transcription
	KCNJ1	11q24.3	3758	Associated with Bartter syndrome characterized by salt wasting, hypercalciuria, and low blood pressure
	ABCC8	11p15.1	6833	Regulator of ATP-sensitive K(+) channels and insulin release
	HNF1B	17q12	6928	Involved in diabetes syndrome and noninsulin-dependent diabetes mellitus
	ADCY5	3q21.1	111	Gene variants influence fasting glycemic traits and insulin resistance
	HHEX-IDE	10q23.33	3087/ 3416	Transcription factor involved in hematopoietic differentiation, pancreatic development, and insulin secretion
	GCK	7p14	2645	Modulates insulin secretion, glycolysis, energy pathways
	TCF7L2	10 q25.2	6934	Transcription regulator influences insulin secretion
	HNF1A	12q24.31	6927	Regulates tissue-specific expression of genes especially in pancreatic islets and liver
Obesity	*FTO*	16q12.2	79068	Severe obesity/insulin resistance
	MC4R	18q21.32	4160	Member of G protein-coupled receptor family, signaling hormone involved in energy homoeostasis
	PPARG	3p25.2	5468	Transcription factor involved in adipogenesis and type 2 diabetes risk
	ADIPOQ	3q27.3	9370	Adipose tissue-specific protein involved in insulin sensitizing and anti-atherosclerotic properties
	LEPTIN	7q31.3	3952	Signaling hormone affects central nervous system to inhibit food intake and energy expenditure
	POMC	2p23.3	5443	Mutations in this gene linked with early onset obesity
	SH2B1	16p11.2	25970	Obesity locus associated with myocardial infarction in T2D patients
	BDNF	11p14.1	627	Development, survival, and differentiation of selected neuronal populations
NAFLD[a]	*ADIPOR2*	12p13.31	79602	Hormone secreted by adipocytes with antidiabetic effects
	MTTP	4q23	4547	Catalyzes the transport of triglyceride, cholesterol ester, and phospholipids between phospholipid surfaces
	APOCIII	11q23.3	345	Inhibits lipoprotein lipase; delays catabolism of triglyceride-rich particles
	PNPLA3	22q13.31	80339	Triacylglycerol lipase that mediates triacylglycerol hydrolysis in adipocytes
Dyslipidemia	*APOE-CI-CII-CIV*	19q13.32	2282	Cluster of triglyceride-rich lipoprotein receptor ligands for LDL receptor-related proteins
	APOAV-AIV-CIII-AI	11q23.3	117536	Cluster of apolipoproteins plays an important role in regulating the plasma triglyceride levels
	PCSK9	1p32.3	255738	Decreases plasma and LDL cholesterol and provides protection from coronary artery disease

(*continued*)

Table 1 (continued)

Trait	Gene	Chromosome	Entrez gene ID	Role
	CETP	16q13	1071	Exchanges cholesterol esters for triglycerides from HDL and triglyceride-rich lipoproteins
	LCAT	16q22.1	3931	Required for remodeling HDL particles into their spherical forms
	ABCA1	2p23.3	2646	Mutations cause Tangier' disease and familial HDL deficiency
Hypertension	*WNK1*	12p13.33	65125	A key regulator of blood pressure by controlling the transport of sodium and chloride ions
	KCNJ1	11q24.3	3758	Associated with Bartter syndrome characterized by salt wasting, hypercalciuria, and low blood pressure
	NPR3	5p13.3	4883	Regulate blood volume and pressure, pulmonary hypertension, and cardiac function
	GUCY1A3	4q32.1	2982	Regulate blood volume and Na+ balance
	GNAS	20q13.32	4686	Involved as modulators or transducers in various transmembrane signaling systems
	NPPA-NPPB	1q36.22	9757	Associated with intracellular guanylyl cyclase activity and involved in homeostasis of body fluid volume
	CYP17A1	10q24.32	1586	Variants associated with hypertension
	ARRDC3	5q14.3	57561	Variants associated with diastolic blood pressure
	C21orf91	21q21.1	54149	Variants associated with hypertension
Hyperglycemic traits				
(Pre-T2D)	*GCKR*	2p23.3	2646	Enzyme regulators, controls activity of glucokinase in the liver and brain
Fasting glucose	*G6PC2*	2q24.3	57818	Enzyme, transport channel, key role in glucose homeostasis
	MTNR1B	11q21-q22	4544	Melatonin receptor regulates physiological and neuroendocrine functions
	DGKB-TMEM195	7p21.2	1607/ 392636	Play a key role in cellular processes
	GCK	7p14	2645	Modulates insulin secretion, glycolysis, energy pathways
	ADCY5	3q21.1	111	Variants influence fasting glycemic traits and insulin resistance
	MADD	11p11.2	8567	Variants influence fasting glycemic traits and insulin resistance
	CRY2	11p11.2	1408	Variants influence fasting glycemic traits and insulin resistance
	FADS1	11q12.2	3992	Variants influence fasting glycemic traits and insulin resistance
	GLIS3	9p24.2	169792	Variants affect fasting glucose and T2D
	SLC2A2	3q26.1	6514	Plays role in human beta cell function and impacts glycemic traits
	PROX1	1q41	5629	Gene variants affect fasting glucose and insulin
2 h glucose	*GIPR*	19q13.3	2696	Stimulate insulin release in the presence of elevated glucose
	VPS13C	15q22.2	54832	Gene variants influence glycemic traits and insulin resistance

(*continued*)

Table 1 (continued)

Trait	Gene	Chromosome	Entrez gene ID	Role
β-cell function				
(T2D)	*TCF7L2*	10 q25.2	6934	Transcription regulator influences insulin secretion
	SLC30A8	8q24.11	169026	Facilitates transportation of zinc from cytoplasm into insulin containing vesicles
	IGF2BP2	3q27.2	10644	Regulatory enzyme influences insulin secretion
	CDC123	10p13	8872	Involved in transcription regulation, insulin secretion
	HHEX-IDE	10q23.33	3087	Transcription factor involved in hematopoietic differentiation, pancreatic development, insulin secretion
	CDKN2A/B	9p21.3	1029	Enzyme, anti-oncogene involved in pancreatic carcinomas, type 2 diabetes
	KCNJ11	11 p15.1	3767	Ion channel transporter
	KCNQ1	11p15.5	3784	Encodes a voltage-gated K channel required for repolarization phase of the cardia action, associated with T2D

[a]*NAFLD* Nonalcoholic fatty liver disease

incretin effects on β-cell stimulation, and proinsulin to insulin conversion (Schafer et al. n.d.; De Silva and Frayling 2010). It also appears likely that many of the secondary events described for each of the preceding phenotypes have significant effects on both insulin resistance and β-cell failure.

4 Fetal and Early Childhood Growth and the Metabolic Syndrome

Over the past two decades, accumulating evidence shows a strong relationship of low birth weight (usually defined as <2.5 kg) to metabolic syndrome traits in adulthood including hypertension and progression to T2D (Chernausek 2012). Based on initial studies that showed a relationship of birth weight to impaired glucose tolerance at age 64 years, Barker et al. (Hales and Barker 1992) proposed the "thrifty phenotype" hypothesis. It states that T2D and metabolic syndrome traits result from the effects of poor nutrition in early life, which produces permanent changes in glucose-insulin metabolism. Their pioneering work showed a link between birth weight and both diabetes and CVD in adulthood. The initial observations were well replicated, supporting the argument that fetal growth restriction may result in permanent and progressive changes leading to T2D. It has also been shown that subsequent rapid catch-up shown as an increase in BMI in children who were born small predicts disease risk in adulthood. This suggests that risk is increased when infant nutrition exceeds gestational nutrition but not when the nutritional supply is matched (Eriksson et al. 2000; Forsen et al. 2000). For instance, weight gain in the first 3 months may determine insulin resistance as early as adolescence (Fabricius-Bjerre et al. 2011) or late childhood (Barker et al. 2002). Furthermore, fetal growth restriction by genetic or nutritional causes could set the stage for the small baby to gain fat as the preferential tissue resulting in a "catch-up fat" phenotype (Dulloo et al. 2006) but programmed by restriction of nutrient-dependent pathways during fetal growth.

It is also evident that gestational weight gain of the mother is an independent predictor of obesity during infancy, even occurring when the maternal prepregnancy weight is normal (Dello Russo et al. 2013). Thus maternal weight gain during pregnancy predisposes the child to become obese continuing to adulthood (Schack-Nielsen et al. 2010). In addition, exposure to high maternal glucose during gestation can result in large babies giving rise to observations that risk for T2D is

determined by large birth weight, meaning that the relationship of both low and high birth weight to subsequent T2D can be characterized as bimodal (Tamashiro and Moran 2010). Also, maternal fat intake during gestation influences glucose tolerance of the offspring. Therefore it appears likely that excess maternal nutrient supply, particularly as fat, may have long-term effects (Dabelea and Pettitt 2001). A review of 11 animal model studies investigating glycemic control in offspring of mothers exposed to a high-fat diet during gestation has identified risk for T2D and obesity in the offspring. The effect was stronger in males, and glucose intolerance was independent of maternal obesity, birth weight, or postweaning macronutrient intake (Ainge et al. 2011). Studies have shown that fetal systems are also modulated by metabolic factors such as the hypoxic effect of changes in blood supply, oxidative stress, DNA methylation, histone acetylation, transcription factors, and hormones such as cortisol, insulin, and leptin. These factors could serve as a basis for prevention, treatment, and for further studies to determine interaction of the metabolic factors with genotypes (Sebert et al. 2011). Epigenetic effects in the form of biochemical modification of DNA, such as methylation, may not only occur in the fetus but continue in later life (Sinclair et al. 2007; Gemma et al. 2010) and influence traits such as nonalcoholic fatty liver disease (NAFLD) (Sookoian et al. 2010).

Evidence for a genetic background for fetal growth is increasing significantly supporting possible interaction with gestational factors. Observation that mutations in the glucokinase gene (*GCK*) resulted in reduced birth weight gave rise to the hypothesis that rare variants that modify insulin secretion or action could not only cause monogenic diabetes but also low birth weight (Hattersley et al. 1998; Hattersley and Tooke 1999). This has been supported by findings that reduced birth weights occur due to other known monogenic mutations causing early onset diabetes, such as *INS*, *INSR*, *IPF1*, *KCNJ11*, *ABCC8*, and *HNF1B* (Stoy et al. 2007; Edghill et al. 2006; Slingerland and Hattersley 2006; Babenko et al. 2006). A GWAS for birth weight has revealed association of fetal loci near *ADCY5*, *CDKAL1*, and *HHEX-IDE* genes. The same risk allele at the *ADCY5*, associated with low birthweight, also predisposes to T2D (Yaghootkar and Freathy 2012). Incidentally, the effects on fetal growth restriction can potentially be offset by maternal alleles at *GCK* and *TCF7L2* that result in reduced maternal insulin and consequent growth stimulation by fetal hyperinsulinemia secondary to transplacental passage of maternal glucose (Yaghootkar and Freathy 2012). The hyperglycemic effect on the fetus is known to interact with fetal *HNF1A*, a known maturity onset diabetes of young (MODY) gene, resulting in earlier onset of the diabetes (Stride et al. 2002). GWAS conducted by the "Meta-Analyses of Glucose- and Insulin-related traits Consortium" (MAGIC) has identified seven maternal loci associated with birth weight accounting for a similar proportion of variance to maternal smoking. Two of the loci, *ADCY5* and *CDKAL1*, were replicated from previous studies (Freathy et al. 2009) and predicted T2D supporting association of common variants with fetal growth and subsequent metabolic events predisposing to T2D (Horikoshi et al. 2013). However, due to possible population differences, the low birth weight was not explained by genetic variation in the *ADCY5* in Asian Indians, although these variants were associated with elevated glucose and reduced insulin response in early adulthood (Vasan et al. 2011).

5 Thrifty Genes, Obesity, and the Risk of CVD

To explain the relationship of obesity to T2D and CVD, it has been proposed that an array of "thrifty" genes are latent in the normal state and efficiently store nutrients for times of need (Neel 1999); but with constant nutritional excess over extended periods, dyslipidemia and ectopic fat deposition in the liver and muscle lead to insulin resistance and diabetes (Samuel et al. 2010; Shulman 2000). Constant and excessive nutritional intake, common in modern cultures, has contributed to the worldwide escalation in obesity and subsequent morbidities by interacting with the genetic backgrounds beginning with

measurable traits for fetal growth, fatty liver disease, dyslipidemia and hypertension, and their metabolic effects. However, common genetic variation in few obesity or T2D genes has been identified to promote excess nutrient storage, suggesting that trait-specific metabolic processes are primed to promote excessive nutrient storage and subsequently lead to dysfunctional carbohydrate homeostasis and fat metabolism. For example, accumulation of excessive diacylglycerol in the liver is associated with accumulation of liver and muscle fat leading to defective insulin action (Kumashiro et al. 2011), particularly in genetically susceptible populations such as Asian Indian men (Petersen et al. 2006). Ectopic liver fat is highly associated with atherogenic dyslipidemia, even in adolescents (Targher et al. 2005; Cali et al. 2007).

6 Nonalcoholic Fatty Liver Disease (NAFLD), Obesity, and CVD Risk

NAFLD is the buildup of extra fat in liver cells that is not caused by alcohol and results from excessive obesity. There is a growing evidence to support that traits representing NAFLD are also significant pre-T2D phenotypes. NAFLD is also regarded as a new component of the metabolic syndrome (Kotronen and Yki-Jarvinen 2008) with an independent genetic background. Predisposition to T2D is supported by observations that liver fat is increased in T2D compared to equally obese nondiabetic patients (Kotronen et al. 2008). Also patients with NAFLD have insulin-resistant adipose tissue and tend to have higher rates of glucose intolerance which is associated with increased risk for T2D (Ortiz-Lopez et al. 2012; Lomonaco et al. 2012). The association of NAFLD with insulin resistance begins in childhood and adolescence (Ciba and Widhalm 2007) and with increased visceral fat and low adiponectin in adolescence (Burgert et al. 2006), supporting association with adiponectin's effects via adiponectin receptor 2 (*ADIPOR2*) in three independent Finnish cohorts (Kotronen et al. 2009). The association between insulin resistance and NAFLD has been confirmed in a meta-analysis of 21 prospective population-based studies of fatty liver disease diagnosed by liver ultrasonography (Fraser et al. 2009). Also there is evidence for NAFLD progressing to T2D (Ekstedt et al. 2006). Excess storage of fat in the liver is associated with activation of inflammation and production of cytokines, particularly IL-6 (Kumar et al. 2012), which may lead to further insulin resistance activated via signaling pathways such as toll-like receptors (Petrasek et al. 2013) and possibly by the receptor activator of nuclear factor-kB (RANKL) (Kiechl et al. 2013). Simple steatosis progresses to inflammation with risk for cirrhosis and liver cancer (Kotronen and Yki-Jarvinen 2008) and is independently associated with increased risk of coronary artery disease (CAD) (Targher et al. 2010).

Large-sized VLDL has been observed in NAFLD in an adolescent population independent of adiposity and insulin resistance, and the NMR (nuclear magnetic resonance) lipid profile was characterized by small dense LDL and reduced number of large HDL particles (Cali et al. 2007), revealing the association of NAFLD with a lipid profile predisposing to atherosclerosis in adults (Targher and Arcaro 2007) and with increased intima-media thickness (IMT) in adolescents (Pacifico et al. 2008). These data suggest pleiotropic effects, or alternatively, the effects arise from a biochemical cascade leading to excessive hepatic fat storage, inflammation, and lipoprotein abnormalities. Maturation of the VLDL particle in the golgi, at the stage when triglyceride is transferred to apoB by microsomal triglyceride transfer protein encoded by *MTTP*, determines liver fat storage and if defective may lead to NAFLD (Sparks and Sparks 2008). Carriers of the *MTTP*-493 G/T allele also have a more atherogenic lipid profile (Gambino et al. 2007), which may have a deleterious effect on β-cell function (Musso et al. 2010). Furthermore, the *MTTP-I128T* variant is associated with central obesity, elevated liver enzymes in fatty liver disease with and without association with alcoholism (Jun et al. 2009). In addition, a manganese superoxide dismutase (*MnSOD*) variant was associated, possibly working by reducing mitochondrial fatty acid oxidation. Genetic

determinants of VLDL formation and disposal may result in both atherosclerosis and fatty liver disease. In a study conducted on Asian Indian men revealed that the carriers of two *APOCIII* variant alleles (C-482T, T-455C, or both) had a 30 % increase in apoC-III levels and a 60 % increase in triglyceride, as compared with the wild-type homozygotes. The prevalence of NAFLD was 38 % among variant allele carriers compared to 0 % among wild-type homozygote carriers showing a significant correlation with insulin resistance (Petersen et al. 2010). Furthermore, the apoC-III overexpression model is predisposed to diet-induced hepatic steatosis and hepatic insulin resistance (Lee et al. 2011).

A GWAS of 2,111 participants of the Dallas Heart Study revealed a robust association of liver fat defined by magnetic spectroscopy with the I148M allele of the *PNPLA3* gene (Romeo et al. 2008), and the association was replicated in children and adolescents (Romeo et al. 2010a), when it may act jointly with *GCKR* (Santoro et al. 2012). A meta-analysis of 16 studies showed *association* of *PNPLA3* with disease severity with strong effect on more aggressive disease susceptibility indicated by higher inflammation indices and progression to fibrosis (Sookoian and Pirola 2011). The gene *PNPLA3* codes for patatin-like phospholipase domain-containing protein 3, or adiponutrin, which plays a role in hepatic triglyceride hydrolysis. It catalyzes conversion of lysophosphatidic acid into phosphatidic acid, an important regulatory reaction in lipid synthesis. Adiponutrin is upregulated by sucrose feeding in the mouse model, and the *PNPLA3* l148M variant results in increased cellular lipid accumulation providing a plausible mechanism for its impressive association with NAFLD (Kumari et al. 2012). In addition to *PNPLA3*, diet-induced obesity increases adiponutrin expression (Oliver et al. 2012) which is associated with increased alanine transaminase, a marker of fatty liver disease, in Europeans, Hispanics, and Asian Indians (Romeo et al. 2010b; Yuan et al. 2008). The homozygous carriers of the *PNPLA3 I148M* variant showed increased fasting glucose levels (Krawczyk et al. 2011), and the *PNPLA3* S453I allele was associated with lower hepatic fat content and was more frequent in African Americans who had the lowest hepatic fat content, suggesting a protective effect from NAFLD (Romeo et al. 2008).

7 Atherogenic and Diabetogenic Dyslipidemia

The classic atherogenic dyslipidemia associated with the metabolic syndrome not only precedes and predicts T2D but abnormal LDL and HDL particles have biochemical associations with T2D pathogenesis. Insulin-resistant states such as obesity promote increased triglyceride, low HDL cholesterol, and molding of triglyceride-containing lipoproteins to form atherogenic LDL particles and dysfunctional HDL particles particularly when there is increased abdominal fat (Carr and Brunzell 2004). As in the case of other prediabetic traits, independent genetic determinants of dyslipidemia (discussed below) interact with nutritional excesses and obesity-generated insulin resistance.

In vitro studies have shown that the addition of LDL to human and rat islets decreases glucose-stimulated insulin secretion and is attributed to cholesterol uptake by islet LDL receptors and intracellular cholesterol-mediated toxicity (Rutti et al. 2009). Intracellular accumulation of cholesterol is dependent on HDL-mediated cholesterol efflux via the ATP-binding cassette transporter A1 (ABCA1), which is rate limiting supporting a critical protective role for HDL (Kruit et al. 2010a). Further studies have revealed that high cholesterol content in the β-cell membrane downregulates insulin secretion by influencing membrane depolarization, the signal for calcium influx, and calcium-mediated insulin secretion (Hao and Bogan 2009). Since the classic dyslipidemia associated with the metabolic syndrome precedes T2D onset by several years (Ford et al. 2008a), the effect of low HDL, which is a predictor of CVD, is operative over an extensive time period depending on the duration of a low HDL.

In addition, elevated triglyceride is associated with increased fatty acid levels, which enter the

β-cell and undergo glucose-dependent esterification resulting in lipotoxicity (Briaud et al. 2001). Since not all obese individuals have elevated triglycerides and nonobese cases can present with elevated levels (Lim et al. 2011; Musso et al. 2011), genetic predisposition can account for abnormal levels and for gene-environment interactions with obesity and dietary intake. Four commonly encountered classic hypertriglyceridemia phenotypes (IIb, III, IV, and V) originally described at the National Institutes of Health have been characterized as having an elevated level of triglyceride. Type III hyperlipidemia is an exception since it has a distinct monogenic association with *APOE* polymorphism with homozygous effects of apoE2 isoform when the individual becomes obese. Type IIb, IV, and V phenotypes were associated with common variants which had previously been identified in GWAS performed on subjects with mild triglyceride elevations (Alvarez Caro et al. 2011). Thus clinically relevant dyslipidemia with high triglyceride can often be associated with common triglyceride-associated variants. Homozygous expression of rare variants such as *APOAV* and *APOE* can result in severely increased triglyceride (Hunter et al. 1979); severe cases were found to be carriers of *APOAV* variants, S19W or −1,131 T>C. Epidemiological studies suggest that elevated serum triglyceride concentration is a strong independent risk factor for CAD and ischemic stroke (Hokanson and Austin 1996; Freiberg et al. 2008). Chromosome region 11q23.3 comprising a cluster representing *APOA5-A4-C3-A1* genes has a profound effect on elevating plasma triglyceride levels in animal and human studies (Coram et al. 2013; Baroukh et al. 2004). Recent GWAS and meta-analysis studies using thousands of participants have confirmed SNPs within 11q23.3 (*BUD13*, *ZNF259*, and *APOA5-A4-C3-A1*), and other candidate gene regions representing *LPL*, *GCKR*, *MLXIPL*, *ANGPTL3*, *APOC1*, *APOC2*, and *TRIB1* have been reported to be strongly associated with elevated triglyceride concentrations in multiple GWAS and meta-analysis studies (Coram et al. 2013; Teslovich et al. n.d.; Kathiresan et al. 2008, 2009; Willer et al. 2013; Kamatani et al. 2010). A strong association signal for triglyceride represented by rs964184 (*BUD13-ZNF259*, $p = 1.1 \times 10^{-39}$) was replicated in on 8,530 South Asians from LOLIPOP (UK) and Punjabi Sikhs (Braun et al. 2012).

The −455 T>C variant in the *APOCIII* gene promoter region is associated with increased triglyceride levels. The −455C and −482T alleles, located in the insulin response element (IRE), fail to respond to insulin-mediated downregulation via Foxo1 so that transcription remains active and plasma apoC-III is increased (Chen et al. 1994). This mechanism explains the association of apoC-III levels in non-HDL lipoproteins with insulin resistance in children and adolescents (Blackett et al. 2005). Since apoC-III transcription is activated in insulin resistance, increases in plasma apoC-III and triglyceride (Li et al. 1995) occur in insulin resistance due to obesity. Since transfer proteins and lipolytic enzymes mediate triglyceride and apoC-III transfer, there are increases in the atherogenicity of both LDL (Mendivil et al. 2011) and HDL (Jensen et al. 2012). The finding that apoC-III content of HDL predicts T2D (Onat et al. 2009) could be attributed to change in HDL function. Furthermore, the higher diabetes prediction in females (Onat et al. 2009) follows the appearance of higher levels of plasma apoC-III relative to apoA-I in teenage girls possibly accounting for a higher prevalence of T2D in young females than males (Blackett et al. 2012). In a multiethnic population sample, the serum triglyceride levels were 20 % higher among individuals carrying −455C, particularly in females who were also shown to have low HDL-C (Dallongeville et al. 2001).

It has long been known that cultural, environmental, and hormonal factors determine HDL-C. However, a genetic component accounts for up to 76 % of its variation (Snieder et al. 1999), suggesting that genetic variants may affect HDL regulation and expression of HDL-associated traits with environmental interaction (Vaziri 2006). Regulatory genes involved in HDL metabolism mediated by apoA-I, LCAT, ABCA1, and endothelial lipase have been associated with severe HDL deficiencies (Qin et al. 2000), but only 20 % of cases have been explained by gene

mutations, and the population frequencies of the major gene abnormalities are very low. However, association of these rare variants with atherosclerosis has been ambivalent (Larsen et al. 2002), supporting a case for functional assays to represent the HDL phenotype such as measures of cholesterol efflux (Posadas Romero 2007).

Gene mapping and association studies have identified quantitative trait loci (QTLs) for apoA-I and HDL-C levels at chromosome 6p, 9q, and 15q (Le Goff et al. 2004). Since the studies were done in a predominantly American Indian population, the findings could lead to association of SNPs with insulin-resistant phenotypes including T2D (Alaupovic et al. 2008). The 15q region has been recognized to have a significant interaction with diabetes, BMI, smoking, alcohol intake, and gender (Sakai et al. 1995). After serial adjustments, the LOD score increased from 1.75 to 4.52, supporting multiple endogenous and environmental influences including obesity. A region on 9q contains the *ABCA1* gene coding for the cholesterol transporter regulating efflux from cells to HDL. The gene was found to contain the *ABCA1*-C230 variant which was associated with low HDL cholesterol exclusively in American Indian populations who have increased risk for T2D (Joy and Hegele 2009). This is important since carriers of loss of function mutations in *ABCA1* display pancreatic β-cell dysfunction supporting a role for *ABCA1* in removing cholesterol from β-cells (Kruit et al. 2010b).

Susceptibility to changes in HDL composition and function occurs in obesity in part due to triglyceride elevation. Triglyceride enrichment of HDL is mediated by cholesterol ester transfer protein (CETP) and is followed by degradation of HDL by hepatic triglyceride lipase, dissociation of apoA-I, and subsequent renal catabolism (Thompson et al. 2008). It follows that in hypertriglyceridemic conditions, CETP activity has an HDL-reducing role. Conversely, CETP deficiency secondary to a gene defect results in extreme elevations in HDL-C (Nagano et al. 2001) while maintaining function. Consequently CETP inhibition is the basis for use of pharmaceutical agents designed to raise HDL-C with encouraging recent trial results despite previous setbacks (Bochem et al. 2013). Genetic variation in *CETP* has been studied for association with variation in HDL-C in different populations (Yilmaz et al. 2005; Padmaja et al. 2007). A meta-analysis reported *CETP* genotypes to be associated with moderate inhibition of CETP activity and inverse association with CVD, but the findings are inconsistent (Rhyne et al. 2006). Other studies have reported greater risk associated with low CETP activity secondary to severe genetic deficiency (Bruce and Nishimura 1998). A recent prospective study from the community-based Framingham Heart Study also reported greater cardiovascular risk with low CETP activity (Vasan et al. 2009). More recently, it has been shown that polymorphisms in the *CETP* promoter region determine activity. GWAS in Caucasians has revealed association of the variant −2,568 C/A (rs3764261) with HDL-C, and the finding has been replicated in different ethnic groups (Willer et al. 2008; Hegele 2009). SNPs in the *CETP* promoter region (−2,568 C/A, −1,700 C/T), −998 A/G) and the well-known noncoding SNP (397 A/G) identified as a restriction fragment (Taq1b) in the first intron were studied in the unique Sikh population of Northern India who are known to have a high prevalence of T2D and cardiovascular disease despite much lower obesity rates (Sanghera et al. 2006). The −2,568 C/A allele showed a strong association with increased HDL-C and decreased blood pressure. Although none of the SNPs were individually associated with CETP activity, low activity was associated with greater risk for CAD, and there was significant interaction between the *CETP* SNPs studied as haplotypes and CETP activity for affecting HDL-C (Schierer et al. 2011). These results suggest that more complete genotyping could serve to define individual risk and response to therapies designed to raise HDL-C by inhibiting CETP.

8 Hypertension Pathway to CVD

Obesity has been identified as the most important risk factor for diabetes and hypertension (He et al. 2009). Abundance of evidence supports a strong association of high blood pressure with

insulin resistance (Reaven 2011). This association is attributed to enhanced sympathetic nervous activity, adrenal activity, oxidative stress, and enhanced renin-angiotensin-aldosterone system (Reaven 2011; Cooper et al. 2007). Angiotensin II has a direct effect on increasing insulin resistance independent of alterations in blood flow and interstitial insulin concentration (Richey et al. 1999), but angiotensin II is equally responsible for triggering vascular inflammation and inducing oxidative stress (Ogihara et al. 2002; Savoia and Schiffrin 2007). The insulin resistance is reversible by selective inhibitors of angiotensin II at AT1 receptors (Sloniger et al. 2005). Similar selective antagonism using irbesartan, a clinically used AT1 receptor blocker (ARB), has been shown to improve insulin action in the obese Zucker rat- associated with upregulation of GLUT4, the main glucose transporter in skeletal muscle (Henriksen et al. 2001).

Given substantial experimental evidence for the renin-angiotensin system's involvement in hypertension and vascular pathophysiology, there has been interest in investigating association of common variants such as *ACE* (angiotensin-converting enzyme) and *AGT* (angiotensinogen) with hypertension, but results have not been conclusive (Norton et al. 2010) and they have not been associated with T2D (Conen et al. 2008). However, variants in *ACE* and *CYP11B2* genes have been associated with insulin resistance in hypertensive families in Taiwan (Hsiao et al. 2012). Gene variants in *ACE*, *AGT*, and *AT1R* predicted T2D in a Tunisian population (Mehri et al. 2010). Data from the National Health and Nutrition Examination Survey (NHANES) showed the prevalence of hypertension to be 40 % in African Americans compared to 27 % in European Americans (Hertz et al. 2005; Cutler et al. 2008) leading to the hypothesis that part of the excess burden in African Americans is due to genetic susceptibility (Fox et al. 2011). GWAS and candidate genes examined in the Candidate Gene Association Resource Consortium consisting of 8,591 African Americans identified novel associations for diastolic blood pressure on chromosome 5 near *GPR98* and *ARRDC3* and for systolic blood pressure on chromosome 21 in *C21orf 91*. However, none of these variants were associated with T2D (Fox et al. 2011).

Interestingly, monogenic forms of hypertension have provided evidence for a regulatory role of key metabolic pathways and have been the basis for candidate gene population studies, but none have involved carbohydrate metabolism or insulin action. Using such an approach, 24 h ambulatory blood pressure has been associated with five polymorphisms in the *KCNJ1* gene, which has the potential to cause Bartter syndrome Type 2 when the abnormal allele is inherited (Tobin et al. 2008a). Also ambulatory blood pressure is associated with common variations in the *WNK1* gene known to cause pseudohypoaldosteronism Type 2 or Gordon syndrome. Association of *WNK1* with blood pressure in childhood underscores its possible association with evolving hypertension at young ages (Tobin et al. 2008b). Additional association with variants in *CASR*, *NR3C2*, *SCNN1B*, *and SCNN1B*, all of which are known to have had mutations causing rare Mendelian defects in blood pressure regulation, provides support for the hypothesis that relevant polymorphisms influence conventional pathways involved in blood pressure regulation (Tobin et al. 2008a). However, only a few variants have been discovered in GWAS in the earlier known genes, suggesting new pathways involved in hypertension. A large meta-analysis performed by the International Consortium for Blood Pressure on 200,000 individuals of European descent identified 16 loci of which only 6 contained genes that are known or suspected to regulate blood pressure, which include *NPR3*, *GUCY1A3-GUCY1B3*, *ADM*, *GNAS-EDN3*, *NPPA-NPPB*, and *CYP17A1* (Ehret et al. 2011). *CYP17A1* achieved the most robust GWAS significance and is the site for a known Mendelian-inherited mutation causing hypertension by increasing mineralocorticoids in the adrenal steroid pathway and causing a rare form of congenital adrenal hyperplasia. Diabetes and hypertension share common pathways such as renin-angiotensin system's involvement in insulin resistance and vascular inflammation. However, the evidence from genetic studies, specifically

from GWAS, points to separate genetic backgrounds for hypertension and T2D.

9 Endothelial Dysfunction

Vascular endothelial cells play a pivotal role in regulating blood flow in the entire circulatory system. The endothelium maintains and regulates a wide range of homeostatic functions through the presence of membrane-bound receptors for various molecules including proteins, lipid-transporting particles, metabolites, and hormones. Endothelial dysfunction is characterized by impaired endothelium-dependent vasodilation and increased procoagulant and pro-inflammatory activity (Widlansky et al. 2003). Endothelial dysfunction has also been linked with obesity and elevated C-reactive protein (CRP). CRP is a pro-inflammatory marker whose concentrations are markedly increased in patients with T2D, hypertension, and metabolic syndrome (Ridker et al. 2003). The development of atherosclerosis is considered to be a consequence of a chronic inflammatory process, perpetuated in part by LDL that is trapped and oxidized within the vessel wall (Ross 1993). Specifically, oxidative stress increases vascular endothelial permeability and promotes leukocyte adhesion, which is coupled with alterations in endothelial signal transduction and redox-regulated transcription factors (Lum and Roebuck 2001). On the other hand, oxidized LDL may impair signal transduction activation of nitric oxide synthase, thus lowers the synthesis of nitric oxide (Kugiyama et al. 1990). Reduced nitric oxide could also stimulate the synthesis and release of endothelin, producing enhanced vasoconstrictor tone; release and activity of growth factors; increased smooth muscle cell migration into the intima; and synthesis and release of pro-inflammatory cytokines. Additionally, reduced nitric oxide could promote platelet attachment and release of growth factors in the vessel wall. These consequences of endothelial dysfunction such as lipid peroxidation along with reduced nitric oxide bioactivity may be important in the initiation and progression of atherosclerosis and ultimately result in clinical manifestation of CVD. Angiotensin II is also involved in triggering vascular inflammation and oxidative stress in endothelium by stimulating NAPH/NADPH oxidase, protein kinase C, and mitogen-activated protein kinase (MAPK) (Griendling et al. 1994; Yamakawa et al. 2000). Peripheral endothelial function correlates well with coronary endothelial vasodilation and is reduced in patients with CVD risk factors such as obesity, hypercholesterolemia, hypertension, and diabetes (Anderson et al. 1995).

10 Conclusions

Recognition of risk factors in obese individuals that precede both CVD events and T2D is an essential strategy to achieve reductions in prevalence. Early recognition of traits and their role in increasing risk involves recognition of their independent genetic origins, gene-gene interaction, interacting metabolic pathways, and epigenetic modifications. The respective traits also interact with environmental effects and increase susceptibility. Fetal growth restriction, NAFLD, dyslipidemia, hypertension, and early hyperglycemia all interact with the obesity phenotype progressing from prediabetes to T2D and CVD. A role for primary and secondary metabolic events with separate genetic backgrounds interacting with pathways involving insulin resistance and insulin secretion is likely to be a central factor in pathogenesis of CVD. Early metabolic programming during gestation not only has a genetic background but also is susceptible to metabolic and nutritional changes in the fetal environment and predisposes to metabolic syndrome traits that begin to express in childhood. Individuals with genetic predisposition to obesity are sensitive to early environmental influences beginning during gestation and continuing in childhood to adulthood. Obesity itself like the other phenotypes generates insulin resistance and worsens dyslipidemia and in some cases leads to increased hepatic fat synthesis and storage (NAFLD), suggesting that liver-expressed variants may compound the risk of diabetes and CVD. The classic lipid derangement observed in insulin resistance

consisting of elevated triglyceride (often associated with increased free fatty acid levels), small LDL particles in increased numbers, and low HDL cholesterol has significant association with insulin resistance and progression of β-cell failure and predicts both CVD and T2D onset. GWA studies are identifying hundreds of common risk variants for T2D, obesity, and related intermediate phenotypes. However, these genes collectively account for only 8–10 % of total heritability linked with these conditions. Major efforts are still needed to gain biological knowledge from these genome-wide discoveries. Although obesity has been directly linked with the diabetes and hypertension, the shared genetic etiology of obesity, T2D, and hypertension discovered in GWA studies is limited. Therefore, more work is needed to fully understand the underlying genetic architecture of overlapping disease phenotypes to elucidate mechanisms of pathogenesis and identification of therapeutic targets for prevention and early intervention. Importantly, the screening approaches beginning during early developmental phases could allow assessment of more precise interrelationships of obesity and T2D phenotypes to each other and to CVD.

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11 Cross-References

- Carbohydrate, Fat, and Protein Metabolism in Obesity
- Childhood Environment and Obesity
- Dyslipidemia in Obesity
- Fetal Metabolic Programming
- Genetics of Lipid Disorders
- Genetics of Obesity
- Genetics of Type 2 Diabetes
- Insulin Resistance in Obesity
- Nonalcoholic Fatty Liver Disease
- Overview of Metabolic Syndrome
- Prevention and Treatment of Childhood Obesity and Metabolic Syndrome
- Type 2 Diabetes: Etiology, Epidemiology, Pathogenesis, Treatment

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Part III

Environmental Factors

Fetal Metabolic Programming

13

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Contents

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Abstract

The global increase in the burden of metabolic-related disease, particularly obesity and type 2 diabetes, means that insights into factors contributing to such conditions are of increasing importance. Evidence from both human studies and animal models suggests that suboptimal conditions in early life may play a role in determining the risk of later metabolic dysfunction. Understanding how later metabolic dysfunction arises at least in part from the early-life environment could lead to exciting new routes to tackle adverse later-life outcomes, either in the index pregnancy via maternal intervention or early in the life of the offspring. Currently, our understanding of the mechanisms of developmental programming of metabolic dysfunction arises primarily from work in animal models, and much remains to be recapitulated and validated in human populations. An ability to tackle metabolic dysfunction early in life and to offset adverse programming of metabolism could prove protective to some degree against many later-life metabolic diseases. Of particular importance is the idea that adverse metabolic phenotypes may not only be seen in the offspring directly exposed to adverse conditions in utero but may also be transmitted or re-propagated across generations. This allows developmental programming of metabolic phenotypes to be viewed on a longer-term basis than a single generation and underscores the idea that early interventions to improve the intrauterine and early postnatal environment could have significant metabolic health benefits to both the children of affected individuals and to future generations.

Keywords

Developmental programming • Metabolic dysfunction • Intrauterine environment • Maternal nutrition

1 Introduction

The developmental origins of health and disease have been an area of intense and productive research over the last 30 years. The concept that events at the very start of life can "program" later outcomes was first proposed by Professor David Barker and colleagues in Southampton, UK, in the late 1980s (Barker 1998). He proposed that there are critical "windows" during early development, in utero, and postnatal life, where exposure to suboptimal conditions causes permanent changes to key metabolic and growth pathways, which then influence the health of the offspring in adulthood through irreversible changes in structure and function of tissues and organs (Gluckman et al. 2008). Since this hypothesis was first suggested, a wide variety of offspring outcomes have been investigated and found to be influenced by the early-life environment. These include such diverse outcomes as reproductive function (Aiken et al. 2013), anxiety and stress behaviors (Sullivan et al. 2010), and longevity (Ozanne et al. 2004). However, one of the most commonly studied outcomes of developmental programming is metabolic function, including type 2 diabetes, obesity, and dyslipidemia (Dong et al. 2013). Obese and metabolically deranged offspring phenotypes are well described in human epidemiological studies and in animal models of programming via nutrition and other interventions. Obesity, dyslipidemia, and abnormal glucose/insulin regulation are among the best-understood phenotypes influenced by developmental programming. In contrast to many other developmental programming effects, metabolic dysfunction is widely reported in programmed offspring of both sexes (Aiken and Ozanne 2013) and at various ages.

The idea that an individual's diet in adulthood affects metabolic parameters is intuitively clear, but the idea that alterations to physiology in early life can "program" later metabolism is a relatively new concept. However there is now a substantial body of evidence supporting the idea that the in utero and early neonatal life environment can have a profound influence on the way that metabolic pathways are established, leading to obesity and other adverse effects in adulthood. The "thrifty phenotype" hypothesis (proposed by Hales and Barker in 1992 (Hales and Barker 1992)) proposes that fetuses developing within a suboptimal intrauterine environment maximize their chances of

survival via metabolic adaptations to utilize available resources more efficiently. Viewed in the context of an ongoing suboptimal environment in postnatal life, this is a helpful adaptation of the organism to its surroundings and of evolutionary benefit. The pathology in the system is introduced when a mismatch occurs between the suboptimal intrauterine environment and a nutrient-replete environment after birth (Gluckman et al. 2008). Fetuses born in such conditions display the phenomenon of "catch-up growth" – a rapid postnatal increase in body mass, which has been suggested to be particularly detrimental in terms of metabolic function in later life (Ezzahir et al. 2005; Ong 2007). In particular, catch-up growth is associated with central adiposity (with all its attendant health risks (Kensara et al. 2005)) and with a lower lean mass. Even infants whose birth weight does not fall into the category of small-for-gestational age may have failed to reach their full growth potential in utero and subsequently undergo catch-up growth, meaning that raw birth weight is a less good predictor of future metabolic function than is the infant's growth trend in early life (Ong and Loos 2006). The precise mechanisms by which these changes are regulated are not fully established, but important roles for maternal hyperglycemia, hyperleptinemia, inflammation, and oxidative stress contributing to the suboptimal uterine environment are emerging.

In this chapter, current evidence for early-life programming of metabolic dysregulation is reviewed, and the potential underlying mechanisms explored. More recently, research efforts have been focused on ways to prevent or ameliorate developmental programming, and current thinking on this topic is reviewed at the end of the chapter.

2 Evidence for Fetal Metabolic Programming of Obesity

2.1 Human Studies

Childhood obesity is an increasing problem in developed countries (Ogden et al. 2012) and is predictive of later metabolic dysregulation in adulthood (Ziyab et al. 2014); however, disentangling the developmental aspects of the trend is problematic. Studies of the effects of the environment on adult outcomes are often hampered in humans by long generation times, which influence recall and increase the chances of confounding by postnatal conditions. Furthermore, it can be particularly difficult in cohorts to separate out the effects of genetics, the prenatal, and the postnatal familial environment.

The concepts of developmental programming originally arose from studies of adults who were exposed to famine while in utero. The paradigm of such studies reported higher rates of obesity among adult males whose mothers were exposed to severe undernutrition during the Dutch Hunger Winter (the extreme famine conditions experienced in the Netherlands over the winter of 1944–1945) in late pregnancy (Ravelli et al. 1976). Similar findings have been reported from studies of other famines in human populations, including the Chinese famine of the late 1950s (Li et al. 2010). More recently, increased adiposity later in life has been demonstrated in infants born small-for-gestational age (Jaquet et al. 2005).

Conversely, maternal overnutrition is also highly correlated with offspring obesity later in life. In developed countries, where obesity levels are rising, maternal overnutrition is an increasingly serious population health concern (2011). Maternal obesity is associated with both low (Rajasingam et al. 2009) and high birth weight (Oken and Gillman 2003) and with childhood obesity (Oken et al. 2007; Wrotniak et al. 2008). In the offspring of obese mothers, even small increases in maternal body mass index can correspond to a significantly increased risk of infant adiposity (Modi et al. 2011). Human studies of obese mother/infant pairs are subject to obvious confounding from genetic, social, and environmental factors; however, it is notable that the chance of offspring obesity in conjunction with maternal obesity is higher than with paternal obesity (Lee et al. 1997). Furthermore, the relationship between maternal obesity and early childhood obesity persists even after controlling for other maternal factors, perinatal factors, and

childhood eating behavior (Oken et al. 2007). Maternal imprinting could account for many of these findings; however, an alternative explanation centers on the pivotal role of the intrauterine environment in influencing offspring obesity in later life.

Human studies of childhood and later-life obesity are subject to bias that arises because mothers who are themselves overweight are more likely to provide an obesogenic environment to their offspring postnatally. Some of this bias is accounted for by studies that look only at weight gain during pregnancy (gestational weight gain, GWG) rather than mothers who were obese prior to commencing pregnancy. A large prospective UK cohort study demonstrates that gestational weight gain is independently associated with childhood obesity. This association is greater with weight gain that is earlier in pregnancy and >500 g/week (Fraser et al. 2010). More recently, the specific link between maternal obesity in pregnancy and later obesity in children has been explored in studies of mothers who have undergone bariatric surgery. Compared to siblings born prior to bariatric surgery, those children born after the mother had attained normal weight had a lower risk of later obesity (Kral et al. 2006) and demonstrated improvements in other metabolic parameters including insulin sensitivity, lipid levels, and ghrelin levels (Smith et al. 2009). Conversely, it has been demonstrated that in sibling pairs where the mother experienced significant weight during the inter-pregnancy interval, the later sibling was at increased risk of obesity in later life (Villamor et al. 2008). Other attempts have been made to control for family environment and maternal-related factors by using sibling controls to isolate the effects of gestational diabetes on offspring adiposity. Increased adiposity was observed in children where the mother was diabetic during pregnancy compared to their siblings where diabetes was not present. In particular a large Scandinavian cohort, in which male sibling pairs discordant for maternal gestational diabetes were followed up until age 18, demonstrated that the offspring in utero during diabetic pregnancies had significantly higher BMIs than their siblings from normoglycemic pregnancies (Lawlor et al. 2011).

Children with both very low and very high birth weights are at increased risk of obesity later in life (Parsons et al. 2001). This finding fits with the idea that birth weight per se may be less important in terms of later outcome than perinatal catch-up growth. In terms of growth and nutrition, rapid postnatal weight gain (within the first 9 months of life) is strongly correlated with both increased adiposity in later childhood in both sexes and earlier age at menarche in girls (Ekelund et al. 2006; Ong et al. 2009). As detailed in the thrifty phenotype hypothesis, rapid postnatal growth often signifies a mismatch between the intrauterine and postnatal environment, which makes metabolic pathology considerably more likely. Rapid postnatal catch-up growth is associated with metabolic dysregulation in adulthood (including obesity), even when the birth weight falls within normal range (Tzoulaki et al. 2010). The profound effects of early neonatal growth are seen in studies where infants fed "growth-promoting" formula (which entailed not only increased calorie consumption but also significantly increased protein intake) had a greater chance of developing obesity in mid-childhood (Singhal et al. 2010). These studies demonstrate the importance not only of in utero programming but also of the interaction between fetal and postnatal growth in determining later metabolic outcomes.

2.2 Animal Models

In animal models of developmental programming, particularly rodent models, a range of dietary, surgical, and other interventions (Seckl and Meaney 2004) have been shown to increase the prevalence of obesity in the offspring in adulthood. Animal work both allows increased insight into the mechanistic aspects of developmental programming and allows increased scope to perform early interventional studies.

In rodent models of maternal undernutrition, obesity can be induced in male offspring alongside a phenotype of hyperphagia (Vickers et al. 2000). Offspring obesity is seen in conjunction with important changes in gene expression that suggest it may be linked to mitochondrial dysfunction and an increased stress response (Bispham et al. 2005; Stocker et al. 2005). Similarly, in sheep developmental programming models, maternal undernutrition during gestation results in greater offspring adiposity in later life (Greenwood et al. 1998).

Conversely, maternal overnutrition has also been demonstrated to program offspring obesity in rodent models (Desai et al. 2005). In the sheep model of maternal overnutrition, there is evidence not only of increased adiposity of the offspring in later life, but a possible clue to the mechanism by which this may be brought about. Maternal overnutrition has been observed to lead to dysregulation of leptin levels in the neonate, which may have profound consequences for later body mass and appetite regulation (Long et al. 2011). Subsequent studies have also demonstrated that the offspring obesity in rodent developmental programming models is associated with hyperphagia (Rooney and Ozanne 2011), even when weaned onto a normal diet (Kirk et al. 2009). Hypothalamic programming of energy balance in adult offspring of rat mothers exposed to low-protein diet during gestation is permanently altered in favor of orexigenesis, with increased expression of neuropeptide Y and decreased expression of pro-opiomelanocortin (POMC, which is an important regulator of energy homeostasis) (Cottrell et al. 2009). Aside from hyperphagia resulting in increased offspring obesity, a further important factor modulating offspring obesity may be a tendency demonstrated in some studies toward increased sedentary behavior and decreased physical activity in developmentally programmed offspring (Vickers et al. 2003; Bellinger et al. 2006). Importantly, this effect is seen in maternal undernutrition models as well as in offspring whose mothers were obese during pregnancy (Bellinger et al. 2006). The precise composition of experimental maternal overnutrition diets utilized to program long-term adverse metabolic consequences in offspring is highly variable within the literature, with some studies using increased caloric intake, increased fat, or increased sugar. More recently, highly palatable high-fat/high-sugar diets that most closely mimic a modern Western diet have been used and induce obesity in offspring of both sexes (Samuelsson et al. 2008).

Evidence for developmental programming of obesity in the nonhuman primate is limited, but a maternal high-fat diet in macaques results in a phenotype of increased adiposity (independent of postnatal feeding), which may be a result of hormonal and inflammatory changes (Grayson et al. 2010). Other nonhuman primate studies have added to the weight of evidence suggesting that maternal high-fat diets during pregnancy, even in the absence of maternal obesity, are strong risk factors for increased adiposity in the offspring (McCurdy et al. 2009).

Animal models further demonstrate the importance of the interaction between the pre- and postnatal nutritional environment for long-term programming of obesity (Desai et al. 2005). In rats whose mothers ate a low-protein diet during pregnancy, those offspring who also consumed a low-protein postnatal diet showed no increased body mass later in life relative to the control animals. However those who were weaned onto a normal diet after delivery became obese in adulthood (Ozanne et al. 2004). Evidence points to central leptin resistance as an important mediator of obesity in developmentally programmed offspring. It is proposed that exposure to suboptimal conditions early in life can permanently alter the leptin sensitivity of the arcuate nucleus of the hypothalamus, hence increasing the susceptibility to obesity when exposed to high-fat diet. Leptin resistance in the neurons of the arcuate nucleus has been demonstrated in the neonatal offspring of mouse dams who were diabetic during pregnancy (Steculorum and Bouret 2011). It is unknown precisely how leptin resistance is programmed in early development, but it has been suggested that leptin

transport across the blood-brain barrier may be impaired by elevated circulating triglycerides during early life, and this may account for the impairment in later leptin sensitivity.

3 Evidence for Fetal Programming of Glucose/Insulin Metabolism

3.1 Human Studies

Secondary fetal hyperinsulinemia is believed to result from exposure to high glucose loads throughout gestation in infants whose mothers are obese, are over-nourished, have high gestational weight gain, or develop gestational diabetes (Oken and Gillman 2003). A fetus with a normally functioning pancreas will have the capability to respond to transplacental glucose loads with increased insulin production, which acts a growth hormone in addition to directly driving macrosomia in this capacity. Support for this hypothesis comes from studies that show increased levels of insulin in the amniotic fluid of neonates who become obese later in childhood (Metzger et al. 1990). There may however be some degree of placental modification of the nutrient supply that can ameliorate some developmental programming effects, potentially via Igf2 (Burton and Fowden 2012).

Infants who were born small-for-gestational age have increased risk of insulin resistance in early adulthood (Jaquet et al. 2000). In particular the infants of mothers who were obese and hyperinsulinemic during their pregnancies have a higher likelihood of experiencing insulin resistance in later life (Dorner and Plagemann 1994; O'Reilly and Reynolds 2013). Defining contribution of the suboptimal pregnancy environment, as opposed to genetic or social factors, as driving the later offspring phenotype is complicated in human studies. This complexity is increased by the role that early postnatal dietary modification is likely to play in defining the propensity to glucose intolerance later in life. In one interventional study, infants randomized to early feeding with a high-protein formula showed a pattern of increased circulating branched-chain amino acids that is known to be associated with later development of insulin resistance (Socha et al. 2011).

3.2 Animal Models

Although abundant evidence exists for the developmental programming of offspring glycemic control (Pinney and Simmons 2012; Sandovici et al. 2013), the multitude of maternal interventions and study protocols giving rise to these phenotypes makes dissecting out the mechanism by which these effects are mediated difficult (Ainge et al. 2011). It is hoped that future investigations using targeted metabolomics might help to better define these interventions and outcomes in both human and animal studies (Hivert et al. 2015).

Multiple rodent studies have demonstrated increased circulating insulin levels in offspring of mothers fed high-fat diets during pregnancy. Hyperinsulinemia is usually observed in the context of hyperphagic obese offspring (Samuelsson et al. 2008; Tamashiro et al. 2009; Fernandez-Twinn et al. 2012). A similar phenotype has recently been observed in adult rat offspring whose mothers were exposed to intermittent chronic hypoxia during pregnancy (Iqbal and Ciriello 2013), with both hyperinsulinemia and frank hyperglycemia present in the obese adult offspring. However, dysregulation of offspring insulin sensitivity has been observed prior to the development of adult metabolic dysfunction (including obesity) in the nonhuman primate. These results suggest that exposure to an excess of androgens during in utero development can alter insulin sensitivity in early postnatal life and precede the development of a frankly adverse metabolic phenotype (Abbott et al. 2010). While much attention has focused on the ability of maternal overnutrition in pregnancy to provoke glucose intolerance in the offspring, multiple studies have also observed impaired glucose tolerance and dysregulation of the development of the endocrine pancreas in undernutrition models (Fernandez-Twinn and Ozanne 2010),

particularly low-protein maternal diets (Snoeck et al. 1990; Alejandro et al. 2014).

Separating the phenotypes of glucose and insulin resistance is difficult even in animal models, and studies often conflate these with little regard as to the metabolic driving factors. Interestingly, the offspring of mice that are hyperinsulinemic (via an IRS-1 insufficiency) but remain normoglycemic during pregnancy show evidence of early weight gain and early hyperinsulinemia, with later development of frank hyperglycemia (Isganaitis et al. 2014). This suggests that the simple hypothesis of maternal hyperglycemia during pregnancy driving in utero hyperinsulinemia in the offspring, with subsequent effects on later insulin sensitivity accounting for the developing phenotype, is not sufficient to explain the effects of maternal diet on offspring glucose/insulin sensitivity. Further elucidation of the driving mechanisms behind the offspring response to maternal diet comes from a low-protein maternal diet murine model, in which decreased insulin levels and reduced beta cell fraction in the pancreas were observed in neonatal offspring, followed by glucose intolerance in adulthood (Alejandro et al. 2014). In this study, disruption of endocrine pancreas development was driven by a decrease in mTOR signaling (known to be a key regulator of beta cell mass and function during development as well as in adulthood (Rachdi et al. 2012)). mTOR signaling in this model was inhibited by an abundance of specific microRNAs directly blocking mTOR expression. When the levels of inhibiting microRNAs were experimentally reduced, mTOR protein levels were restored and the offspring phenotype "rescued" (Alejandro et al. 2014), giving important insight into the epigenetic mechanisms that may underlie impaired glucose/insulin tolerance programming in early life. Downstream of regulation of pancreatic development, further evidence from a rat maternal low-protein model demonstrates downregulation of Pdx1 expression (at both the mRNA and protein levels) leading to decreased expression of Glut2 and impaired glucose tolerance (Abuzgaia et al. 2015).

As one of the better established developmental programming phenotypes, with a reliable induction of hyperinsulinemia in the first generation of offspring, particularly by maternal high-fat diets, glucose/insulin resistance has been the target phenotype for a number of pioneering studies looking at transgenerational aspects of developmental programming (reviewed in Aiken and Ozanne 2014). Insulin/glucose dysregulation has been observed in a second generation of offspring following an initial maternal programming stimulus in several rodent models. In a particularly interesting example, maternal high-fat mouse model, the F1 offspring exhibited the classic phenotypic findings of obesity, hyperphagia, hyperinsulinemia, and glucose intolerance (Graus-Nunes et al. 2015). In the F2 generation, however, while hyperinsulinemia and hyperleptinemia were observed, this was in conjunction with normoglycemia and normal body weight. The F2 generation were studied at 3 months of age and may have developed a phenotype of glucose intolerance later in life however, as evidenced by findings of dysregulation of pancreatic development including hypertrophied islets of Langerhans with altered distribution of alpha and beta cells within the islets (Graus-Nunes et al. 2015). By contrast, a different mouse model of maternal obesogenic diet demonstrated a phenotype of hyperinsulinemia and alterations in hepatic gene expression in the second-generation offspring but intriguingly without an apparent phenotype in the first generation (King et al. 2013). A transgenerational effect on glucose/insulin tolerance has also been demonstrated in the sheep. First-generation offspring who were exposed to a maternal obesogenic diet in utero exhibited hyperinsulinemia and hyperglycemia during their own pregnancies, and the resulting second-generation offspring had increased fat mass at birth, with accompanying higher fasting glucose and insulin levels (Shasa et al. 2014).

4 Evidence for Fetal Programming of Dyslipidemia

4.1 Human Studies

Serum dyslipidemia is less well studied in human cohorts than either obesity or glucose/insulin resistance. However observations from a large

prospective UK cohort demonstrate that the offspring of women who had excessive gestational weight gain during pregnancy were more likely to have adverse lipid profiles in childhood (measured at 9 years of age) (Fraser et al. 2010). The offspring in this study showed not only lower levels of HDLc and apolipoprotein A1 but also higher leptin levels in the increased gestational weight gain group. There was no association however with triglyceride or apolipoprotein B1 levels (Fraser et al. 2010).

Recently, the dramatic increase in prevalence of pediatric nonalcoholic fatty liver disease (NAFLD), which has accompanied increased levels of childhood obesity in developed countries, has generated interest in the developmental basis for liver steatosis (Schwimmer et al. 2006). It has been proposed that exposure to a suboptimal intrauterine environment may be the driver behind development of fatty liver via programming of mitochondrial dysfunction, increased levels of oxidative stress, and inflammation (Stewart et al. 2013). Both the children of mothers who are diabetic during pregnancy (Brumbaugh et al. 2013) and also those exposed in utero to maternal obesity have been shown to have an increased risk of pediatric NAFLD (Modi et al. 2011).

4.2 Animal Models

In rodent models, those offspring exposed to maternal hyperinsulinemia in pregnancy show increased circulating fatty acids and hepatic lipid accumulation in older offspring (Isganaitis et al. 2014). Maternal obesity during gestation also gives rise to a phenotype recapitulating the features of early-onset NAFLD (Buckley et al. 2005; Bruce et al. 2009; Oben et al. 2010), which has been demonstrated in other rodent models to persist at least until the offspring have entered adolescence (Bayol et al. 2010). The precise mechanism of this effect is unclear, but some evidence suggests that dysregulation of mitochondrial function may play a key role (Bruce et al. 2009) and that the hepatic changes are accompanied by an increase in molecular markers of inflammation (Ashino et al. 2012).

Many animal models have shown a phenotype of increased lipogenesis in offspring following intrauterine exposure to a high-fat maternal diet (Bruce et al. 2009; Li et al. 2012). A potential mechanism driving the increase in circulating fatty acids is a relatively insulin resistance in the offspring impairing the normal inhibition of lipolysis by circulating insulin (Isganaitis et al. 2014). It is of particular interest from a mechanistic point of view to note that the offspring phenotype of NAFLD occurs after the onset of hyperinsulinemia, but prior to the development of obesity or glucose intolerance (Alfaradhi et al. 2014), potentially under the control of up-regulated peroxisome proliferator-activated receptor gamma (PPAR gamma), which plays a vital role in regulating fatty acid storage. Up-regulation of PPAR gamma is a particularly important finding, as it not only increases storage of triglycerides in mature adipocytes but also stimulates proliferation and differentiation of new adipocytes from the preadipocyte progenitor population. Aside from evidence that serum triglycerides are influenced by developmental programming stimuli, there is important evidence from the offspring of obese mothers in the sheep that levels of triglycerides are elevated within skeletal muscle (Yan et al. 2011). In common with the findings in rodent models, these changes are also accompanied by increased expression of fatty acid transporters and PPAR gamma.

In the nonhuman primate, similar effects are seen. Maternal high-fat diet during pregnancy (regardless of whether the mothers themselves were obese) programmed an increase in liver triglycerides, accompanied by elevation of fetal glycerol levels and changes consistent with the development of nonalcoholic fatty liver disease. These changes persisted in adulthood and were accompanied by later offspring obesity (McCurdy et al. 2009).

5 Mechanisms of Fetal Metabolic Programming of Metabolic Dysfunction

Multiple different mechanisms have been proposed to contribute to the basis of the developmental programming effects observed in animal

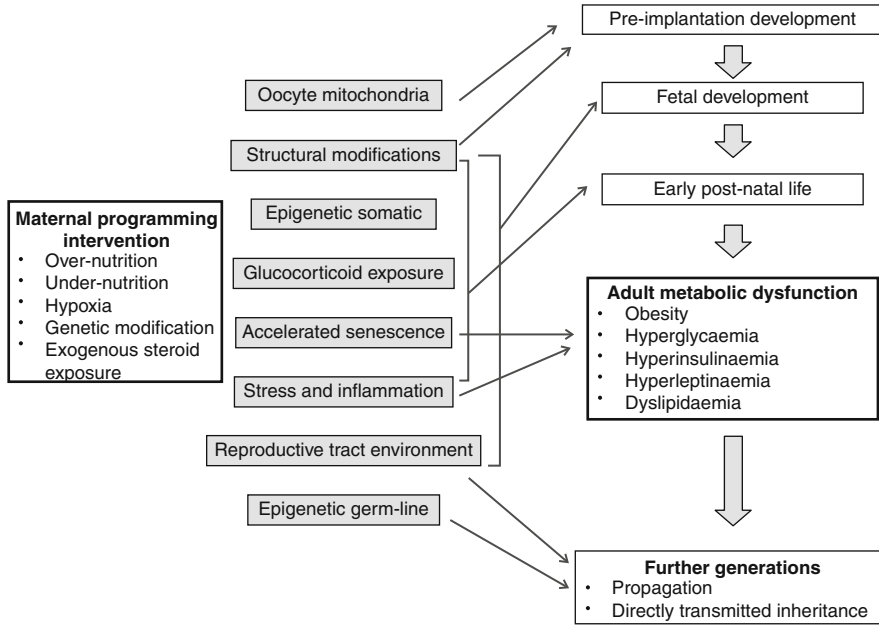

Fig. 1 Potential mechanisms by which interventions in early life may lead to metabolic programming effects in adulthood and in future generations. Possible mechanisms are shown in light gray boxes

models and human studies. Major candidate mechanisms are summarized in Fig. 1 and discussed in more detail below.

5.1 Structural Effects in Early Development

The earliest studies of developmental programming focused on structural changes during development of the programmed offspring as the most obvious and attractive candidate mechanisms to explain the later phenotypic effects. There is evidence from both rodent and sheep (Zhang et al. 2011) models of developmental programming to suggest that the total cell mass of the beta islets of Langerhans is irreversibly reduced in fetuses exposed to maternal dietary manipulations, and that this leads to pancreatic dysfunction in later life (Cerf et al. 2007). One particularly interesting study tracked fetal beta cell development through pregnancy in obese mothers and found that there was an initial increase in beta cell mass early in gestation (with a corresponding increase in circulating insulin levels), but by late gestation beta cell mass was considerably lower than in control animals (Zhang et al. 2011), suggesting that there may be an initial physiological response to increased glucose availability, which is then decompensated by the time of birth. Other evidence, however, despite confirming the findings of decreased beta cell mass in adulthood following a suboptimal intrauterine environment, suggests that glucose intolerance in adulthood is the result of impaired insulin secretion rather than the effect of a decreased beta cell mass per se (Alejandro et al. 2014).

Offspring obesity in developmental programming models is usually associated with hyperphagia and dysregulation of normal appetite control. A large body of evidence suggests that this effect may also be driven by a permanent structural change at the level of the hypothalamus. Evidence is derived from examination of the hypothalamus in the offspring of mothers exposed to high-fat diet during pregnancy, where there was an increase in the number of peptide-producing hormones in the hypothalamus, leading to increased appetite and subsequent obesity (Chang et al. 2008).

Other permanent structural modifications that have been demonstrated in developmentally programmed offspring are present in the cardiovascular system, including a reduction in the number of cardiac myocytes at birth in a rodent model (Corstius et al. 2005). Multiple variants of cardiovascular structural modifications have been observed in programmed offspring, including a decrease in aortic wall thickness and elastin content in a rodent undernutrition model (Skilton et al. 2006) and total cardiac mass, left ventricular free wall hypertrophy, and cardiac myocyte width in a rodent overnutrition model (Fernandez-Twinn et al. 2012). These non-recoverable early differences in the structure of heart and major vessel formation may go some way toward explaining the phenotypes of hypertension and cardiovascular dysfunction often observed in association with fetal metabolic programming (Herrera et al. 2010; Blackmore et al. 2014).

5.2 Glucocorticoid-Mediated Pathways

Maternal stress signals (deriving from both physiological and psychological stressors) have been observed in association with reduced offspring birth weight and accelerated postnatal growth (Street et al. 2012; Entringer 2013). Dissecting out the key regulators from stress pathways that influence fetal growth has been the subject of intense research. The activity of the maternal hypothalamic-pituitary-placental axis determines the fetal exposure to glucocorticoids; however, a direct relationship between fetal development and exposure to glucocorticoids of maternal origin has been difficult to define (Khan et al. 2011; Duthie and Reynolds 2013). Recently, the role of placental corticotropin-releasing hormone (pCRH), which is of placental rather than maternal origin, has been further elucidated. Placental CRH is an attractive candidate for influencing fetal metabolic programming as it is known to be involved in regulating fetal growth (Wadhwa et al. 2004), and has an effect on length of gestation (Sandman et al. 2006). Furthermore, pCRH is up-regulated in response to expression of other maternal stress pathway components including cortisol (Cheng et al. 2000; Sandman et al. 2006), inflammatory signals (Petraglia et al. 1989), and catecholamines (Voltolini and Petraglia 2014). A pattern of catch-up growth has recently been observed in association with high levels of pCRH in a prospective human cohort (Stout et al. 2014), suggesting a potential role in mediating developmental programming effects.

5.3 Stress- and Inflammation-Mediated Pathways

It is well established that maternal obesity is associated with higher levels of proinflammatory cytokines (Hans et al. 2009), adipokines (Ouchi et al. 2011), and oxidative stress (Matsuda and Shimomura 2013) in fetal and offspring tissues. Recently, the endoplasmic reticulum stress response has been highlighted as a key mediator of the relationship between the maternal obesity environment and fetal programming of metabolic dysfunction (Li et al. 2012; Westermeier et al. 2014). An extensive body of literature links the development of insulin resistance, and its subsequent consequences of obesity and diabetes, with oxidative stress via interference with normal insulin signaling pathways (Furukawa et al. 2004). Importantly, in insulin-responsive tissues such as white adipose tissue and liver, the changes associated with oxidative stress precede those derived from insulin resistance and may be rescued by addition of antioxidant therapy (Campion et al. 2006). A phenotype of up-regulated oxidative stress markers has been observed in many diverse developmental programming models across different organ systems and species (McCurdy et al. 2009; Aiken et al. 2013; Alfaradhi et al. 2014). Oxidative stress may constitute a final common pathway linking offspring phenotypes across a variety of study protocols.

Attention has also focused on the key role of mitochondria in generating free radical species, particularly when subjected to a substrate influx, stress, or age-associated damage. Mitochondrial mass, DNA copy number, and electron transport chain dysfunction are implicated in the

pathogenesis of a number of developmentally programmed phenotypes in various model systems (Aiken et al. 2013; Tarry-Adkins et al. 2013). All cells have a normal free radical "leak" from the electron transport chain, which is balanced by a variety of intrinsic cellular antioxidant defense mechanisms. These antioxidant defense mechanisms are themselves altered in the tissues of programmed offspring, suggesting that permanent programming effects occur when the limits of normal physiological compensation for mitochondrial-induced oxidative stress are exceeded (Tarry-Adkins et al. 2013b). Beyond this point, a positive feedback of reduced oxidative capacity and increasing free radicals can result in an ever-increasing cellular stress phenotype, leading ultimately to the irrecoverable phenotype of metabolic dysfunction arising from developmental programming. In support of this, an up-regulation of electron transport chain complex I and II activity has been observed in response to a developmental programming challenge in the hepatic tissue of young offspring (Alfaradhi et al. 2014), but may then decline with increasing offspring age (Bruce et al. 2009). This cycle is often the end result of initial exposure to a suboptimal substrate balance for cellular metabolism in utero, for example, lipid availability that far outstrips normal mitochondrial oxidative capacity (Wei et al. 2008). During early development, mitochondria are actively replicating their DNA at key periods when maternal nutritional insult may program the fetus (Aiken et al. 2008), and there is some evidence that exposure to high-fat maternal diet may influence mitochondrial function at these very early stages (Luzzo et al. 2012). Furthermore, key regulators of mitochondrial function and ability to buffer stress such as Sirtuin-3 (SIRT3) have been shown to be down-regulated in the offspring of rodent mothers fed a high-fat diet during pregnancy (Borengasser et al. 2011).

5.4 Epigenetic Pathways

Epigenetic effects, including DNA methylation patterns, histone modifications, or the influence of small noncoding RNA molecules (miRNA, mir), are frequently postulated to be the primary mechanism by which developmental programming effects on metabolic and other fetal parameters are mediated. The effect of the maternal nutritional environment and overall energy balance on the abundance and distribution of epigenetic modifications provides a link between the early-life environment and stable long-term offspring gene expression. Studies of epigenetic mechanisms in developmental programming have largely focused on the influence of methylation patterns on offspring phenotype, although exciting new data regarding the role of miRNAs are emerging (Alejandro et al. 2014). The ability of maternal dietary alterations and other suboptimal in utero stimuli to provoke a programmed phenotype in the offspring may be the result of an altered pool of available methyl donors early in development. During the very earliest stages of development, there are at least three windows of opportunity to reset methylation patterns: at the germ cell stage, during preimplantation development, and during the post-implantation phase. During preimplantation development, methylation patterns are reset asynchronously, first from the paternal and then from the maternal alleles (Rivera and Ross 2013). The re-methylation of key promoter genes germane to metabolic pathways may account for observed developmental programming effects in many model systems, in an attempt to adapt the offspring to a metabolic phenotype in keeping with maternal diet (Godfrey et al. 2007). Numerous loci playing key roles in regulation of glucose homeostasis and other important metabolic parameters have been shown to be differentially methylated following maternal interventions, including pancreatic-duodenal homeobox 1 (Pdx1, which is a key regulator of beta cell development) (Park et al. 2008) and hepatic fatty acid-metabolizing enzymes (Lane et al. 2001). In rat pups exposed to an increased nutritional plane by litter culling early in postnatal life, hypermethylation of the POMC and insulin receptor promoter regions were observed and could be responsible for the later offspring phenotype of obesity and insulin resistance (Plagemann

et al. 2009). Aside from methylation, developmental programming phenotypes have also been observed in association with key histone modifications (MacLennan et al. 2004), including those that regulate expression of glucose transporter 4 (Raychaudhuri et al. 2008). A small human study of placental tissue and cord blood has demonstrated different methylation patterns in the fetal tissues from pregnancies complicated by gestational diabetes compared to those where the mother was normoglycemic (Finer et al. 2015).

Epigenetic modification is a particularly attractive candidate molecular mechanism to explain developmental programming results, as it takes account of effects passed via the paternal as well as the maternal line. Furthermore, modification of the epigenome is a useful model to consider the transgenerational developmental programming effects reported by many studies (reviewed in Aiken and Ozanne (2014)), particularly where transgenerational effects are mediated via the paternal line or can be induced via either parent.

5.5 Utero-placental Effects

In nonhuman primates, maternal overnutrition has been demonstrated to have a direct effect on uterine blood volume and to increase the rate of stillbirth and placental infarcts, with an exacerbation of the phenotype when the mothers are frankly obese (Frias et al. 2011). Other placental changes in both structure (Jones et al. 2013a) and function (Farley et al. 2009; Zhu et al. 2010) have also been demonstrated as a result of maternal dietary manipulations, across species including rats (Jones et al. 2013b), sheep (Zhu et al. 2010), and nonhuman primates (Farley et al. 2009). In the rat, it has been demonstrated that exposure to a maternal low-protein diet can cause accumulation of oxidative stress and accelerated aging within the tissues of the female reproductive tract itself (Aiken et al. 2013), suggesting that the reproductive tract environment, rather than direct effects on the conceptus, may be key in modulating the transgenerational effects seen in many developmental programming models (Aiken and Ozanne 2014).

5.6 Cellular Senescence and Accelerated Aging

Telomeric shortening is associated with tissue aging (Haussmann et al. 2003), particularly in response to accumulated oxidative stress (Richter and von Zglinicki 2007) and can activate cellular senescence and apoptosis pathways (Sharpless and DePinho 2004). Oxidative stress is increasingly emerging as a common mechanism underlying a variety of fetal metabolic programming effects. The increased accumulation of cellular level oxidative stress in tissues of animals exposed to suboptimal conditions in utero is well described across a variety of organ systems (Simmons 2012; Aiken et al. 2013). Similarly, nitrosative stress has been associated with exposure to developmental programming stimuli in cardiac tissue (Tarry-Adkins et al. 2013b). This is especially relevant to the programming of fetal metabolic dysfunction, as telomere length in the islet of Langerhans is particularly susceptible to premature shortening, under the influence of the excess free radical damage generated by suboptimal conditions in utero (Tarry-Adkins et al. 2009). Telomeric shortening in this context is accompanied by impairment of the mitochondrial antioxidant defense mechanisms and an increase in other markers of cellular senescence (Tarry-Adkins et al. 2009). Interestingly, increased oxidative stress may result in a significant downregulation of DNA repair mechanisms in affected tissues, leaving them particularly susceptible to telomeric shortening as the animal ages (Tarry-Adkins et al. 2013b).

6 Improving Outcomes in Fetal Metabolic Programming

Much current research effort has been invested in understanding initially the phenotype and, more recently, the mechanisms of fetal metabolic programming. Thirty years from the initial studies describing the developmental origins of health and disease, our knowledge is approaching the crucial juncture where attention can usefully turn toward ways to ameliorate offspring outcomes. There are two basic strategies that might be

adopted in preventing the development of adverse metabolic phenotypes; the first is to intervene in the index pregnancy by improving the metabolic milieu of the mother and hence preventing fetal programming of the offspring. The second is to find a way to "rescue" or improve the function of the already-programmed offspring later in life. While the first strategy, preventing programming from ever occurring, is the obviously more attractive candidate for intervention, it poses a number of practical and theoretical challenges. One such problem is identifying pregnancies at risk. Many pregnant women globally who face metabolic challenges during gestation do not have access to adequate health care and do not present at stages of pregnancy where interventions might be possible. There is also the risk of inadvertently exposing fetuses not at high risk of developmental programming complications to harm by mis-identifying those pregnancies in which intervention would be beneficial. Furthermore, while pregnant women may be highly motivated during pregnancy to make lifestyle changes for the benefit of their developing fetus, changes within the immediate preconception and gestational period may be insufficient in which to reverse the adverse effects of previous lifestyle, for example, in the case of maternal obesity where weight loss during pregnancy itself would not be advisable. Pregnant women are also, on the whole, highly conservative regarding medications and supplements during pregnancy, as adverse fetal effects are widely feared. The second strategy, intervening postnatally to attempt to ameliorate the phenotype of the already-programmed fetus, may therefore be a more plausible as a strategy to improve outcomes in human populations. This approach however is complicated by the relative lack of plausible mechanisms for correction.

6.1 Maternal Interventions in Animal Models to Improve Metabolic Programming Outcomes

Several different types of maternal intervention to improve developmental programming outcomes have been trialed in various animal models including nutritional manipulations, exercise, and pharmaceutical interventions.

Early data suggested that taurine supplementation to mother's exposed to a low-protein diet might have a role in preventing dysregulation of fetal pancreatic islet development (Reusens et al. 2008). Other maternal supplements that may have a role in preventing developmental programming include folic acid supplementation, which has been shown to prevent epigenetic modification of fetal hepatic gene expression (Lillycrop et al. 2005). Recently, attention has been focused on antioxidants as a maternal intervention to improve offspring outcomes, the rationale for this being the rapid accumulation of oxidative stress seen in the metabolic tissues of many developmentally programmed offspring. Some initial success has been seen with these strategies, in particular maternal supplementation with a mixture of antioxidants (vitamins A, C, E, and selenium) can improve offspring phenotype in terms of both decreased adiposity and improved glucose tolerance following maternal high-fat diet during gestation (Sen and Simmons 2010). Other studies have demonstrated roles for maternal antioxidant supplementation in preventing cardiovascular phenotypes in adult offspring (Cambonie et al. 2007; Giussani et al. 2012). The drawback to applying these results in human populations is that many of the antioxidant doses used in animal studies have been at supra-therapeutic, nonphysiological concentrations.

In relation to the programming of obesity and metabolic dysfunction in human populations, there is also much that remains unknown regarding subtypes of obesity and particularly those individuals who are overweight but metabolically healthy (in terms of lipid profiles, cytokines, and other inflammatory markers such as C-reactive protein) (Karelis 2008) and conversely the "metabolically unhealthy normal weight" individual (Thomas et al. 2012). A more detailed understanding of these phenotypes may help to improve our understanding of the variable offspring outcomes of apparently similar nutritional environments and thus to better target primary interventions that would ameliorate these outcomes.

6.2 Postnatal Interventions in Animal Models to Improve Metabolic Programming Outcomes

A wide variety of studies have attempted to exacerbate developmental programming phenotypes by altering postnatal diet relative to maternal diet; however, fewer specific interventions have been trialed to prevent the development of programmed metabolic effects.

One such study demonstrated in a rat model that neonatal leptin administration in the early postnatal period (during the time when maternal dietary interventions can blunt the usual high levels of leptin in the neonate) can prevent the phenotype of hyperphagia, sedentary behavior, obesity, and glucose intolerance seen in control offspring subjected to maternal undernutrition in pregnancy (Vickers et al. 2005). This is an important demonstration of the potential for plasticity in developmental programming phenotypes through the postnatal period and provides important insight into the neonatal period as a window of opportunity for intervention in developmental programming. A later study using the same treatment in the rat illustrated the very important point that interventions should only be considered where there is a clear rationale that the pregnancy is at high risk of developmental programming effects. When male rats whose mothers ate a normal chow diet during pregnancy were subjected to the same neonatal leptin treatment, they showed hyperinsulinemia and increased adiposity, which were not phenotypic features in offspring whose mothers were undernourished during pregnancy (Vickers et al. 2008). This study very clearly illustrates the problems with applying interventions across populations without being able to adequately characterize pregnancies at risk.

More recently however studies have evaluated a role for supplementing postnatal offspring diets with antioxidants at normal therapeutic doses. In particular, in a rodent model of maternal low-protein diet, supplementation of the offspring diet with coenzyme Q (ubiquinone) has shown great promise in reducing levels of oxidative and nitrosative stress in tissues and hence preventing premature telomere shortening in the heart (Tarry-Adkins et al. 2013a). Coenzyme Q is the most abundant and powerful endogenous antioxidant and has data demonstrating safety in human populations, making this a potential target for clinical trials in the future.

There is further limited evidence for the beneficial effects of postnatal exercise in the offspring of mothers who experienced undernutrition during pregnancy (Miles et al. 2009) in a rat model. In this study, a moderate daily exercise intervention (running on a wheel) prevented the development of obesity and improved glucose handling in the offspring. Postnatal exercise is a promising intervention that may be suitable for application in human populations.

6.3 Human Population Interventions

Data regarding interventions to improve developmental programming outcomes in human populations are currently limited. More work establishing the feasibility and safety of interventions in animal models is required prior to adopting human interventional studies on a large scale. Some early work has attempted to study the effect of exercise in obese pregnant women in order to try to improve offspring outcomes (Hayes et al. 2014). However, diet and exercise interventions in human cohorts remain methodologically problematic, with many subjects finding it onerous to adhere closely to study protocols. This was the case with the pilot study of exercise in obese pregnant women, where no objective difference in physical activity could ultimately be measured between those randomized to control and exercise interventions (Hayes et al. 2014). Specific supplementation and pharmaceutical interventions in humans remain some way off, although animal model work looks promising in this regard. As more is understood about the mechanisms by which longer-term exercise leads to improvements in metabolic function (Huffman et al. 2011), more targeted interventions suitable for use in human pregnancy may become available in this area. Evaluation of the efficacy and

safety of human interventions is also problematic in terms of study design because of the long generation time in humans and the very high potential for confounding of the effects of the early-life environment by widely varying postnatal experiences of human offspring. Such studies may be made more feasible by improved understanding of robust markers that can reliably predict later metabolic dysfunction. A number of markers, particularly circulating levels of branched-chain amino acids, look promising in this regard (Hivert et al. 2015) and may be key in assessing the efficacy of early interventions to improve later metabolic function in humans.

7 Conclusions

The remarkable increase in recent decades of metabolic-related disease, particularly obesity and type 2 diabetes, worldwide means that insights into factors contributing to such conditions are of increasing importance. While various genetic susceptibilities to type 2 diabetes and obesity have been identified, known genetic variants contribute relatively little to the overall predisposition to metabolic dysfunction. This suggests that other factors are important in determining risk of metabolic disease, and suboptimal conditions in early life may play a vital role. Particularly in view of the rising incidence of metabolic dysfunction observed in young populations and even in childhood, increasing knowledge of contributory factors is of significant global concern. Understanding that later metabolic dysfunction arises at least in part from the early-life environment could lead to exciting new routes to tackle adverse later-life outcomes, either in the index pregnancy via maternal intervention or early in the life of the offspring. Currently, our understanding of the mechanisms of developmental programming of metabolic dysfunction arises primarily from work in animal models, and much remains to be recapitulated and validated in human populations. However, an increasing number of human pregnancy cohorts are including plans to follow up the long-term development of the children including growth and metabolic parameters. These new observational studies should help to confirm many of the valuable findings from animal model work and pave the way for the initial interventional studies in human cohorts. An ability to tackle metabolic dysfunction early in life and to offset adverse programming of metabolism could prove protective to some degree against many later-life metabolic diseases. Of particular importance is the idea that adverse metabolic phenotypes may not only be seen in the offspring directly exposed to adverse conditions in utero but may also be transmitted or re-propagated across generations (Aiken and Ozanne 2014). This allows developmental programming of metabolic phenotypes to be viewed on a longer-term basis than a single generation and underscores the idea that early interventions to improve the intrauterine environment could have significant metabolic health benefits to both the children of affected individuals and to future generations.

8 Cross-References

- ▶ Brain Regulation of Feeding and Energy Homeostasis
- ▶ Childhood Environment and Obesity
- ▶ Diet, Exercise, and Behavior Therapy in the Treatment of Obesity and Metabolic Syndrome
- ▶ Linking Inflammation, Obesity, and Diabetes
- ▶ Overview of Metabolic Syndrome
- ▶ Prevention and Treatment of Childhood Obesity and Metabolic Syndrome
- ▶ Principles of Energy Homeostasis

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Childhood Environment and Obesity

14

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Contents

Abstract

US children are at risk for developing childhood obesity. Currently, 23 % of children ages 2–5 are overweight or obese, i.e., at or above the 85th percentile. This prevalence becomes even higher as children age, with 34 % of children ages 6–11 being overweight or obese. Ethnic minority children are at a higher risk for overweight/obesity with 46 % of Hispanic and 38 % of Black school age children above the 85th percentile. This is an important area of interest because childhood obesity is associated with health risks and social/emotional problems while children are young as well as long-term health risks when they reach adulthood. Because identifying the environmental factors that contribute to childhood obesity will help practitioners develop effective prevention and treatment programs for childhood obesity and metabolic syndrome, the purpose of this chapter is to provide a brief overview of the literature in this area. Because the literature is voluminous, the review is selective – focusing on the primary environmental risk factors that have been identified for the development of childhood obesity. Five major areas are addressed: diet and food environment, physical activity and sedentary behaviors, feeding practices, parenting styles, and family routines.

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1 Introduction

US children are at risk for developing childhood obesity. Currently, 23 % of children ages 2–5 are overweight or obese, i.e., at or above the 85th percentile. This prevalence becomes even higher as children age, with 34 % of children ages 6–11 being overweight or obese (Ogden et al. 2014). Ethnic minority children are at a higher risk for overweight/obesity with 46 % of Hispanic and 38 % of Black school age children above the 85th percentile (Ogden et al. 2014). Childhood obesity tracks into adulthood with 80 % of overweight/obese children maintaining their overweight/obese status as adults (Parsons et al. 1999). Childhood obesity has been associated with health risks in childhood such as Type II diabetes (Dietz 1998), cardiovascular disease (Goran and Gower 1998), and social/emotional problems (Sgrenci and Faith 2011) (Fig. 1).

Childhood obesity, as measured by BMI ≥95th percentile for age and sex (Centers for Disease Control and Prevention 2005), also is a major risk for the development of metabolic syndrome among children. US data on children 12–19 years

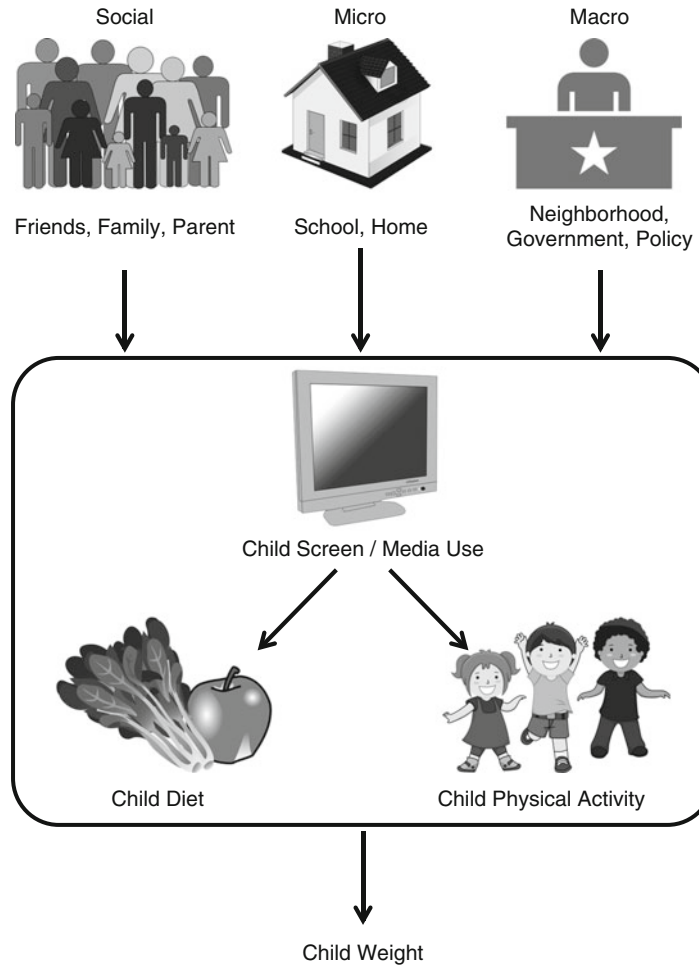

Fig. 1 Social, micro, and macro influences on child weight (adapted from Davison and Birch 2001)

old from the National Health and Nutrition Examination Survey (NHANES) found that obese children were at 16 times the risk of having metabolic syndrome (using criteria slightly different from the International Diabetes Federation) than healthy weight children (BMI $\leq$95th percentile for age and sex) (Centers for Disease Control and Prevention 2005) (5.1 % vs. 0.9 %, $p < 0.0001$) (International Diabetes Federation 2007).

Because identifying the environmental factors that contribute to childhood obesity will help practitioners develop effective prevention and treatment programs for childhood obesity and metabolic syndrome, the purpose of this chapter is to provide a brief overview of the literature in this area. Because the literature is voluminous, the review is selective – focusing on the primary environmental risk factors that have been identified for the development of childhood obesity. Five major areas are addressed: diet and food environment, physical activity and sedentary behaviors, feeding practices, parenting styles, and family routines.

2 Diet and Childhood Obesity

Proper nutrition promotes the optimal growth and development of children (Dietary Guidelines Advisory Committee 2010). Healthy eating helps prevent high cholesterol and high blood pressure and helps reduce the risk of developing obesity and other chronic diseases such as cardiovascular disease and diabetes (Dietary Guidelines Advisory Committee 2010). The Dietary Guidelines for Americans recommend a diet rich in fruits and vegetables, whole grains, and fat-free and low-fat dairy products for persons aged 2 years and older. The guidelines also recommend that children, adolescents, and adults limit intake of solid fats (major sources of saturated and *trans*-fatty acids), cholesterol, sodium, added sugars, and refined grains (The US Department of Agriculture 2010). Unfortunately, most young people are not following the recommendations set forth in the Dietary Guidelines for Americans (Briefel and Johnson 2004; The US Department of Agriculture 2010). A poor diet can lead to energy imbalance (e.g., eating more calories than one expends through physical activity) and can increase one's risk for overweight and obesity (Koplan et al. 2005; Dietary Guidelines Advisory Committee 2010). Research has shown that individuals who eat fast food one or more times per week are at increased risk for weight gain, overweight, and obesity (Dietary Guidelines Advisory Committee 2010). In addition, drinking sugar-sweetened beverages can result in weight gain and obesity over time (Dietary Guidelines Advisory Committee 2010). Among children from low-income families, hunger and food insecurity (i.e., reduced food intake and disrupted eating patterns because a household lacks money and other resources for food) also might increase the risk for lower dietary quality and obesity (Kaiser and Townsend 2005).

3 Food Environment and Childhood Obesity

What children choose to eat plays a large role in determining their risk of gaining too much weight. However, their choices are shaped by the complex world in which they live – by the kinds of food their parents make available at home, by how far they live from the nearest supermarket or fast-food restaurant, and even by the ways that governments support nutrition policies (Khan et al. 2009; Larson and Story 2009). In the United States and many parts of the world, the food environment, both physical and social, that influence what children eat makes it far too hard to choose healthy foods and all too easy to choose not so healthy foods. Such an environment is also referred to as "toxic" because of the way it corrodes healthy lifestyles and promotes obesity. These environments include the home, schools, childcare facilities, and the neighborhoods. With the high prevalence of childhood obesity in the United States, supporting healthy food environments is a key strategy to reach the public health goals of reducing childhood obesity and improving nutrition.

4 Food Environment Research by Setting

4.1 Home

Families influence children's dietary choices and risk of obesity, and children develop food preferences at home that can last well into adulthood (Gruber and Haldeman 2009). The food that families keep at home and how family members share meals influence what and how much they eat. A recent review of published studies found a strong association between the availability of fruits and vegetables at home and whether children, adolescents, and adults eat these foods (Jago et al. 2007). Eating meals as a family has also been linked with increased child and adolescent intake of fruit and vegetables and other healthy foods (Larson et al. 2007). More information on family meals can be found in the section below titled "Family Routines."

Low-income families face additional barriers to healthy eating that may contribute to the higher rates of obesity seen in lower-income groups (Singh et al. 2011). Low-income groups perceive fruits, vegetables, and whole grains as more expensive than less healthful foods, such as refined grains and sweets (Darmon and Drewnowski 2008). In addition, lower-income households often have single parents working full time and taking care of children, who may have less time for meal preparation (Dubowitz et al. 2010). Thus, it is a matter of lack of time and convenience for them to buy convenience foods or fast food.

4.2 Childcare Facilities

More than 3.5 million children younger than 6 not yet in kindergarten attend childcare facilities and receive meals through the Child and Adult Care Food Program (Food Research and Action Center 2013). In addition to the childcare facilities such as Head Start centers, a substantial number of children also attend commercial childcare facilities operated in caregivers' homes (family childcare homes) (America's Children: Key National Indicators of Well-Being 2009). However, state regulations regarding nutrition and physical activity are not consistent in their treatment of childcare centers and family childcare homes. Regulations that ensure both types of facilities maintain healthy food environments could help instill healthy eating habits among a large proportion of America's young children.

State regulations restrict sugar drinks in childcare centers and family childcare homes and require access to drinking water throughout the day in childcare centers and family childcare homes. Ensuring the availability of drinking water and limiting access to sugar drinks are ways to improve the food environment of childcare facilities. Displacing sugar drinks with drinking water, a calorie-free and thirst-quenching beverage, can substantially reduce excess energy intake among children (Wang et al. 2009). Staff can also teach the importance and healthfulness of drinking water and nonfat/low-fat milk as primary beverages.

4.3 Schools

Children spend much of their day at school. In the United States, the National School Lunch Program and related federal school meal programs, administered by the US Department of Agriculture, serve more than 30 million children every day, including breakfast, lunch, and after-school snacks (The US Department of Agriculture – Food and Nutrition Service 2013). Researchers have found that participating in the School Breakfast Program is associated with lower BMI in children, while participating in the lunch program did not impact obesity (Gleason and Dodd 2009). Students participating in the School Breakfast Program were also less likely to skip breakfast, which may reduce risk of overweight (Gleason and Dodd 2009).

Most schools sell foods to students outside of the school meal programs. These competitive foods are widely available in the cafeteria, vending machines, and school stores (Finkelstein et al. 2008). Eating competitive foods has been linked with poorer quality diets and increased risk of obesity in several studies (Larson and Story

2010). However, based on the Institute of Medicine recommendations, the sale of competitive foods in schools are now limited (Institute of Medicine 2007). Schools are uniquely positioned to facilitate and reinforce healthful eating behaviors by eliminating sugar drinks and high energy density foods (foods high in calories for their volume) from the selection of foods offered on the school campus.

Although sodas are prohibited in an increasing number of schools, other sugar drinks that may not be commonly perceived as sources of added sugar and excess calories (Ranjit et al. 2010) may be available, such as sports drinks and fruit-flavored drinks that are not 100 % juice. Schools should consider adopting policies that limit access to all sugar drinks in vending machines and schools stores. Policies that curb access to sugary drinks on school property could be a promising strategy for helping children cut back. Boston banned sugary drinks in public schools in 2004 and researchers found that after the policy change took place, students' intake of overall sugary drinks decreased (Cradock et al. 2011).

4.4 Neighborhoods

Several aspects of the neighborhood food environment have drawn research attention, specifically how the presence or lack of supermarkets, convenience stores, and fast-food restaurants relates to obesity risk. Researchers have also examined whether economic and racial/ethnic disparities in neighborhood food environments may, in part, explain the higher rates of obesity found in children from low-income families (Darmon and Drewnowski 2008) and in Blacks and Hispanics (Flegal et al. 2012; Ogden et al. 2012).

Researchers have used the term "food desert" to refer to neighborhoods with limited or lack of access to full-service grocery stores or supermarkets (Walker et al. 2010). Living in food deserts has been associated with a lower-quality diet (Zenk et al. 2009) and increased risk of obesity (Giskes et al. 2011). Likewise, some studies suggest that greater access to convenience stores and fast-food restaurants, where healthy choices may not be readily available and may cost more, has been associated with greater likelihood of obesity and lower dietary quality (Larson et al. 2009). There is evidence that low-income neighborhoods, as well as Black or Hispanic neighborhoods, are less likely to have access to large supermarkets offering high-quality and low-cost food, compared to middle-income neighborhoods and white neighborhoods (Zenk et al. 2006). Not only does lack of access to supermarkets seem to be associated with an increased risk of obesity, but simply having greater access to small food stores may increase the risk as well (Powell et al. 2007), though again, not all studies find this relationship (Lee 2012). Convenience stores often offer less variety, higher prices, and lower-quality produce than supermarkets (Zenk and Powell 2008). When small stores do stock healthier foods, however, people living nearby eat better (Sturm 2008). If small stores changed the food that they stock, they could have a positive influence on community members' diets and obesity risks.

In addition to lack of access to supermarkets, fast food has been shown to increase caloric intake and the risk of becoming obese (Rosenheck 2008). Some studies have found that living near fast-food restaurants is linked to increased risk of obesity (Boone-Heinonen et al. 2011). Fast-food restaurants are more likely to locate near schools (Austin et al. 2005), and close proximity of fast-food restaurants to schools has been linked to increased risk of obesity in schoolchildren (Davis and Carpenter 2009).

4.5 Food Marketing

Children and adolescents represent a vast market opportunity for food companies. In the United States, these age groups spend an estimated $200 billion per year, much of it on food products (Institute of Medicine 2005). The extent of marketing targeted directly to children and adolescents is striking, but the content also alarms health experts. Many researchers have documented the predominance of advertising for calorie-dense, low-nutrient foods on children's television (Folta et al. 2006; Institute of Medicine 2005). In a review of the reviews, Livingstone

(2005) concludes that there is tacit consensus among reviewers that, "food promotion has a causal and direct effect on children's food preferences, knowledge and behavior." In addition, the Institute of Medicine has concluded that "food advertising to children affects their preferences, purchase behaviors, and consumption habits for different food and beverage categories, as well as for different product brands" (Institute of Medicine 2005). In schools, advertising can take the form of posters and signage; logos or brand names on food and beverage coolers, cups, and plates or vending machines; food sales as fundraisers and corporate sponsorship of events; advertising in school publications; and corporate-sponsored classroom curricula and scholarships (Institute of Medicine 2005). Such advertising may impact children's ability to make healthy choices in their diets.

5 Physical Activity and Sedentary Behaviors

Both physical activity (Janssen and LeBlanc 2011) and sedentary behaviors (Tremblay et al. 2011) have been linked to children's risk of obesity and are independently associated with children's metabolic risk (Ekelund et al. 2006) and physical fitness (Moore et al. 2013). Sedentary behaviors can be measured objectively with activity monitors, called accelerometers, but more commonly have been measured by quantity of TV viewing and other screen media used by children (Marshall et al. 2004; Biddle 2007; Tremblay et al. 2011). A meta-analysis found that children's sedentary time only had a small negative effect on their physical activity, suggesting that children's physical activity and screen media use do not strongly correlate (Marshall et al. 2004). Therefore we will discuss physical activity and sedentary behaviors separately in this chapter.

5.1 Physical Activity Among Children

There is an ongoing debate as to how much children's physical activity has contributed to the increased rates of overweight and obesity in the past several decades. Some reviews have found that children are experiencing a decline in context specific physical activity (e.g., physical education opportunities in schools, active transport, and organized sports) over time, but available data across decades and countries is limited, making it difficult to draw strong conclusions (Dollman et al. 2005). European studies also found decreased fitness levels in adolescents over the last two-to-three decades (Matton et al. 2007; Huotari et al. 2010). US data from NHANES found 70 % of 6–11-year-old children in 2009–2010 met US guidelines for physical activity ($\geq$1 h physical activity/day) (Fakhouri et al. 2013). In Europe, the "Identification and prevention of dietary- and lifestyle-induced health effects in children and infants" (IDEFICS) Study assessed physical activity among children 2–10 years old across eight countries and found that the majority of children (61.7 % boys and 58.2 % girls) did not achieve their recommended 2 h of physical activity per day (Santaliestra-Pasias et al. 2013).

Cross-sectional (Belcher et al. 2010; Fakhouri et al. 2013) and longitudinal (Basterfield et al. 2011) studies have found that children's physical activity decreases as children get older. For example, elementary school age children (6–11 years old) average 88 min/day of moderate to vigorous physical activity as measured by accelerometers, but this is reduced to 26 min/day in 16–19-year-old adolescents (Belcher et al. 2010). From a developmental viewpoint, it follows that there are likely different influences on children's physical activity as they grow up.

Among preschool age children, a systematic review found that child sex (with boys more active than girls), having active parents, and time spent outdoors were most consistently associated with preschoolers' physical activity (Hinkley et al. 2008); however, age and weight status were not associated with preschooler's physical activity (Hinkley et al. 2008). The importance of time outdoors as a determinant of younger children's physical activity has been of interest among researchers. A study investigating 5-year-olds found that the family environment, parental habit

strength, and rules were the strongest predictors of children's outdoor play over a 2-year period (Remmers et al. 2014). As children grow older, child sex (male) remains an important correlate of objectively measured physical activity for 6–19-year-olds, as was younger age, and lower weight status (Belcher et al. 2010). In addition to these, less TV viewing/videogame playing and greater access to recreational facilities were associated with more after-school physical activity among 8–14-year-olds (Stanley et al. 2012).

To date, the majority of interventions to increase children's physical activity have been conducted through schools. Systematic reviews of physical activity interventions found that such school-based interventions had no significant effect on children's weight or weight status as assessed by BMI (Harris et al. 2009; Guerra et al. 2013). Other reviews also found that physical activity interventions were not effective in impacting children's physical activity (Metcalf et al. 2012), suggesting that our current methods for promoting physical activity are not sufficient. This supports the need for alternative methods of intervention. Reviews have identified that involving parents directly in ways to encourage child's physical activity (O'Connor et al. 2009) and targeting physical activity parenting practices (Van Lippevelde et al. 2012) may be promising methods for promoting increased child's physical activity for children and warrant further study.

In part due to these findings, there has been a growing interest to understand how parents influence their children's physical activity to better inform interventions. A few studies have investigated the role of parenting styles on children's physical activity. One study of a rural US sample found that children whose parents reported an uninvolved parenting style had less physical activity, while permissive parenting style moderated the effect of parental monitoring on children's physical activity such that monitoring had a positive influence on children's physical activity in families with permissive parents, but not other parents (Hennessy et al. 2010). A larger study among urban 10–11-year-olds in the UK found that permissive parenting style was associated with greater physical activity among children compared to the authoritative parenting (Jago et al. 2011). Both of these studies illustrate that promoting authoritative parenting for better child outcomes may not be correct for all contexts.

The majority of the observational studies however have focused on parenting practices, rather than parenting styles. A systematic review identified that paternal and maternal physical activity, engaging in physical activity with one's parent, and parental logistic support were the most consistent correlates of children's physical activity (Verloigne et al. 2012). Mothers and fathers may also have different influences depending on the sex of their child, with fathers having a greater impact on their son's physical activity and mother's on their daughters (Jago et al. 2011). However, limitations in the current methods used to measure physical activity parenting practices have been identified (Trost et al. 2013), including significant variability in the conceptualization of physical activity parenting and validity of the instruments used (Sleddens et al. 2012). There is a need for a better conceptualization of physical activity parenting based on developmental and behavioral theory (Davison et al. 2013).

There is some evidence to suggest that targeting parents to help promote physical activity among their children is important to facilitate behavior change leading to child obesity prevention. However, the optimal way of targeting parents has not been identified. A review of home-based programs found little support for this approach, although the number of studies is limited (Showell et al. 2013).

5.2 Sedentary Behavior Among Children

US data from 2009 to 2010 NHANES found 54 % of 6–11-year-old children met US guidelines for screen viewing ($\leq$2 h/day) (Fakhouri et al. 2013), and only 38 % met both physical activity and screen-viewing recommendations. Similarly to physical activity, screen use changes over time, with children spending more time using screen media as they get older (Fakhouri et al. 2013). A longitudinal study similarly found that objectively

measured sedentary time among elementary school age children increased from 78 % of their day to 81 % of their day from 7 to 9 years of age (Basterfield et al. 2011). Among European children 2–10 years old, screen use was greater on weekends (52 % viewed >2 h/day) than weekdays (20 % viewed >2 h/day) and increased with age and gender (boys watched more) (Santaliestra-Pasias et al. 2013).

Screen media use is believed to be related to children's weight status through its influence on children's dietary intake, physical activity, and sleep (O'Connor et al. 2013a; Biddle et al. 2014). Therefore, targeting screen time has become an increasing priority for public health programs with greater evidence of success than for physical activity interventions. Meta-analyses found that interventions that targeted a reduction in sedentary behaviors had a significant effect on reducing children's weight status (Tremblay et al. 2011; Liao et al. 2014).

A systematic review of family and school-based correlates of children's sedentary behaviors emphasizes the need to focus more on parents. They found the strongest evidence for parental rules/restriction of screen-based media as a correlate, which had an inverse association with both children's screen media use and sedentary time (Verloigne et al. 2012). Having a TV in the child's bedroom has also been consistently identified as an important correlate of children's screen time (Santaliestra-Pasias et al. 2013). Ultimately, the decision to allow a TV in the child's room is up to the parents.

While physical activity parenting research lags behind the nutrition-related parenting field by several years, screen media parenting is really just emerging. Few studies have thoroughly assessed screen media parenting. Several studies have combined the concept of promoting physical activity and restricting screen time into one concept (Larios et al. 2009). However, parents appear to use these concepts differently, with supportive physical activity practices associated with greater amount of child's physical activity, while restrictive TV practices were associated with less physical activity (O'Connor et al. 2013a) when one might expect them to have a similar influence on children's activity. This study was conducted in a small cross-sectional sample, but it illustrates the need to better understand how parents interact with their children regarding sedentary behaviors differently from physical activities. Analogous to the call for improved conceptualization of physical activity parenting practices, a working group of experts have proposed a better understanding of how parents influence their child's screen media use across three domains: content, context, and amount, all of which may be influencing the child's weight status through different mechanisms (O'Connor et al. 2013b).

Interventions to reduce children's sedentary time that include a family component have some promising findings (Biddle et al. 2014; Marsh et al. 2014). A systematic review found that greater parental involvement was associated with greater intervention effect (Marsh et al. 2014). Interventions targeting younger children were also found to be more effective. Interestingly, the intervention effects appeared to be related to energy consumption rather than children's physical activity (Marsh et al. 2014). In fact, sedentary behaviors have been linked to less healthy eating patterns among children, adolescents, and adults (Pearson and Biddle 2011) including less fruit and vegetable consumption, greater intake of energy-dense snacks, and total energy intake.

6 Feeding Practices Among Parents

Parents play a major role in the development of child obesity – not only through the foods that they serve their children as described above but through the ways that they feed them – especially in the preschool and middle childhood years (Ventura and Birch 2008). The major feeding practices that researchers have focused on to date are parental restriction and pressure to eat. The assumption behind these studies is that highly controlling feeding practices (e.g., having the child finish all of the food on the plate, bribing the child to eat, restricting access to palatable foods) lead children to focus more on external cues (e.g., parent demands, food characteristics, food left on the plate) than internal

cues (e.g., feelings of hunger and fullness) in determining whether they had eaten enough (Birch et al. 1987; Johnson and Birch 1994; Fisher and Birch 1999a). As a consequence, especially in today's obesogenic environment (Wansink 2004; Lake and Townshend 2006), children who are fed in this way may eat more in the absence of hunger (Fisher and Birch 1999b) or not stop eating when they are full (Johnson and Birch 1994).

A number of experimental studies in laboratory settings (using research assistants, not parents) confirm these hypotheses. For example, in experiments where children were either bribed with another food or pressured to eat (Birch et al. 1982, 1984; Newman and Taylor 1992; Galloway et al. 2006), children typically showed more consumption of the target food in the short term, but showed less consumption when later given the opportunity to freely eat the target food. In such situations, they were also less likely to develop a preference for the target food over time. Similar results have been found in experimental studies of restriction – restricting access to a food decreased consumption in the short term, but increased preferences and consumption of these same foods in the long term (Fisher and Birch 1999a, b). Experimental laboratory studies have shown that the most effective way for children to develop preferences for new foods is through low-pressure, repeated exposure (often taking 8–12 separate presentations) (Cooke 2007), although recent studies have shown that the use of small nonfood rewards (e.g., stickers) can increase preferences for novel foods as well (Cooke et al. 2011). In recent experimental studies in the home using parents rather than research assistants, Wardle and colleagues demonstrated the effects of repeated exposure (Wardle et al. 2003) and small nonfood rewards (Remington et al. 2012) on the development of food preferences.

Correlational studies examining parental feeding practices and child obesity partially confirm these conclusions. The most consistent data are for restriction – several longitudinal studies show that parents who restrict their children's consumption of high-calorie, low-nutrient-dense foods have children who show greater weight gain over time (even after controlling for children's initial weight status) (Ventura and Birch 2008). Restriction also is associated with poor regulation of energy intake. Birch and colleagues (2003), for example, found that maternal restriction at age 5 predicted the greatest increase in eating in the absence of hunger from ages 5 to 9. Similarly, Johnson and Birch (1994), in a cross-sectional study, found that mothers who engaged in more control over their preschooler's eating had children who demonstrated the poorest self-regulation in a compensation trial (an assessment of children's ability to stop eating when full). Correlational studies of pressure to eat, in contrast, show it is more common in mothers of healthy weight children, probably reflecting their tendency to use this strategy with picky eaters. Most of these studies, however, are cross-sectional (Ventura and Birch 2008). The results of longitudinal studies are mixed. Two studies by Gregory and colleagues (2010, 2011) found that pressure to eat was associated with lower interest in food and less fruit consumption 1 year later, whereas two other studies (Webber et al. 2010; Jansen et al. 2014) found that child BMI predicted maternal restriction and pressure to eat over time, rather than maternal feeding predicting child BMI.

Besides restriction and pressure to eat, researchers have examined a wide range of other feeding practices, including those thought to be positively associated with child obesity (e.g., soothing with food, using food to reward good behavior) and those thought to be negatively associated (e.g., providing healthy choices, encouragement, praise, support, reasoning), but research on the relationships of these strategies with child obesity to date is limited or inconsistent (de Lauzon-Guillain et al. 2012; Vaughn et al. 2013).

7 Parenting Styles and Feeding Styles

Parents influence their children through both their practices and their styles of parenting. Parenting practices are goal-oriented parenting behaviors specific to a context (Maccoby and Martin 1983; Baumrind 1989), whereas styles refer to the

overall attitude the parent has about child-rearing. General parenting styles are characterized by levels of demandingness/control (setting clear expectations and monitoring the child's behavior) and responsiveness/nurturance (warmth and approval). These dimensions translate into four styles of general parenting: authoritative (high demandingness, high responsiveness) characterized by parental involvement, nurturance, and structure; authoritarian (high demandingness, low responsiveness) characterized by restrictive, punitive, and power-assertive behaviors; permissive/indulgent (low demandingness and high responsiveness) characterized by warmth and acceptance in conjunction with a lack of monitoring; and uninvolved (low demandingness, low responsiveness) characterized by little control and involvement. The authoritative style provides the most protective parenting resulting in better child health outcomes (Vollmer and Mobley 2013). Children of authoritative parents consume greater amounts of fruit and vegetables (Lytle et al. 2003; Pearson et al. 2010; Park and Walton-Moss 2012; Rodenburg et al. 2012) and fewer amounts of high fat and/or sugar (Chen and Kennedy 2005; Van der Horst et al. 2007; Pearson et al. 2010). In a study of predominantly White families, childhood overweight was least prevalent in children with authoritative parents (Rhee et al. 2006). In this same study, the indulgent parenting style – those who were highly nurturing but made few demands on their child – was associated with an increased risk for childhood overweight (Chen and Kennedy 2005; Rhee et al. 2006; Wake et al. 2007).

More recently, the concept of feeding styles has been introduced into the literature which uses a framework similar to general parenting styles. A feeding style refers to the overall attitude and emotional climate a parent creates with their child during eating episodes. Feeding styles are measured along two dimensions of feeding: parental demandingness and responsiveness (Hughes et al. 2005). Demandingness refers to the number of demands parents place on their child to eat, while responsiveness refers to how sensitive parents are to the child's needs in the eating domain. Differences on the two dimensions result in four styles of feeding similar to general parenting styles: authoritative parents (high demandingness/high responsiveness) place reasonable nutritional demands on their child as well as being sensitive to the child's needs; authoritarian parents (high demandingness/low responsiveness) are highly controlling during feeding episodes showing little sensitivity toward the child; indulgent parents (low demandingness/high responsiveness) are highly responsive to their child's needs, but provide few rules and little structure allowing the child the freedom to determine their own nutritional intake; and uninvolved parents (low demandingness/low responsiveness) exhibit little control and involvement during feeding.

Across a series of studies with African American, White, and Hispanic low-income families with children ages 3–11, the indulgent feeding style has been associated with higher child weight status (see El-Behadli et al. 2015 for a review). The indulgent feeding style has also been associated with self-selected portion sizes and intake in children ages 4–6 (Fisher et al. 2013); lower intake of fruit, vegetables, and dairy in low-income preschoolers (Hoerr et al. 2009); and higher intake of low-nutrient energy-dense snacks in rural low-income ethnically diverse children (Hennessy et al. 2012). The uninvolved feeding style was also associated with higher intake of energy-dense foods in preschoolers (Hoerr et al. 2009). Conversely, the authoritative feeding style was associated with lower child intake of low-nutrient energy-dense snacks (Hennessy et al. 2012). In general, these studies support the theory that parents who are highly responsive to their children during eating episodes but do not set appropriate boundaries around food deter the development of appropriate eating behaviors that may contribute to child weight gain.

Cultural differences have been observed across feeding styles. Among the two permissive feeding styles, Hispanic parents were more likely to be indulgent, whereas African Americans were more likely to be uninvolved (Hughes et al. 2005). In a separate study conducted among immigrant mother-child dyads of Brazilian, Haitian, or Latino descent living in the Boston area, the majority of mothers were either authoritarian or indulgent in their feeding style (Tovar et al. 2012).

Higher stress among these immigrant mothers was associated with an authoritarian feeding style.

Although the information provided above supports evidence for the promotion of authoritative parenting and/or feeding in the fight against childhood obesity, to date, few interventions have been developed that directly address general parenting or feeding styles in the prevention of childhood obesity (Gerards et al. 2011).

8 Family Routines

Family routines are considered the ways that parents organize family activities taking into consideration family goals, values, and individual differences in their children. The goal of family routines is to provide a predictable structure that is sustainable over time (Spagnola and Fiese 2007). Because parents control the home environment including what, when, and how the family eats, one important way that parents influence the development child's eating behaviors is through family eating routines such as the frequency of family meals. Frequency of family meals has been associated with lower rates of obesity in children (Hammons and Fiese 2011). Hammons and Fiese (2011) conducted a meta-analysis of 17 studies including over 180,000 children and adolescents and found that regularly sharing meals as a family reduced the odds for child and adolescent overweight by 12 % and increased the odds for eating healthy foods by 24 %. However, this meta-analysis did not account for whether the study design was cross-sectional or longitudinal nor did it account for possible confounders (e.g., sex, age, ethnicity). In a separate review, inconclusive evidence was found regarding the protective nature of family meals on childhood obesity (Valdes et al. 2013). In this review of 15 studies, 6 out of 11 cross-sectional studies and 1 out of 4 longitudinal studies found a statistically significant inverse relationship between frequency of family meals and the child being overweight (odds ratios from 0.11 to 0.93) (Valdes et al. 2013). However, only one study adjusted for all relevant confounding factors (sex, age, ethnicity, SES, diet, and physical activity-related variables), and this study did not find any association between frequency of family meals and child weight after stratifying for sex and age (Fulkerson et al. 2008). Furthermore, of the reported studies, there was no standard definition for what was considered a family meal (at home or away from home, seated at a table or not, number of family members present, length of meal, food served and consumed, and whether the TV was on or not). In summation, some studies have shown that family meals are associated with greater fruit and vegetable consumption (Gillman 2000; Neumark-Sztainer et al. 2010) and more family cohesion (Neumark-Sztainer et al. 2003). One can argue that family meals help children establish firm routines around food (e.g., eating breakfast and avoiding snacking) (Anderson and Whitaker 2010; Fulkerson et al. 2009). However, based on current information, it is still unclear whether sharing family meals prevents childhood obesity after controlling for other associated variables (Valdes et al. 2013).

9 Structure of the Home Environment

Besides family meals, there are also other ways that the structure of the home food environment can be important in the development of child obesity. These include such aspects as (with examples representing behaviors that likely decrease child obesity risk) organization of meals (e.g., is there a designated space for eating? are distractions minimized?), the meal preparation process (e.g., is the child involved in food preparation?), availability and accessibility of food (e.g., are healthy foods available and easily accessible to the child and unhealthy foods not present or not easily accessed by the child?), parent modeling of food consumption (e.g., do parents model healthy patterns of consumption?), rules and limits on consumption (e.g., do parents have clear expectations for what, when, and where children eat?), and parental monitoring of consumption (e.g., are parents aware of their children's consumption patterns – especially unhealthy foods?) (Hughes et al. 2008; Vaughn et al. 2013).

Unfortunately, insufficient research has been conducted in most of these areas on their direct relationship with child weight status. Monitoring is the only variable with sufficient research, and the results are inconsistent (Jansen et al. 2012). Indirect evidence comes from studies of the correlates of children's food consumption – especially fruits and vegetables. Both availability of fruits and vegetables in the home and parental modeling of their consumption are positively associated with children's fruit and vegetable consumption (Pearson et al. 2010). Although some research on other aspects of parental structure is promising (De Bourdeaudhuij 1997; Verzeletti et al. 2010), additional research is necessary to clarify their relationships with child obesity and child obesity risk.

10 Conclusions

Despite a considerable amount of research on the environmental factors that contribute to childhood obesity, most of this research is cross-sectional and correlational and does not allow for strong inferences about the direction of causality. As described throughout this review, most intervention studies have been school based and have not led to long-term changes in children's behavior or to long-term reductions in childhood obesity rates. As a consequence, some researchers are now turning to family based programs in an attempt to change the home feeding environment (Hingle et al. 2010) to lead to long-term effects.

Another limitation of research in this area is that most studies have been conducted on young children and less attention has been paid to middle childhood and adolescence. An assumption of many researchers is that they should focus on young children since eating habits develop early (Birch and Ventura 2009), but there is evidence that obesity rates continue to increase into adolescence and young adulthood, as physical activity levels decrease (Belcher et al. 2010), sedentary behavior increases (Basterfield et al. 2011; Santaliestra-Pasias et al. 2013), and individuals begin to make more choices about their food intake (Lytle et al. 2000). Further studies on the risk and protective factors during these later developmental periods could help us better understanding the increasing obesity rates with age.

Despite these limitations, the literature has identified a large number of factors associated with the development of child obesity, ranging from individual eating behaviors to family factors to neighborhood to cultural factors (Davison and Birch 2001). Very few studies to date, however, have examined how these factors interact with one another in predicting childhood obesity risk. For example, do certain parenting practices protect children from the development of childhood obesity in high-risk neighborhoods (e.g., neighborhoods with few supermarkets and a large number of fast-food restaurants) or do high levels of physical activity protect children from obesity even though they consume a large number of calories?

Finally, the role of culture in childhood obesity deserves more attention. Childhood obesity rates vary considerably across cultures (Ogden et al. 2014), and second-generation immigrants from Asia and Latina America have higher obesity rates than first-generation immigrants (Popkin and Udry 1998; Hernandez-Valero et al. 2007). However, our understanding of the risk and protective factors that account for these differences is limited. Are these differences in obesity rates due to diet, to physical activity, to parenting practices, or to some combination of all three?

Future research needs to examine the interactions between the various risk and protective factors identified here, with close attention to the cultural context. Studies should be longitudinal, employ multiple measures and methods, and contemporary approaches to the analysis of longitudinal data (Singer and Willett 2003; Little 2013). Moreover, a greater number of intervention studies must be conducted that not only demonstrate causal impact on the development of childhood obesity but also to identify the critical intervention components that contribute to their effects. Such studies would go a long way in helping us identify effective approaches to addressing this important societal problem.

11 Cross-References

- Diet and Obesity (Macronutrients, Micronutrients, Nutritional Biochemistry)
- Fetal Metabolic Programming
- Prevention and Treatment of Childhood Obesity and Metabolic Syndrome
- The Built Environment and Obesity

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Diet and Obesity (Macronutrients, Micronutrients, Nutritional Biochemistry)

15

Laura E. Matarese

Contents

Abstract

The global prevalence of overweight and obesity as a public health concern is well established and reflects the overall worldwide lack of success in achieving and maintaining a healthy body weight. The major concern is that overweight and obesity is associated with numerous comorbidities and is a risk factor for several of the leading causes of death, including cardiovascular disease, diabetes mellitus, and many types of cancer. These are for the large part preventable diseases. The cornerstone of therapy has been diet, exercise, and behavioral modification. Considering the plethora of existing diet programs and the global expansion of the obesity crisis, a conclusion can be drawn that no one diet has been universally successful at inducing and maintaining weight loss and improving metabolic parameters. This enigma provides some evidence as to the complexity of obesity and weight management. The achievement of a healthy body weight is far more complex than a simple reduction of caloric intake relative to energy expenditure. The factors affecting obesity are complicated, dynamic, and interrelated and involve numerous host factors as well as the environment. This chapter will review the physiological basis of scientifically validated weight loss diets, their effects on energy expenditure, body weight, body composition, and metabolic parameters.

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1 Introduction

Obesity, and its related comorbidities, is no longer a disease of Western cultures and has become a global epidemic (WHO 2000). In June of 2013, the American Medical Association recognized obesity as a disease (AMA 2013). It has become a serious public health problem, including childhood obesity, in many countries worldwide (Janssen 2005; Wang and Beydoun 2007; Wang and Lim 2012). Obesity is a chronic disease that contributes to the development of diabetes, cardiovascular disease, hypertension, cancers, and serious medical conditions, resulting in an adverse effect on quality of life and an estimated economic burden of $2.0 trillion annually (WHO 2015; Patel and Abate 2013). The seriousness of this disease has led to the search for an effective and lasting treatment. There are three main categories for treatment of obesity: (1) lifestyle modification including dietary intervention, physical activity, and behavioral modification, (2) pharmacotherapy, and (3) surgery. Although the mechanisms differ, each of these interventions is designed to generate a negative energy balance, stimulate lipolysis, and induce weight loss. This chapter will focus on dietary interventions including macronutrients, micronutrients, and the nutritional biochemistry forming the basis for the design of the specific diet.

2 Popularized Weight Loss Diets

There are well over 1,000 weight loss diets that have been popularized in the lay literature and throughout the media. The sheer number of available diets would suggest that as a global society, we have not been successful in managing this disease. Most of these weight loss plans have little to no scientific evidence behind them. They may recommend intermittent fasting, eliminate one or more food groups, or suggest consumption of a particular type of food or a specific macronutrient. In the short term, these diets may produce weight loss, but their effects are generally not lasting. There are, however, some diets that are based on sound nutritional, physiological, and biochemical principles which have been studied under controlled conditions.

3 The Weight Loss Equation: Is It Simple Math?

The induction of weight loss has been thought of in terms of an equation; energy intake exceeding expenditure leads to weight gain; intake less than expenditure results in weight loss; and intakes equivalent to expenditure result in weight maintenance. This concept is often attributed to the laws of thermodynamics which define the fundamentals of heat and work. But when these laws which govern the physical aspects of temperature, energy, and entropy are applied to living biological systems, the equation becomes far more complex. Biological systems are complicated. The second law of thermodynamics, the law of dissipation, states that the entropy increases during any spontaneous process and that for any irreversible reaction, there is a loss or dissipation of energy in that reaction. This is the law that describes the inefficiency in biological systems associated with metabolic processes. From a metabolic standpoint, it is impossible for a biological system to turn a given amount of energy into an equivalent amount of work. Thus, a "calorie" is not always a "calorie." Calories are not converted to energy on a one-to-one basis because of this loss of energy, this inefficiency, described by the second law of thermodynamics. Oxidation of carbohydrates is more thermodynamically efficient and requires less energy than oxidation of protein or fat which is why it is the preferential fuel for the body. The inefficient protein and fat oxidation leads to extra energy loss, thus creating a metabolic advantage during weight loss interventions (Fine and Feinman 2004). Whether or not this metabolic advantage is clinically significant has been debated.

4 Other Factors Affecting Weight Loss

To consider weight loss as the mere application of an intervention designed to reduce intake and increase expenditure in order to mobilize adipose stores for fuel is an oversimplification. There are numerous biochemical, physiological, psychological, emotional, economic, and social factors associated with weight loss and gain (Fig. 1). To complicate matters, they are multifaceted, interrelated, and dynamic such that a change in one factor will affect others.

It is intriguing to think that there may be a genetic component to this disease and that alteration of the genetic expression could influence the progression to obesity or that some of these obesogenic or leptogenic genes may influence the response to weight loss interventions (Hainer et al. 2008). The existence of one or more family members who are overweight or obese suggests that there may be a genetic component and that it may also be associated with specific socio-environmental factors (Serene et al. 2011). Yet, it is not unusual to find both lean and obese members within the same family. The obese gene that is located on chromosome 7 encodes for leptin which regulates energy intake and energy expenditure (Green et al. 1995). The percentage of obesity that can be attributed to genetics varies widely, depending on the population examined, and ranges from 6 % to 85 % (Yang et al. 2007). It is also possible that the development of obesity begins in utero during fetal development at which time nutritional, hormonal, physical, and psychological processes are preprogrammed to activate specific physiological functions at defined periods later in life (Tounian 2011). At least 71 genes have been implicated in the development of obesity (Doo and Kim 2011). One of the genes known to contribute to polygenic obesity is the fat mass–obesity-associated (FTO) gene (Baturin et al. 2011). There are other gene mutations that have been associated with morbid obesity including Alstrom syndrome, Bardet–Biedl syndrome, Cohen syndrome, Ayazi syndrome, MOMO syndrome, and Prader–Willi syndrome. These observations provide a strong argument for a

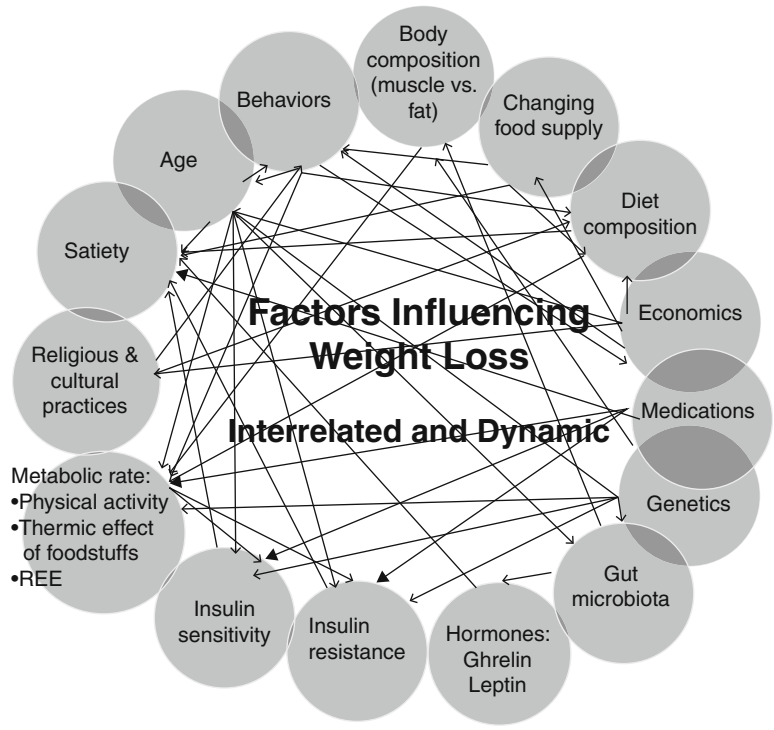

Fig. 1 Factors influencing weight loss (With permission from: Matarese LE, Pories WJ. Adult Weight Loss Diets: Metabolic Effects and Outcomes. Nutrition In Clinical Practice; 2014; 29 (6):759–767)

genetic component. Yet obesity cannot be attributed to genetics in all cases.

One cannot overlook the contribution of physical activity to weight management. Engagement in physical activity, particularly aerobic exercise, will influence the metabolic rate and caloric expenditure. Physical activity also affects insulin sensitivity and insulin resistance. The positive changes on insulin sensitivity and insulin resistance are sustained as long as exercise is sustained (Houmard et al. 1996). This in turn may affect the success of a planned dietary intervention. With aging, there is a reduction in lean body mass, metabolic rate, energy expenditure, and physical activity, all of which will result in increased weight gain if one continues to consume the same level of calories throughout the life span.

If weight gain and loss are related to insulin, does it matter if someone is insulin sensitive or insulin resistant? Cornier and colleagues conducted a small study on obese nondiabetic women over a 4-month feeding period (Cornier et al. 2005). The subjects received a high-carbohydrate low-fat (60:20) or a low-carbohydrate high-fat (40:40) diet. Both diets were hypocaloric. The high-carbohydrate low-fat diet was more effective in producing weight loss in the insulin-sensitive women, and the low-carbohydrate high-fat diet was more effective for the insulin-resistant woman. The differences were not explained by intake, activity, or resting metabolic rate. A similar study was conducted by Ebbeling and colleagues. In this study, a low-glycemic diet resulted in greater weight loss in those individuals who were insulin resistant (Ebbeling et al. 2007). Thus, reducing the glycemic load may be important to achieve weight loss in those individuals with high insulin secretion.

Our food supply has changed dramatically over the years and has become far more processed and inclusive of highly refined sugars, chemicals, and preservatives. The role that these chemicals and preservatives have on hunger, satiety, and ultimately food consumption is unclear . The overall refinement in the diet has also led to a reduction in fiber intake which in turn affects satiety value. The influence of the food supply on the development of obesity is also closely related to socioeconomic factors. When there are economic constraints, people will purchase low-cost foods, which tend to be low in nutritional value but high in calories, fat, and refined carbohydrates.

There clearly is a role of hormones such as ghrelin and leptin in the development of obesity. Leptin is derived from adipose tissue and is released into the circulation at a level which is proportional to the increased energy stores in fat. Leptin is a product of the OB gene and stimulates the neural circuits that decrease food intake and increase energy expenditure (Friedman and Halaas 1998). In contrast, ghrelin is an orexigenic gut hormone which is decreased in obesity (Tschop et al. 2001). These hormones affect appetite and satiety level, and the differences among individuals and populations are still being elucidated. The ability to manipulate the secretion of these hormones may someday aid in the prevention and cure of obesity.

All of these factors affect the gut microbiota, which in turn influences the storage and release of energy from the adipocytes. However, the precise mechanism by which these alterations occur is still unclear. Most of the data has been extrapolated from epidemiological or animal studies. For example, fiber has been shown to be protective and reduce body weight in a number of conditions (Anderson and Pasupuleti 2008). Women who consume more refined grains tend to have greater weight gain than those who consume viscous or fermentable fibers (Liu et al. 2003). The use of fiber supplements has been shown to result in greater weight loss (Anderson et al. 2009). Fiber is a prebiotic and can change the microbiota of the gut. Thus, diet can influence commensal microbiota. There are numerous factors which affect the ecology of gut microbiota. Even the process of aging will influence the gut microbiota (Biagi et al. 2012). There are differences in individual characteristics such as changes in diet, lifestyle, antibiotic use, bile acids, country of residence, and, eventually, frailty. The aged-type microbiota shows a low microbial biodiversity, and it is characterized by an increase in opportunistic environmental facultative aerobes, *Staphylococcus*, *Streptococcus*, and Enterobacteriaceae,

as well as a reduction in anaerobes, such as *Clostridium* clusters IV and XIVa and Bacteroidetes. However, differently from the infant-type microbiota, the aged type is characterized by a low abundance of *Bifidobacterium* (Biagi et al. 2012). For bifidobacteria, a consistent difference was found in the meta-analysis between 159 obese subjects and 189 controls from six published studies showing that the digestive microbiota of the obese group was significantly depleted in bifidobacteria (Angelakis et al. 2012). Recently, the use of artificial sweeteners was linked to the changes in the gut microbiota (Suez et al. 2014). There are two phyla, mainly anaerobes, that appear to be linked to obesity, Firmicutes (positively) and Bacteroidetes (negatively). However, it is not certain if these microorganisms cause obesity or are a result of obesity. Obese mice have altered gut flora. When gut flora is transferred from an obese mouse to a lean mouse, the lean mouse gains weight (Ley et al. 2005; Turnbaugh et al. 2006). Short-chain fatty acid (SCFA) content of mice that are ob/ob has higher SCFAs than lean mice – meaning they ferment carbohydrates and are more efficient energy extractors. There is less energy in the stool of the obese mice than lean mice because of more efficient extraction of energy via enhanced fermentation by the gut microbiota. The question becomes can we modulate the gut microbiota to induce weight loss? At this point it is important to recognize that there is no substitute for a healthy lifestyle. Other things such as antibiotics, probiotics, synbiotics, genetically modified bacteria, and fecal microbial transplantation do modify the gut microbiota.

5 Dietary Macronutrients

Most dietary interventions center on modification of the macronutrient portion of the diet (i.e., carbohydrate, protein, and fat) and may or may not include an overall energy restriction. When the percentage of one macronutrient is changed, there will be a corresponding increase or decrease in the other macronutrients. The particular diet may or may not define the characteristics of each of these macronutrients. For example, a carbohydrate is not a uniform organic compound and may be defined as simple or complex, by the glycemic index (GI), glycemic load (GL), or fiber content (viscous vs. fermentable). Proteins have varying amino acid profiles and may be derived from animal, plant, or marine sources. In addition, these protein sources may contain varying amounts and types of fat. There are also some protein sources such as those derived from dairy sources which contain some carbohydrate. Fat sources include monosaturated, polyunsaturated, saturated, and *trans* fats. Depending on the composition included in the weight loss diet will vary in the content of omega-3, omega-6, and omega-9 fatty acids. Foods are generally composites of each of these macronutrients. This lack of precision in defining the dietary prescription makes comparisons of weight loss diets difficult.

6 Low-Carbohydrate and Ketogenic Diets: Metabolic Rationale

The use of low-carbohydrate and ketogenic diets has been extensively studied. The metabolic rationale for the restriction is that when the carbohydrate content of the diet is sufficiently reduced, especially simple and highly refined carbohydrates, there will be a decline in blood glucose and insulin levels, which in turn will shift metabolism from lipogenesis to lipolysis, resulting in weight loss. Accordingly, when the carbohydrate content of the diet is reduced, there is a corresponding increase in the protein and fat content. The oxidation of protein and fat for energy results in the production of ketones, which causes an increase in the satiety value and a voluntary caloric reduction. The oxidation of protein and fat is less efficient than the oxidation of carbohydrate. The extra energy required to oxidize protein and fat may be as high as 400–600 kcal/day (Fine and Feinman 2004). Aside from the additional energy required to metabolize protein and fat, increasing the protein content of the diet has been shown to have a beneficial effect

on resting energy expenditure (REE) and total energy expenditure (TEE) during weight loss (Pereira et al. 2004; Ebbeling et al. 2012). Lipolysis is maintained even if there is an excess of calories because glycerol from fat is needed as a gluconeogenic precursor. Thus the rapid weight loss observed during the use of these diets is probably multifactorial and results from a combination of increased lipolysis and decreased de novo lipogenesis, increased energy expenditure from the conversion of glycerol and glycogenic amino acids to glucose, as well as the satiety value associated with ketone bodies and higher protein intakes.

The exact amount of carbohydrate required to produce these metabolic alterations has been debated and not clearly elucidated. It should also be noted that a low-carbohydrate diet is not necessarily a ketogenic diet. Considering the wide range of carbohydrate levels used in studies throughout the literature, Feinman and colleagues proposed that the low-carbohydrate diet be defined as less than 130 g/day or less than 26 % of total energy and the very low-carbohydrate ketogenic diet defined as carbohydrate between 20 % and 50 g/day or less than 10 % of a 2,000 kcal/day diet, whether or not ketosis occurs (Feinman et al. 2015).

Another approach to controlling carbohydrate intake has been with the utilization of the glycemic index (GI) which measures the rate at which blood glucose levels rise when a particular food is ingested and how quickly the blood glucose levels drop. This ranking system was originally developed to aid those with diabetes and manage their carbohydrate intake relative to insulin requirements. Pure glucose has a rating of 100; thus, the closer a food is to 100, the higher the GI rating is. Foods with a low GI rating will be absorbed more slowly, keeping blood glucose levels lower and more sustained. The GI has some inherent irregularities. For example, white bread and whole wheat bread have very similar rankings as do brown and white rice, yet clearly the whole grain choices are healthier. The glycemic load (GL) is the mathematical product of the GI and the amount of carbohydrate in the diet. Diets with a high GL result in higher postprandial insulin concentration than those with a low GL.

7 Low-Fat and Very Low-Fat Diets: Metabolic Rationale

Fat is the most calorically dense of all the macronutrients with 9 kcal/g. It was therefore logical to assume that reduction in fat would result in a reduction of energy intake and body weight. As with the other macronutrients, the exact composition of the low-fat diet varied but generally contained between 20 % and 30 % of calories from fat and the very low-fat diet often be as low as 10 %. As the fat content is reduced, the carbohydrate is increased and in some instances there may be a slight increase in the protein content of the diet. These diets tended to be lower in calories when properly employed and resulted in weight loss when done correctly. Unfortunately, for many the diet was low in satiety value and often led to overconsumption. Others believed that a low-fat diet meant they could eat as many calories as desired as long as these foods were low in fat. Dietary fat was replaced with carbohydrates, primarily in the form of simple sugars and refined carbohydrates, increasing caloric intake by 200 cal a day (Volek and Phinney 2013; Feinman et al. 2015). Overall, the low-fat diet prescribed for the management of obesity and lowering of cardiovascular risk factors failed to produce the desired results (Feinman et al. 2015). The use of the low-fat diet without calorie restriction will not result in weight loss.

8 Dietary Intervention Trials

Comparisons of interventional trials of weight loss diets are difficult due to differences in study design and outcome parameters. There are numerous differences in the composition of the diets, the length of time of the intervention, the outcome parameters (i.e., weight loss, metabolic parameters, body composition), adherence, and setting (inpatient vs. outpatient). Additionally, some of the diet interventions employed an isocaloric prescription, while others allowed the patients to consume an unrestricted amount in order to evaluate the effects on appetite.

There have been a number of human trials (Table 1) which compared isocaloric diets

Table 1 Isocaloric weight loss intervention trials with varying CHO contents[a]

Reference	% CHO (Low)	% CHO (High)	Wt loss (kg) ± SEM Low CHO	High CHO	P
Young et al. (1971)	7	23	16.2 ± 0.9	11.9 ± 0.8	<0.05
Rabast et al. (1978)	10	68	14.0 ± 1.4	9.8 ± 1.0	0.10
Rabast et al. (1981)	12	70	12.5 ± 0.9	9.5 ± 0.7	<0.01
Piatti et al. (1994)	35	60	4.5 ± 0.4	6.4 ± 0.9	0.3
Golay et al. (1996b)	15	45	8.9 ± 0.6	7.5 ± 0.5	0.1
Golay et al. (1996a)	25	45	10.2 ± 0.7	8.6 ± 0.8	0.13
Lean et al. (1997)	35	58	6.8 ± 0.8	5.6 ± 0.8	0.1
Baba et al. (1999)	25	68	8.3 ± 0.7	6.0 ± 0.6	<0.05
Greene et al. (2003)	5	55	10.4 ± 2.1	7.7 ± 1.1	0.25
Layman et al. (2003)	44	59	7.5 ± 1.4	7.0 ± 1.4	0.8

[a]Adapted with permission from Fine and Feinman (2004)

containing a low versus high carbohydrate content (Young et al. 1971; Rabast et al. 1978, 1981; Piatti et al. 1994; Golay et al. 1996a, b; Lean et al. 1997; Baba et al. 1999; Greene et al. 2003; Layman et al. 2003). The fact that these studies were isocaloric is an important point and permits the examination of effect based on the macronutrient percentages. Overall, greater weight loss was observed in the lower-carbohydrate diets in comparison with the higher-carbohydrate diets.

If diet is modified relative to the individual's usual intake, it is likely to produce weight loss regardless of the composition of the diet. To investigate the effects of altering the macronutrient content of weight loss diets, Shai and colleagues conducted a 2-year trial in which 322 moderately obese individuals were randomized to one of three diets: a calorie-restricted low-fat diet providing less than 30 % fat, a calorie-restricted Mediterranean diet supplying less than 35 % fat, or a very low-carbohydrate (less than 20 g initially up to 120 g carbohydrate) diet with no calorie restrictions (Shai et al. 2008). Each of the diets resulted in weight loss. However, the low-carbohydrate diet produced the greatest weight loss followed by the Mediterranean diet and then low fat (Fig. 2). The ratio of serum total cholesterol to HDL-C decreased in all groups, with the low-carbohydrate group showing the greatest improvement with a relative decrease of 20 % compared with the low-fat group with a decrease of 12 % (Fig. 3).

One of the few studies that evaluated the effect of the low-carbohydrate diet on body composition beyond absolute weight loss was conducted by Brehm and colleagues (2003). Healthy women were randomized to receive a low-fat or very low-carbohydrate diet. Weight loss and reduction of body fat as measured by DXA was greatest in the group receiving the very low-carbohydrate diet both at 3 and 6 months. Blood pressure, lipids, fasting glucose, and insulin were within normal limits for both groups at the beginning of the trial but continued to improve throughout the study period. The greatest weight loss occurred in the low-carbohydrate diet, and those subjects had the greatest reduction in body fat.

Gardner and colleagues attempted to evaluate the effects of four popular weight loss diets with varying levels of carbohydrate in a public health setting over the course of 1 year (Gardner et al. 2007). They randomized 311 overweight premenopausal women to the Atkins diet (<20 g CHO/day, no calorie restriction), Zone (40 % CHO, calorie restricted), LEARN (55–60 % CHO, calorie restricted), and Ornish (<10 % fat, no calorie restriction). Subjects were provided with books explaining the diet and attended weekly instructions for 2 months. Subjects on the Atkins diet (low CHO) had the greatest weight loss and had the highest retention in the study. The Atkins group also experienced the greatest improvement in metabolic effects, with positive changes in HDL cholesterol, triglycerides, and

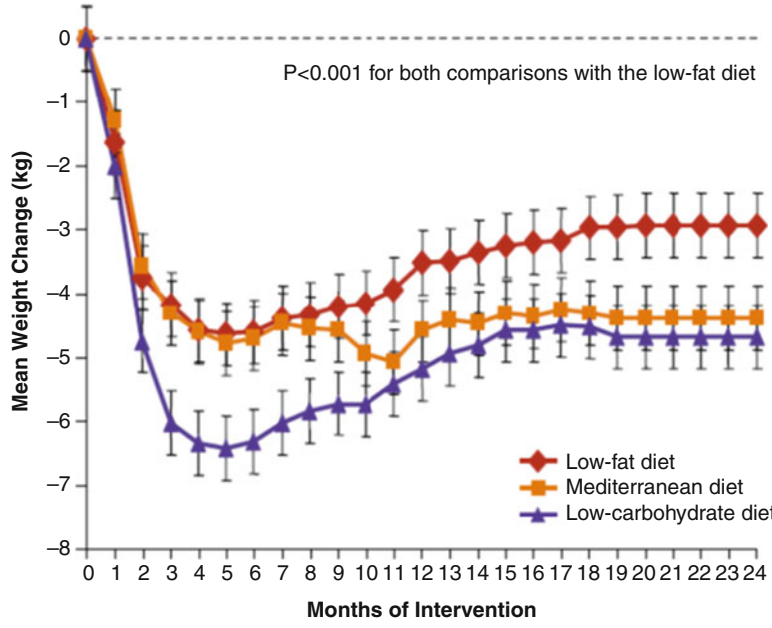

Fig. 2 Weight loss on three different diets (With permission from: Shai et al. (2008)

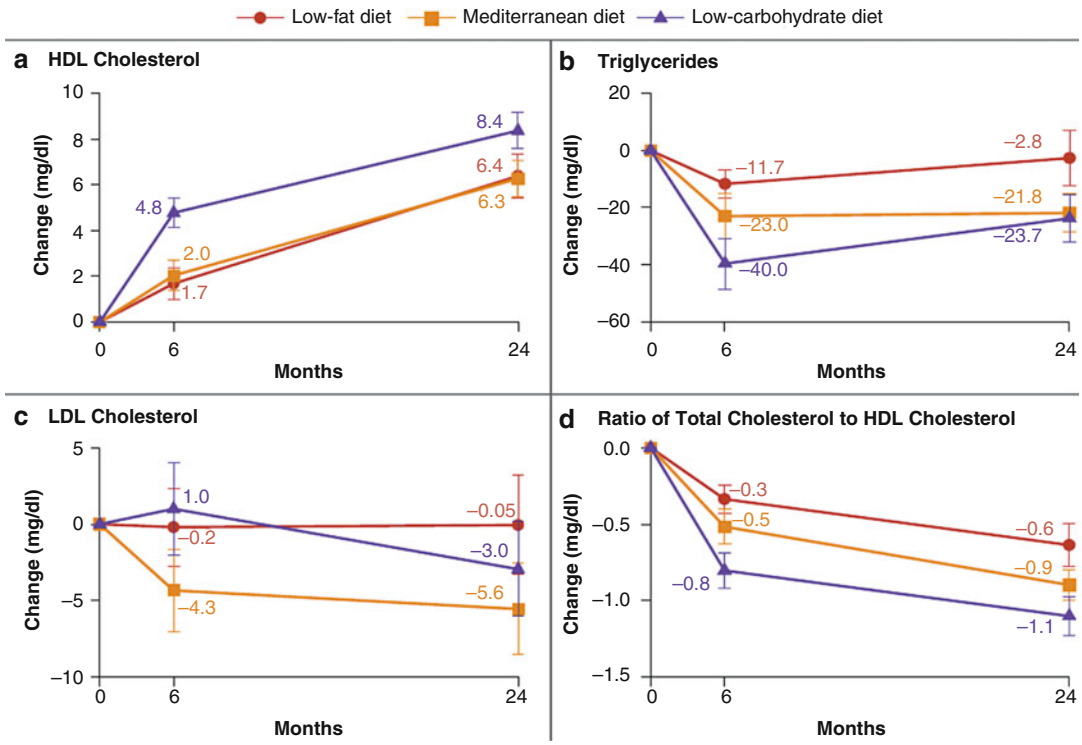

Fig. 3 Changes in metabolic parameters while on different diets (With permission from: Shai et al. (2008)

systolic blood pressure. These studies demonstrate that the low-carbohydrate diet, despite unrestricted caloric intake, is at least as effective if not more efficacious as other dietary plans with regard to weight loss and improvement in metabolic parameters.

The effects of the low-carbohydrate or a low-fat diet on weight loss and cardiovascular risk factors were evaluated over the course of 1 year in a randomized trial (Bazzano et al. 2014). Subjects without cardiovascular disease or diabetes ($n = 148$) were randomized to a low-carbohydrate or low-fat diet along with dietary counseling at regular intervals throughout the trial. The low-carbohydrate diet proved to be more effective for weight loss and cardiovascular risk factor reduction than the low-fat diet.

Because of the difficulties in evaluating these diets, a number of systematic reviews and meta-analyses have been conducted to try and discern if there are advantages of one approach over the other. Hession and colleagues conducted a systematic review of the effects of low-carbohydrate diets with low-fat diets on weight loss and coronary disease risk factors (Hession et al. 2008). A total of 13 studies that lasted at least 6 months with a total of 1,222 participants were included. The data demonstrates that low-carbohydrate, high-protein diets are more effective at 6 months and are as effective, if not more, as low-fat diets in reducing weight and cardiovascular risk parameters for up to 1 year. In addition, higher retention rates were found in the low-carbohydrate group compared with the low-fat group.

Johnston and colleagues conducted a meta-analysis of popular weight loss diet programs (Johnston et al. 2014). The outcome parameters were weight loss at 6 and 12 months. There was no evaluation of other metabolic parameters. A total of 48 studies including 7,268 subjects were included in the analysis. Although not statistically significant, the largest weight loss was associated with low-carbohydrate diet both at 6 and 12 months. With a lack of statistical significance between the different weight loss interventions, it may be that the best practice should be to recommend a diet that a patient is likely to adhere to in order to lose weight.

9 Micronutrients

In general, the major focus of weight loss diets has been on the modification of the macronutrient portion of the diet. However, along with altering the macronutrient content of the diet, attention must be given to the micronutrient portion to ensure adequate intake of vitamins, minerals, and trace elements. This is especially important since overweight and obese individuals may have deficiencies of micronutrients prior to initiation of a diet intervention due to previous poor food choices. The data is limited and this aspect of weight management has not been well studied. There have been some micronutrient evaluations of sample menus from various weight loss diets using a nutrient analysis database (Anderson et al. 2000; Freedman et al. 2001; Ma et al. 2007). Overall, these analyses demonstrate that the proposed diet plans were deficient in many micronutrients. There were some studies that attempted to evaluate micronutrient intake during weight loss interventions but presented only partial data from a small percentage of the sample population (Yancy et al. 2004) or included only select nutrients (Brehm et al. 2003; Clifton et al. 2008; Shai et al. 2008). Some of the weight loss programs included multivitamin supplementation as part of the protocol. Others did or did not address it in the report. Brehm and colleagues observed a significantly lower vitamin C intake in participants consuming a very low-carbohydrate diet at an intermediate 3-month time point (Brehm et al. 2003). Inadequate intakes of vitamin C, calcium, iron, and magnesium were reported among 18 adults in a 4-week study of the high-protein low-carbohydrate Atkins diet (Miller et al. 2003). Gardner and colleagues evaluated the micronutrient intake of overweight or obese women randomly assigned to four popular diets, Atkins, Zone, LEARN, and Ornish, using a 3-day unannounced 24-h recall at baseline and after 8 weeks of instruction (Gardner et al. 2010). At 8 weeks, there was a significant proportion of individuals whose intakes were associated with the risk of inadequacy. These varied with the type of diet. The Atkins group was at risk for thiamine, folic acid, vitamin C, iron, and magnesium. Although Atkins recommends including multivitamin and calcium supplementation,

only three of the participants in the Gardner study actually took a multivitamin supplement and six participants took a calcium supplement. Participants in the LEARN group had an increased risk for vitamin E, thiamine, and magnesium, and the Ornish group were at risk for vitamins E and B-12 and zinc. Those participants following the Zone diet actually had a reduction in the risk of inadequacy for vitamins A, E, K, and C. Although this study provides some insight into the potential deficiencies, it should be noted that the information on vitamin and mineral intake was obtained by self-reported dietary recall. Nonetheless, it points out the potential risk of multiple vitamin and mineral deficiencies with weight loss diets.

9.1 Chromium

Aside from the issues of nutrient deficiencies associated with various weight loss diets, there has been interest in providing specific nutrients to promote weight loss, such that these nutrients would act in a pharmacologic manner. Chromium (III), the biologically active form found in food, is essential for carbohydrate and lipid metabolism; it acts as a cofactor in the action of insulin. Chromium may play a role in regulating appetite, reducing carbohydrate cravings, and increasing lean body mass. Supplemental chromium is available in several forms with chromium picolinate being the most common over-the-counter supplement used to enhance weight loss.

There have been several trials which have investigated the use of chromium to induce weight loss, alter body composition, and change resting metabolic rate. A longitudinal, double-blind study of obese female subjects over the course of 16 months with supplementation of 200 μg chromium picolinate along with a very low-energy diet did not demonstrate any significant changes in body composition or metabolic parameters (Pasman et al. 1997). Volpe and colleagues studied the effects of chromium supplementation and exercise on body composition, resting metabolic rate, and selected biochemical parameters in moderately obese women following an exercise program (Volpe et al. 2001). This was a double-blind trial in which women received either 400 μg/day of elemental chromium as chromium picolinate or placebo and participated in a supervised weight training and walking program 2 days per week for 12 weeks. Body composition and resting metabolic rate were measured at baseline, 6 and 12 weeks. Supplementation with chromium picolinate did not affect body composition or resting metabolic rate. A meta-analysis of ten double-blind, placebo-controlled trials provides evidence of a relatively small reduction in body weight (1.1–1.2 kg over 10–13 weeks) in overweight and obese individuals receiving chromium picolinate (Pittler et al. 2003). In a pilot study Yazaki and colleagues assessed the effects of chromium picolinate supplementation alone and combined with a nutrition education intervention on weight loss and body fat distribution (Yazaki et al. 2010). Subjects were randomly assigned to daily ingestion of 1,000 μg of chromium picolinate or placebo for 24 weeks along with passive nutritional education at the 12-week point. There was no change observed in BMI in the intervention group as compared to placebo at 12 or 24 weeks. Overall, supplementation of 1,000 μg of chromium picolinate alone, and in combination with passive nutrition education, did not affect weight loss in this patient population. There have been a number of trials which have looked at the use of chromium picolinate in male football players and wrestlers as well as female softball athletes undergoing the standard training for each of their respective sports (Clancy et al. 1994; Walker et al. 1998; Trent and Thieding-Cancel 1995; Livolsi et al. 2001). Supplementation with chromium picolinate failed to demonstrate any difference in body composition or performance in any of the athletic groups studied. Although chromium plays an important role in carbohydrate and lipid metabolism, the data thus far does not demonstrate efficacy in weight management.

9.2 Calcium

Intracellular calcium has been shown to play a role in the insulin resistance associated with

obesity (Draznin et al. 1988; Byyny et al. 1992). It was therefore logical to consider calcium's role in the induction of weight loss. The specific mechanisms by which calcium and dairy foods regulate body weight have not been unequivocally elucidated. A number of hypotheses have been suggested. It is possible that adequate dietary calcium lowers parathyroid levels which suppress intracellular adipocyte calcium levels enhancing lipolysis and decreasing lipogenesis (Zemel et al. 2004). Increased calcium intake may increase fat oxidation (Melanson et al. 2003) and/or increase fecal fat excretion through the formation of insoluble calcium–fatty acid complexes (Bendsen et al. 2008). It has also been suggested that calcium intake may affect satiety level (Major et al. 2009). The effects of both dairy-enriched diet and calcium supplementation on weight loss have been extensively studied. Some of these trials included energy restriction; others did not. In a review of 49 randomized controlled trials, 42 showed no effect and two trials actually demonstrated an increase in body weight with consumption of dairy foods when there was no energy restriction suggesting that the increase in dairy foods also added additional calories to the diet (Lanou and Barnard 2008). There were four trials in which energy was restricted demonstrating weight loss with dairy or calcium supplementation (Zemel et al. 2004, 2005a, b). Each of these was from the same investigator (two of which were reported in the same manuscript) with commercial funding. The possibility that calcium may increase fecal fat loss was evaluated in a meta-analysis (Christensen et al. 2009). There were 15 randomized controlled trials included which showed increased fecal fat loss with increase calcium intake. It appears that calcium may help with appetite control but only when calcium intake is low (Major et al. 2009). Certainly, calcium is an important nutrient in human nutrition and dairy products are high in calcium. However, the studies to date provide little evidence that consumption of dairy foods or calcium supplementation provides any benefit in reducing body weight or fat mass.

10 Conclusion

Obesity has become a global problem and a major health concern due to the associated comorbidities. The foundation of therapy has been diet, exercise, and behavioral modification. Unfortunately, no one diet has been universally successful at inducing and maintaining weight loss and improving metabolic parameters reflecting the complexity of the disease. The factors affecting obesity are complex, dynamic, and interrelated and involve numerous host factors as well as the environment. Interventions to induce weight loss should have solid physiological and metabolic basis and be scientifically validated.

11 Cross-References

- ▶ Adipokines and Metabolism
- ▶ Carbohydrate, Fat, and Protein Metabolism in Obesity
- ▶ Diet, Exercise, and Behavior Therapy in the Treatment of Obesity and Metabolic Syndrome
- ▶ Dyslipidemia in Obesity
- ▶ Endocrine Disorders Associated with Obesity
- ▶ Genetics of Obesity
- ▶ Gut Hormones and Obesity
- ▶ Gut Microbiome, Obesity, and Metabolic Syndrome
- ▶ Insulin Resistance in Obesity
- ▶ Obesity and Cardiac Disease
- ▶ Principles of Energy Homeostasis
- ▶ The Built Environment and Obesity
- ▶ Type 2 Diabetes: Etiology, Epidemiology, Pathogenesis, Treatment

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The Built Environment and Obesity

16

Andrea Garfinkel-Castro, Keuntae Kim, Shima Hamidi, and Reid Ewing

Contents

Abstract

The built, or physical, environment consists of its man-made, constructed components – roads and sidewalks, buildings and houses, parks and plazas, and more. Currently, our physical environment is built to accommodate and prioritize motorized transport, cars especially. Travel has been redirected to cars, reducing opportunities for active travel. In examining the built environment and its relationship to obesity, we must acknowledge that the built environment has no direct or immediate effect on obesity; rather, obesity is linked to the built environment as a consequence of human behavior – in this case physical activity. This chapter strives to objectively connect the built environment at varying urban scales – macro, meso, and micro – to the issue of obesity. Aspects of the built environment – specifically, conditions attributable to walkability and urban sprawl – are examined as contributing factors to (in)active travel. Also discussed is the importance of and need for more longitudinal studies to counter the plethora of cross-sectional studies. While cross-sectional studies can adequately define conditions at a point in time, longitudinal studies provide opportunities to establish causality. Self-selection bias is also considered, as it is a source of concern in some studies. We conclude by noting that rates of obesity have risen as our cities have become less walkable and more auto-dependent. Research at all three urban scales finds some

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relationship between the built environment and active travel but research is not without its shortcomings. More research is still needed, longitudinal and that which controls for self-selection bias in particular, and remains an important arena for further inquiry.

Keywords
Urban design • Physical activity • Walkability

1 Introduction

The built environment is, increasingly, an urban environment. As of 2008, more than half of the world's population lived in a city, in widely varying built environments. In 1970, the French urbanist and philosopher (Lefebvre 2003) declared, rather controversially: "Society has been completely urbanized." He argued that even rural hinterlands had become urbanized by virtue of a social relationship to cities. It is in this spirit that, in the process of examining obesity and the built environment, we focus on the urban – including suburban – built environment. In doing so, we must also acknowledge that the built environment has no direct or immediate effect on obesity; rather, obesity is linked to the built environment as a consequence of human behavior – in this case physical activity. One further caveat is that while research points to an associative relationship between specific built environments (sprawl, e.g.,) and levels of physical activity, there is scant evidence as of yet of a causal relationship.

The built, or physical, environment consists of its man-made, constructed components – roads and sidewalks, buildings and houses, parks and plazas, and more. It also consists of in-between spaces, spaces of flow, and movement. Currently, our physical environment is built to accommodate and prioritize motorized transport, cars especially, and shaped by Euclidean zoning – municipal policies that regulate how land can be used, typically locating shops and jobs far from housing. Movement from home to work, home to school, and home to shopping has been redirected to cars, reducing opportunities for active travel.

According to the Centers for Disease Control, the two primary modifiable risk factors for obesity are unhealthy diets and physical inactivity, and the greatest areas for prevention and treatment are behavior modification and environmental change (Centers for Disease Control 2009; Danaei et al. 2009; McGinnis and Foerge 1993; Mokdad et al. 2004). The built environment may affect both levels of physical activity and access to healthy foods. That is to say, both may have a spatial component.

The forces that contribute to active travel or the relative degree of walkability of a community occur at all scales, from macro to micro. In this chapter, the characteristics of the built environment at various urban scales and in varying forms, the forces that shape them, and their respective relationships to obesity are discussed in three parts: the macro or regional scale, the meso- or neighborhood scale, and the micro- or block scale. Environmental determinism, the theory that the built environment influences human behavior, is of necessity discussed briefly, first in this introduction. In addition, two research considerations are also discussed: longitudinal studies and self-selection bias.

As a theory, environmental determinism continues to be debated across a number of disciplines – social science, planning, and architecture, to name a few. An alternate to the theory that the physical or built environment has greater influence over human behavior is the assertion that sociocultural or structural conditions more greatly influence human behavior. These two theories are also viewed as representing opposite ends of a spectrum and as complementary (Gans 1968). The either-or problem may be overcome by addressing two specific shortcomings identified by Franck (1984): overstating the effects of the environment while understating sociocultural factors and assuming that the effects of the physical environment are direct, static, and uninfluenced by human agency (Franck 1984). Rather than negating or invalidating environmental determinism, these shortcomings, when addressed and combined with a complementary environment-structural approach, point the way to creating a rigorous theoretical framework that recognizes

the built environment as first and foremost a sociocultural product that exercises influence over structurally mediated behavior.

Environmental determinism notwithstanding, identifying the degree to which the built environment can be said to have causal effect on behaviors related to obesity remains a significant challenge to researchers. One challenge to research is that the bulk of research is based on cross-sectional data. Additionally, self-selection, or the choice to be present and (in)active within a specific environment, cannot be ruled out and carries merit as an explanation for some of this research (these issues will be discussed separately, below).

It bears noting that the literature on the built environment and obesity is vast, too vast to be covered in this short chapter. A recent literature research uncovered 5,642 articles on the subject (Mackenbach et al. 2014). The reviewers selected a random sample of 500 titles and abstracts and further narrowed the sample to 212 full articles that were read by the first two authors of the review. Of these articles, 92 were included in the final literature review. We concur with the conclusion: "With the exception of urban sprawl and land use mix in the US the results of the current review confirm that the available research does not allow robust identification of ways in which that physical environment influences adult weight status, even after taking into account methodological quality" (Mackenbach et al. 2014). The following sections present a selection of research that strives to objectively connect the built environment, at varying urban scales, to the issue of obesity.

2 Built Environment at the Macro Scale

The earliest recognized article on the built environment and obesity correlated urban (or suburban) sprawl with obesity (Ewing et al. 2003). At the macro level, the built environment comes in varying degrees of two basic forms, sprawling and compact (and of course everything in between). Initial attempts to measure urban sprawl emphasized the one characteristic often attributed to sprawl, low density. Density has the advantage of being easy to measure with available data, and so initial attempts to measure sprawl in the early 2000s focused primarily on metropolitan average population density. However, this produced curious results, including ranking Portland, OR (with its strict urban growth boundary), and New York (the ultimate of American vertical cities) metropolitan areas as more sprawling than Los Angeles, the typical bastion of congestion and development spread (Fulton et al. 2001; Nasser and Overberg 2001; Malpezzi and Guo 2001; Burchfield et al. 2006; Lopez and Hynes 2003). Clearly, an additional means of measuring regional urban form was necessary. Accessibility, or the relative ease with which a person can access or reach goods and services within a community (Litman 2014), has become one such measure.

If poor accessibility is also a common denominator of sprawl, then sprawl is understood as more than low-density development. A study by the US Environmental Protection Agency and Smart Growth America aimed to better address this complexity (Ewing et al. 2002). The study examined 22 different land use and street network variables, producing metropolitan and county indices of compactness for four primary factors: (1) *density*, compact development concentrates activity at medium to high densities; (2) *mix*, compact development mixes homes, shops, and workplaces; (3) *centeredness*, compact development has distinct, thriving activity centers, such as strong downtowns or suburban town centers, as opposed to commercial strips; and (4) *street connectivity*, compact development has streets marked by small blocks and high connectivity (Ewing et al. 2003).

Taking these four characteristics into consideration, Ewing and Hamidi (2014) created new indices for metropolitan areas, urbanized areas, and counties in the USA. All indices have a mean value of 100 and a standard deviation of 25, and higher scores are more compact while lower scores are more sprawling. Using the new indices for 2010 data, New York County (which includes Manhattan) was the most compact county in the USA – index value 425.2. Oglethorpe County in Georgia, on the other hand,

was the most sprawling – index value of 45.5. This is one of the important tools researchers are using to establish clearer understanding and stronger relationship between our built environments and risk of obesity.

Research has now established statistically significant links between various measures of sprawl and the risk of obesity (Papas et al. 2007). It may be that some environments are more "obesogenic" than others (Black and Macinko 2008). After controlling for age, education, fruit and vegetable consumption, and other sociodemographic and behavioral covariates, Ewing et al. (2003) found that adults living in sprawling counties had higher body mass index (BMI) and were more likely to be obese (BMI >30) than those living in compact counties. The effect was statistically significant, though small compared to sociodemographic influences. We would not expect the built environment to overwhelm the many genetic, behavioral, and other environmental influences that contribute to overweight and obesity, and it does not.

Other studies linking the Ewing et al.'s earlier sprawl indices to obesity include Cho et al. (2006), Doyle et al. (2006), Fan and Song (2009), Griffin et al. (2013), Joshua et al. (2008), Kelly-Schwartz et al. (2004), Kim et al. (2006), Kostova (2011), Lee et al. (2009), and Plantinga and Bernell (2005, 2007). To update the earlier findings, Ewing et al. (2014) replicated the original 2003 study and found a slightly stronger relationship between urban sprawl and obesity. Residents of the more compact counties were found to have lower BMI values and less prevalence of chronic diseases such as high blood pressure, coronary heart disease, and diabetes. The positive impacts of urban sprawl on obesity at the macro level have been also confirmed by other recent studies (Guettabi and Munasib 2014; James et al. 2013; Zhao and Kaestner 2010). For instance, Guettabi and Munasib (2014), using the 1979 National Longitudinal Survey of Youth, found that urban sprawl is significantly and positively related to child BMI among girls and middle/high school children.

Feng et al. (2010) and some others such as Plantinga and Bernell (2007) and Gregson (2011) are less convinced that characteristics of the built environment are strong risk factors for obesity. By evaluating studies according to their methods of research and analysis, as well as comparing their results, Feng et al.'s review found that little can be determined from the available findings. Almost all of the studies considered were cross sectional, making it difficult to infer causality, and there were various definitions of foundational concepts, such as "place," "walkability," and "sprawl," leaving the authors to wonder whether the studies were really measuring the same variables.

3 Built Environment at the Mesoscale

The above definition of sprawl may describe metropolitan areas or counties, but is there any comparable way of describing built environment at the neighborhood (or meso) scale, where people of all ages and ability perform most of their active behaviors? In the 1990s, planners began describing neighborhoods in terms of "D variables." The original three Ds, coined by Cervero and Kockleman (1997), were density, diversity, and design. The Ds were later expanded to include destination accessibility and distance to transit (Ewing and Cervero 2010). Development scale is a sixth D, included in a few studies. While not part of the environment, demographics are the seventh D, controlled as confounding influences in travel and physical activity studies.

Table 1 shows the most common D variables in the travel and the built environment literature. A recent meta-analysis of more than 200 individual studies of the built environment and travel concluded that all of the D variables influence household travel decisions, but the strongest influences are diversity, design, and destination accessibility, while the weakest influence is density (Ewing and Cervero 2010).

Note that these are rough categories, divided by ambiguous and unsettled boundaries that may change in the future. Additionally, some variables overlap (e.g., diversity and destination accessibility). Nonetheless, it is still useful to use the D

Table 1 The most common D variables in travel and the built environment literature

D variable	Measurement
Density	Density is always measured using a variable of interest per unit of area. The area can be gross or net, and the variable of interest can be population, dwelling units, employment, or building floor area
Diversity	Diversity measures pertain to the number of different land uses in a given area and the degree to which they are balanced in land area, floor area, or employment. Entropy measures of diversity, wherein low values indicate single-use environments and higher values more varied land uses, are widely used in travel studies. Jobs-to-housing or jobs-to-population ratios are less frequently used
Design	Design measures include average block size, proportion of four-way intersections, and number of intersections per square mile. Design is also occasionally measured as sidewalk coverage (percent of block faces with sidewalks); average building setbacks; average street widths; or numbers of pedestrian crossings, street trees, or other physical variables that differentiate pedestrian-oriented environments from auto-oriented ones
Destination accessibility	Destination accessibility measures ease of access to trip attractions. It may be regional or local (Handy 1993). In some studies, regional accessibility is simply distance to the central business district. In others, it is the number of jobs or other attractions reachable within a given travel time, which tends to be highest at central locations and lowest at peripheral ones. The gravity model of trip attraction measures destination accessibility
Distance to transit	Distance to transit is usually measured as an average of the shortest street routes from the residences or workplaces to the nearest rail station or bus stop. Alternatively, it may be measured as transit route density, distance between transit stops, or the number of stations per unit area. In this literature, frequency and quality of transit service are overlooked

variables to organize the empirical literature and provide order-of-magnitude insights.

Several studies have found an association between obesity and the built environment at the neighborhood scale. The earliest of these studies was done by Larry Frank and his colleagues (2004). They objectively measured three built environmental variables (land use mix, net residential density, and street connectivity) within a 1-km network distance of individuals and concluded that land use mix has the strongest association with obesity. They found each quartile increase in land use mix to be associated with a 12.2 % reduction in the likelihood of obesity across gender and ethnicity. In a series of coauthored studies, Frank found similar relationships for adults living in sprawling neighborhoods versus compact, walkable neighborhoods (Frank et al. 2006, 2007, 2008). This is in line with the findings of Pendola and Gen (2007) that having a mix of commercial and residential land uses within walkable distance contributes to a greater reduction in a risk of obesity than higher population density. Several studies since Frank et al. (2004) confirmed the significant and negative effects of low land use mix on obesity (Mobley et al. 2006; Rundle et al. 2007; Li et al. 2008; Rutt and Coleman 2005).

Brown et al. (2009) and Yamada et al. (2012), however, argue that the presence and distance to walkable destinations (parks and transit stations) are more important than having an equal mixture of land uses or "entropy" in relation to healthy weight. This assertion is supported by other studies that found proximity to parks (Berry et al. 2010b.; Rundle et al. 2013; West et al. 2012) and transit stations (Rundle et al. 2007; Brown and Werner 2009) is associated with lower rate of obesity. Other relevant built environment characteristics may include measures of food access and types of food outlets. Proximity of supermarkets and grocery stores, in particular, is associated with lower rates of obesity (Black and Macinko 2009; Block et al. 2011; Chen et al. 2010; Drewnowski et al. 2012; Inagami et al. 2006; Wang et al. 2007). and the presence of convenience stores and fast-food restaurants is associated with higher rates of obesity (Pereira et al. 2005).

4 Built Environment at the Microscale

Shifting to the microscale allows us to zero in on the individual within the built environment – the pedestrian, in particular. This urban scale relates to the on-the-ground experience, where the subtle conditions of the built environment are most keenly felt. Block level details such as shade from street trees, the visual interest provided by store windows, and the widths of sidewalks are noticed by pedestrians. This is where the most nuanced and qualitative D variable, design, becomes intimate and human scaled. This is an important point of contact among community members (including children) and where face-to-face social networks can be experienced as well. At this urban scale, design is often assessed in terms of walkability.

One challenge for walkability research is that some of the more salient features cannot be captured by way of remote or secondary data, such as GIS (geographic information systems) (Neckerman et al. 2009). Direct observation is effective but time (and cost) consuming (Rundle et al. 2011). Criteria such as aesthetics are also identified as important to walkability yet are elusive without direct observation (Neckerman et al. 2009); definitions are likewise variable and subjective.

A walkability audit instrument is a data collection instrument used to quantify different aspects of the pedestrian environment such as sidewalks, traffic calming devices, and building setbacks. The Active Living Research (2015) website hosts more than a dozen such instruments. The website also provides a summary of micro features covered by leading instruments (The Audit Tools Comparison Table).

One audit instrument in particular seeks to build on the classic urban design literature (e.g., that of Kevin Lynch, Jane Jacobs, and Jan Gehl). Ewing (2005, Ewing et al. 2006b) identified nine key urban design qualities for which measurement protocols were developed: imageability, enclosure, human scale, transparency, complexity, coherence, linkage, legibility, and tidiness. The operationalization of the first five qualities has provided researchers, planners, and designers with a set of empirical design metrics with which to understand and implement walkable environments (see Table 2).

Table 2 Streetscape features contributing to urban design qualities

Urban design quality	Significant physical features
Imageability[a]	Proportion of historic buildings
	Courtyards/plazas/parks (#)
	Outdoor dining (y/n)
	Buildings with non-rectangular silhouettes (#)
	Noise level (rating)
	Major landscape features (#)
	Buildings with identifiers (#)
Enclosure	Proportion street wall – same side
	Proportion street wall – opposite side
	Proportion sky across
	Long sight lines (#)
	Proportion sky ahead
Human scale	Long sight lines (#)
	All street furniture and other street items (#)
	Proportion first floor with windows
	Building height – same side
	Small planters (#)
Transparency	Proportion first floor with windows
	Proportion active uses
	Proportion street wall – same side
Complexity[a]	Buildings (#)
	Dominant building colors (#)
	Accent colors (#)
	Outdoor dining (y/n)
	Public art (#)

[a]Number of people on the street was also a significant determinant of imageability and complexity ratings. However, as it is our dependent variable, it has been dropped as an analytic variable

Subsequent research has sought to validate the five urban design qualities previously operationalized (Ewing 2005; Ewing et al. 2006b). In New York City, Neckerman (2013) conducted pedestrian counts at 588 locations within the city. This study confirmed that as a group the design metrics helped explain the presence of pedestrians, with one metric – transparency – standing out as more significant than the other four. Indeed, the urban design quality of transparency – measured in terms of *windows*

overlooking the street, *continuous building facades forming a street wall*, and *active street frontage* – had a stronger relationship to pedestrian counts than any of the standard D variables that were also modeled. A subsequent study conducted in Salt Lake City sought to validate the design metrics in a less dense and more auto-dependent urban environment (Ameli et al. 2015). This research also found that the metrics as a whole and transparency in particular are significant predictors of pedestrian counts.

What is the relationship between the built environment at the microscale and obesity? The question remains largely unanswered. Neckerman and colleagues correlated their measurements of urban design qualities with BMIs of New York residents. They found that the quality of imageability was negatively related to BMI after controlling for population density. The quality of human scale had the opposite relationship. Transparency was not significant. All of this is to say that we are just in the beginning stages of relating the microenvironment to obesity.

A literature search uncovered only one other study using a walkability audit instrument to assess the association between the microenvironment and obesity. Boehmer et al. (2007) developed a comprehensive audit instrument to measure the built environment in Savannah and St Louis. Street segment data from the audit were summarized within a 400-m radius (an approximately 5-min walk) surrounding each participant's residence. They found that being obese is significantly associated with the absence of sidewalks, lack of interesting sites, and observed indicators of poor sidewalk quality, physical disorder, and presence of garbage (Boehmer et al. 2007).

5 Longitudinal Studies

The majority of studies on the built environment and obesity are cross sectional in design and in general support the idea that certain neighborhood characteristics are associated with a lower prevalence of overweight and obesity and higher levels of physical activity (Mackenbach et al. 2014). One major limitation of cross-sectional studies is their failure to establish causality as opposed to only correlation. As the National Research Council (2005) report, *Does the Built Environment Influence Physical Activity*? *Examining the Evidence*, states: "Cross-sectional studies can quantify the presence and magnitude of associations between variables. Unlike longitudinal studies, however, they cannot be used to determine the temporal relationship between variables, and evidence of cause and effect cannot be assumed" (p. xiv).

A recent literature review by Mackenbach et al. (2014) reported that only 8 studies out of 92 in their sample used longitudinal data, with a follow-up time ranging from 4 to 25 years. Our own search of literature found only 12 longitudinal studies. Of the 12, only 3 studies focused on the characteristics of the built environment and its relation to changes in obesity and BMI (Bell et al. 2008; Berry et al. 2010a; Coogan et al. 2011). Eight studies focused on residential location of participants who moved to investigate the effects of changes in the built environment before and after moving on obesity (Arcaya et al. 2014; Berry et al. 2010b; Eid et al. 2008; Ewing et al. 2006a; Hirsch 2014; Mumford et al. 2011; Beenackers et al. 2012; Plantinga and Bernell 2007). One study alone focused on the relationship between changes in the built environment and changes in obesity over a 30-year time period (Michael et al. 2014).

Longitudinal studies have reported mixed results. Despite fairly consistent cross-sectional literature, most of these longitudinal analyses do not show a significant relationship between the environment and a risk for obesity (Berry et al. 2010a; Eid et al. 2008; Ewing et al. 2006a; Michael et al. 2013, 2014). Additional longitudinal evidence is needed to increase our understanding of how the built environment at different urban scales affects the risk of obesity (Ding et al. 2011; Hirsch 2014).

6 Self-Selection Bias

Within this area of research, one consistently identified confounder is residential self-selection. The theory of residential self-selection suggests that

individuals choose where they live based on travel preferences. Individuals who prefer to be physically active choose to live in neighborhoods that facilitate physical activity. These individuals will likely be more physically active than their neighbors, regardless of where they lived. The question becomes one of the chicken or the egg. Do people choose to live in particular neighborhoods because those neighborhoods facilitate a particular activity or behavior, or do individuals engage in certain behaviors regardless of the opportunities available in their neighborhood? According to a National Research Council report (2005): "If researchers do not properly account for the choice of neighborhood, their empirical results will be biased in the sense that features of the built environment may appear to influence activity more than they in fact do. (Indeed, this single potential source of statistical bias casts doubt on the majority of studies on the topic to date) (p. 5–7)."

In the travel (movement and transportation) literature, more than anything else, the possibility of self-selection bias has engendered doubt about the magnitude of travel benefits associated with compact urban development patterns. At least 38 studies using nine different research approaches have attempted to control for residential self-selection (Mokhtarian and Cao 2008; Cao et al. 2009a). Nearly all of them found decisive evidence of statistically significant associations between the built environment and travel behavior, independent of self-selection influences (Cao et al. 2009a, p. 389). However, nearly all of them also found that residential self-selection attenuates the effects of the built environment on travel.

Periodically, household travel surveys are conducted across the USA (and other nations) to better understand travel needs; travel diaries are used to collect this data. Using travel diary data from the New York/New Jersey/Connecticut regional travel survey, Salon (2006) concluded that the built environment accounted for one-half to two-thirds of the difference in walking levels associated with changes in population density in most areas of New York City. Using travel diary data from the Austin travel survey, Zhou and Kockelman (2008) found that the built environment accounted for 58–90 % of the total influence of residential location on vehicle miles traveled (VMT), depending on model specifications. Using travel diary data from northern California, Cao (2010) reported that, on average, neighborhood type accounted for 61 % of the observed effect of the built environment on utilitarian walking frequency and 86 % of the total effect on recreational walking frequency. Using data from a regional travel diary survey in Raleigh, NC, Cao, Xu, and Fan (2009b) estimated that anywhere from 48 % to 98 % of the difference in VMT was due to direct environmental influences, the balance being due to self-selection. Using data from the 2000 San Francisco Bay Area travel survey, Bhat and Eluru (2009) found that 87 % of the VMT difference between households residing in conventional suburban and traditional urban neighborhoods is due to "true" built environment effects, while the remainder is due to residential self-selection. So while the environment seems to play a more important role in travel behavior than do attitudes and residential preferences, both effects are present.

The literature on residential self-selection and obesity is not as rich as that on residential self-selection and travel, but the same cautions have been raised (Boone-Heinonen et al. 2011). There is some evidence that self-selection contributes to the association between the built environment, physical activity, and weight (Berry et al. 2010a; Frank et al. 2007). Research suggests that residential self-selection can be both negative and positive depending on the selection motivation (Berry et al. 2010a).

A longitudinal research design is one strategy that can be used to control for residential self-selection bias (Boone-Heinonen et al. 2010; Frank et al. 2007), particularly if it focuses on the effects of changes in an individual's built environment on changes in obesity (see, e.g., Michael et al. 2014). Using a longitudinal study design, two studies have garnered media attention by contending that residential self-selection, not environmental determinism, accounts for the relationship between sprawl and obesity (Plantigna and Bernell 2007; Eid et al. 2008). Both conclude that people with higher body mass indices choose to live in sprawling neighborhoods, and those with

lower body mass indices choose to live in compact neighborhoods. Intuitively, it is hard to see why obese people would have a preference for environments that discourage physical activity. At most, it seems they would be indifferent to the walkability of their neighborhoods. It is easier, however, to see why those wishing to be physically active would prefer walkable neighbors. Let it suffice to say that this is an area of obesity research that requires a lot more study, particularly of the kind of study being conducted in travel research.

7 Discussion

What, if any, relationship does the built environment have to human obesity? To address this question, this chapter examined the built environment at various urban scales in relation to human activity – the primary link between the built environment and obesity. It has been said that "[f]irst we shape the cities – then they shape us" (Gehl 2010, p. 9). How, then, have we shaped our cities, and in doing so, how have they shaped us?

We know that obesity is on the rise as our cities have become generally less walkable and more auto-dependent. At the macro or regional scale, research on the characteristics of the built environment is making use of increasingly nuanced and updated sprawl measures. At this scale, researchers are able to identify and track major trends, information critical to understanding how regional environments impact daily lives. Five "D" variables describe characteristics of the meso- or neighborhood scale built environment that most influence household travel decisions: diversity (of land uses), design, destination accessibility, distance to transit, and density (Ewing and Cervero 2010). While research does indicate a relationship to active travel and the D variables, there is no agreement as to how much each variable impacts active travel. This remains an important arena for further research. At the microscale, research continues on identifying which qualities contribute to walkability and how we might measure or quantify these qualities. By better understanding the contributing factors to walkability, planners and designers will be more equipped to replicate walkable conditions, providing ever more opportunities for active travel.

How we study is as important as what we study. Studies reviewing the methodologies of previous research have identified areas for improvement as the discipline matures. One such area for improvement is in self-reports, which are often used to evaluate activity behaviors and neighborhood environments. Self-reports are found to lead to perception bias as well as low agreement on neighborhood characteristics. Few studies attempt to verify reported information, which would be an important step in assuring accurate results (Black and Macinko 2008; Booth et al. 2005). Booth and associates also suggest that instruments of measurement may present problems. Many studies gather information about the built environment from indirect sources, such as geographic information system (GIS) software and publicly available data sets. While easy to obtain, they may not accurately represent the area at the time of the study. Feng et al. also criticized the often-used practice of combining the various environmental factors into composite indices (Feng et al. 2010). Presenting an additional challenge at the microscale is that data at this scale is often unavailable as secondary data, making field-based research necessary though costly and time consuming.

Research on the relationship between the built environment and obesity must continue and continue to improve in rigor and methodology, before we can confirm any causal relationships. Longitudinal studies will add significantly to our understanding, as will a broader range of methodologies including mixed methods and qualitative studies. Opportunities for active travel and increased physical activity are increasingly seen as desirable qualities in a built environment. And, research such as that presented in this chapter is helping to identify how to make these opportunities available in the built environment.

8 Cross-References

▶ Childhood Environment and Obesity
▶ Social and Community Networks and Obesity

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Social and Community Networks and Obesity

17

Jacques Demongeot, Adrien Elena, and Carla Taramasco

Contents

Abstract

The aim of the paper is to describe the first results of a research about therapeutic education, with biofeedback and personalization taking into account the place of a chronic patient inside his social network. The techniques used are (i) serious games in their pedagogical dimension of elaboration of therapeutic education scenarios and their local dimension of information capture using specific sensors and biofeedback processes allowing the customization of the game and (ii) tools of visualization of social networks to which the patient belongs, in order to bring him to an awareness of belonging to a community sharing the same pathology and therapy. We built three scenarios, dealing with (i) the dietary of a type II diabetic, (ii) the detection and monitoring of diabetic retinitis, and (iii) the detection and monitoring of diabetic foot ulcers. We have also developed a software for the representation of the dynamics of a new category of social network called "homophilic." The introduction of computer techniques such as serious games and biofeedback processing in the field of therapeutic education is not new and dates about 10 years, but the coupling with individual identification techniques in a social group for the visualization and customization of the game is original. The joint use of new educational methods of therapeutic education, combined with the recognition of the presence of the patient in a local social network of people

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suffering from the same disease, will maximize the effectiveness of serious games and biofeedback necessary to the educational personalization.

Keywords
Obesity • Type II diabetes • Social networks • Therapeutic education • Serious games

1 Introduction

Obesity can be considered as one of the most characteristic social "contagious" diseases. Both stigmatization and mimicking (Myers and Rosen 1999) constitute the way of dissemination of obesity into a familial or social network. Obesity is defined as an excessive accumulation of fat in adipose tissue, leading to important health problems at the individual level (diabetes, cardiovascular diseases, etc.). Currently, obesity would reach a pandemic state everywhere in the world, with a rate of development suggesting that this pathology involves a sociocultural problem grafted into a predisposition at the individual level.

All specialists agree that, for decades, we are witnessing an increase in worldwide obesity prevalence. This is true in developed as well as in developing countries. No society seems to be immunized against this epidemic. Classical data from the WHO MONICA project (Tunstall-Pedoe 2003) show that obesity prevalence in the majority of the European countries increased in 10 years (1992–2002), going from 10 % to 20 % in men and from 10 % to 25 % among women. In France, between 1980 and 2006, obesity prevalence went from 6.4 % to 16 % in men and from 6.3 % to 17.6 % among women (International Association for the Study of Obesity 2000; Maillard et al. 1999). In the UK, 36 % of men and 33 % of women are predicted to be obese in 2030 compared with 26 % of both sexes in 2010, and the percentages are predicted to be 74 % for men and 64 % for women being overweight in 2030 compared with respectively 70 % and 59 % in 2010 (Breda 2015; Cauchi et al. 2015; Jones and Breda 2015). In France, 25 % of men and 29 % of women are predicted to be obese in 2030 compared with respectively 14 % and 16 % in 2010, and the percentages are predicted to be 66 % for men and 58 % for women being overweight in 2030 compared with respectively 54 % and 43 % in 2010. Greece, Spain, Austria, and the Czech Republic are also European countries facing growing obesity with no evidence of reaching a plateau in their evolution, the Netherlands being the only exception (Kriaucioniene et al. 2015; Shaw et al. 2015).

Based on these facts, several studies have been performed to identify risk factors associated with this affection as well as to contain the epidemic, because obesity became a real public health problem (Barth 2002). It is well known that obesity has a genetic component as a familiar predisposition toward this affection testifies. However, the genetic component does not explain the increasing progression in disease prevalence. Additional behavioral, social, and economic factors must be considered (Laitinen et al. 2001; de Saint-Pol 2008; Scharoun-Lee et al. 2009). In this context, in Christakis and Fowler (2007), authors showed the possibility of person-to-person obesity contagion in a social network. Moreover, in Cohen-Cole and Fletcher (2008), it is suggested that obesity diffusion could occur via a common exogenous source applied to a set of individuals.

Realistic models of contagious diseases incorporate new information about the social networks through which the disease spreads out as well as data about demographic and genetic changes in the susceptible population (Diehl et al. 2013; Fouquet et al. 2013; Franco et al. 2015; Noury et al. 2009; Demongeot 2011; Virone et al. 2002, 2014; Vukadinovic Greetham 2011). They also include all the possible knowledge about the contacts between susceptible and sick individuals. In section "Social Network Framework," we will present the mathematical framework necessary to take into account at a microscopic level the dynamics of contacts between susceptible and obese individuals. Then we will introduce the description of the dynamics of obesity in section "Serious Games Design and Setting," taking into account collective behaviors mimicking some

dominant habits of nutrition transmitted through social networks. Obesity spread modeling will use the notion of homophilic graphs: to investigate obesity in a multifactorial manner, we have taken into account the impact through time that obese individual transformation may have on the social structure, by developing a network model in which individual interactions are in part due to homophilic selection/deselection, i.e., a process of preferential attachment and detachment of interindividual links according to characteristics of the individuals involved. Homophily is here defined as the tendency of an individual to create links with other individuals sharing similar attributes with him and to cut links with other dissimilar individuals. Homophily suggests that individuals tend to interact with those who resemble them. Second, and reciprocally, we study if obesity can be considered as a "contagious" social disease through the role which could be played by the structure of the social fabric in its current development: we evaluate the impact of relations between individuals (micro-level) as well as the impact of relations between districts (meso-level) and between countries (macro-level). This approach highlights the necessity to integrate the dynamics of each scale to better understand the evolution of the pathology. It is proposed through an individual-centered network model, considering three influences: exogenous heterogeneous (individual-cultural), exogenous homogeneous (individual-social), and endogenous (individual-individual).

Then, in order to improve the prevention of obesity, we propose in section "Serious Games Design and Setting," to use e-health technology, which allows accessing to all the facilities of the cloud, the local data acquisition devices, and the processing power of the domestic electronic devices, helping a patient suffering from a chronic disease to know about it and manage his treatment in the framework of a personalized health information system at home. Both the personalized electronic health records (PeHRs) and the therapeutic education tools can be used for improving the patient empowerment, accountability, and engagement for preventing and detecting early the complications. Moreover, a social approach that accounts for these elements is required to address the effectiveness, safety, security, integrity, and confidentiality of the therapeutic educative system. We conducted a research first on three different serious games devoted to nutrition, vision, and locomotion of a person suffering from type II diabetes, in order to detect and prevent its complications (Talbot 2011; Demongeot 2013a; Demongeot et al. 2013b; Diabeo 2015). In order to improve the efficiency of the system, we propose to personalize it by taking into account the environment of the patient, i.e., to introduce demographic, geographic, professional, familial, and associative aspects coming from civil and social data concerning the networks to which the person belongs. After presenting the methodology corresponding to this research, we will give in section "Coupling Between Surveillance in Social Networks and Serious Games" the main results and, then, propose in section "Conclusion" some perspectives for the future work to perform in order to achieve the main aim of the system, that is, to involve the patient through the proposed education techniques inside his social network.

2 Social Network Framework

Given that each individual is immersed in a social system, linked together with other individuals through diverse and complex interactions, each individual i can then be characterized, in a first approach, by their number of neighbors k_i, whereas the overall system is characterized by the connection structure between individuals. To study the role played by the social interactions in obesity spreading, five simple network topologies are considered to describe interindividual connections: random Erdös-Renyi, scale-free, small-world, and two empirical networks.

The empirical networks are built from degree distributions found by Christakis and Fowler (2007) in real networks. On Fig. 1, we can find examples of architecture simulated following the above topologies. We will use these architectures for starting from initial configurations of the

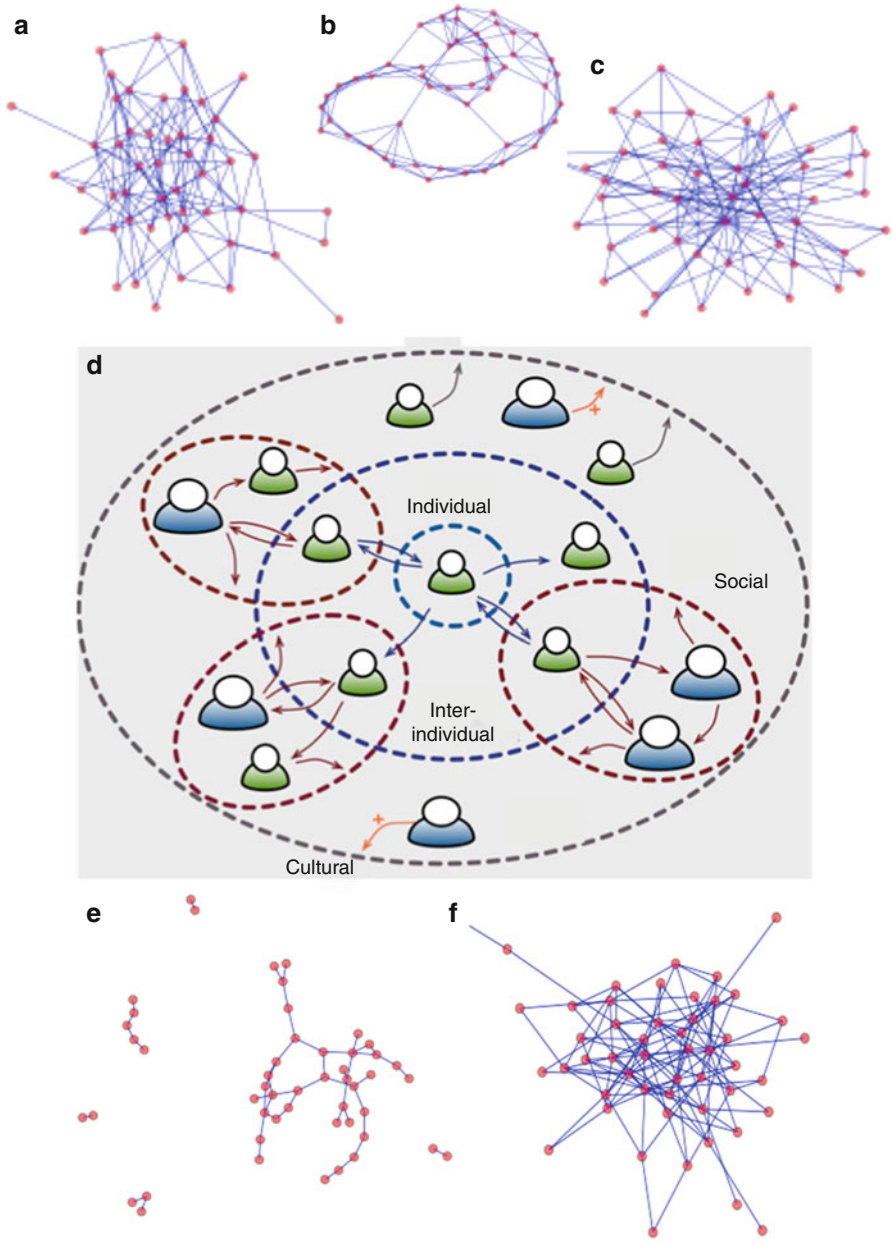

Fig. 1 Representation of interaction graphs in case of random (**a**), small-world (**b**), and scale-free (**c**) networks. (**d**) Different types of links, *blue* between individuals, *red* between groups of individuals, and *orange* with the environment (like cultural interactions). Representation of interaction graphs in case of empirical type I (**e**) and II (**f**) social networks

network, before applying the homophilic rule and converging to an "attractor" of its dynamics, i.e., a stable configuration of links and node states of the interaction graph related to the social network involved in contagion of the obesity.

2.1 Homophilic Hebbian Graphs

The function homophily (resp. heterophily) will be defined as the tendency of an individual to create links with other individuals sharing similar

attributes with him and to cut links with other dissimilar individuals, by playing with the probability to have an infectious contact between agents having the same given state (e.g., normal weight susceptible S, overweight W, and obese O). The tendency an agent or node i has to create or cut a link with another agent j in a social interaction graph G having N agents depends on similarity distances $d(i,j)$ in the graph, like the Hebbian rule of pruning/strengthening in neural networks, which is based on state correlations, destroying (resp. reinforcing) links between nodes weakly (resp. highly) correlated.

For example, if the state $x(t,i)$ of the node i at time t equals 1 (S), 2 (W) or 3 (O), are considered as well as some biological characteristics like age $A(t,i)$ and body adiposity index $B(t,i)$ (Bergman et al. 2011), social variables like sizes of the family $F(t,i)$ and of the circle of friends $C(t,i)$, environmental parameters like the numbers of accessible green areas $G(t,i)$ and supermarkets $M(t,i)$, behavioral variables like sedentary lifestyle index $L(t,i)$ (resp. sport index $S(t,i)$), that is, the number of hours at home (resp. on a sports area) during the last 24 h, they are all the components of a large state vector $V(t,i)$, we can correlate with the vector $V(t,j)$, e.g., by calculating the average cross-correlation between the V components.

Then, the Hebbian rule eliminates links between uncorrelated nodes and builds a positive (resp. negative) link between positively (resp. negatively) sufficiently correlated nodes. The dynamics of creation/cancelation of links can be separated from the state dynamics, if it is slower. Then, we can first study with a fixed architecture the fast state dynamics, considered as autonomous, and then study the bifurcations (in number and nature) of the attractors due to the slow link dynamics.

Let us suppose that there are states x and y in the social graph and denote at time t by $L_{x,y}(t)$ (resp. $L_{x,x}(t)$, $L_x(t)$, and $L(t)$) the number of heterophilic links (resp. homophilic links of type x, links coming from type x nodes, and total links) and by τ the relaxation time. We suppose in each time lapse of duration τ a certain proportion of nodes (agents) create (resp. cancel) links toward nodes being in the same (resp. different) state, with a certain tolerance threshold, supposed to be the same in each state group. The simulation follows the successive steps:

1. At $t = t_0$, generate a random value τ from an exponential distribution of parameter $1/\beta$.
2. At $t = t_0 + \tau$, do the following operations:
   - Choose a fraction ϕ of nodes in the interaction graph G. Let $M = \phi N$.
   - For each node i of these M nodes ($i = 1,\ldots, M$), define its state $x(k,i)$ (known initial conditions, denoted $x(k)$ in the following if there is no ambiguity) and its out-degree $k_i \in \mathrm{IN}$ (equal to the number of links exiting from i); generate the tolerance to difference, a real number $0 \leq h_i \leq 1$, from a probability distribution $g(h)$; and do the following operations:
     - For $k_i = 0$, connection from i to j:
       - Choose a node j by chance among N–1 other nodes.
       - Create a link from i to j with probability $h_i^{d(i,j)}$, where $d(i,j)$ is the direct distance between i and j, with three levels, 0, 1, and 2, as follows:

$$\begin{aligned} &\mathrm{d}(i,j) = 0, \ \text{if } x(i) = x(j) = 1, \\ &\text{if } x(i) = S, x(j) = W \ \text{and vice versa} \\ &\quad = 1, \ \text{if } x(i) = W, x(j) = O \ \text{and vice versa} \\ &\quad = 2, \ \text{if} \\ &x(i) = S, x(j) = O \ \text{and vice versa} \end{aligned}$$

     - For $k_i \geq 1$, connection or disconnection from i to j:
       - If V_i denotes the set of neighbors of i, let choose a node j among the $|Vi|$ neighbors of i with the probability $1/k_i$ and V_j^i denotes the set of neighbors of j minus i
       - Let $r(i, j)$ be the total similarity distance between nodes i and j. The link between i and j will be cut with the probability $1 - h_l^{r(i,j)}$, where the total distance r is defined by:

$$\begin{aligned} &r(i,j) = d(i,j), \ \text{if } c(i,j) = 0 = \alpha d(i,j) + \\ &(1-\alpha) \times c(i,j), \ \text{if } c(i,j) \neq 0, \end{aligned}$$

where the indirect distance c is given by:

$$c(i,j) = \sum_{k \in V_{ji}} d(i,k)/\left(k_j - 1\right) = 0, \text{ if } k_j = 1.$$

- If the link between i and j has been cut, we choose by chance a new node k in $G \setminus V_i \setminus V_j^i$, and we create a link from i to k with the connection probability:
  $P(i \to k) = f(d(i,k)) n_{x(k)} h_i^{d(i,k)} / \left[\sum_{l \in G \setminus Vi \setminus Vji} n_{x(l)} h_i^{d(i,l)}\right]$, where $n_{x(k)}$ is the number of nodes in the set $G \setminus V_i \setminus V_j^i$ having the same state as k, i.e., $n_{x(k)} = n_S$ (resp. n_W and n_O) if k is susceptible (resp. overweight and obese). We will consider in simulations three versions for function f:
  - Version 1: $f(d(i,j)) = 1$, if $d(i,j) = 0$; $= 0$ elsewhere
  - Version 2: $f(d(i,j)) = 1$, if $d(i,j) = 0$ or 1; $= 0$ elsewhere
  - Version 3: $f(d(i,j)) = 1$, if $d(i,j) = 0$, 1 or 2

  These versions are being used in the individual-centered social network for representing three types of progressively increasing influence: exogenous heterogeneous (individual-cultural, version 1), exogenous homogeneous (individual-social, version 2), endogenous (individual-individual, version 3).
3. Change the states $x(j)$, for all j at the end of links created, by increasing their obesity weight of one level (S to W, W to O, O to O).
4. Generate a new τ and go to 2.
5. Stop when the graph G is no more changing.

2.2 Social Contagion

On Fig. 2b, we have fixed the corporal states (obese, overweight, and normal) following the distribution of the BMI (body mass index) in a Chilean child (between 5 and 17 years by population) in 2010 (MinSal 2010): obese (9.6 %), overweight (23.2 %,), and normal (67.2 %). The tolerance has been taken at the level 0.25, and the connection probability has been chosen following the version 1. Directed (not directed) networks with 1000 nodes each have been simulated, with a probability to have forward directional (resp. bidirectional) links equal to $a = 0.6$ (resp. $b = 0.2$). The node positioning has been done following the attraction-repulsion by Fruchterman and Reingold algorithm (1991).

On Fig. 2, each individual is represented in its social neighborhood: he can influence (red arrow) the narrow contexts to which he belongs. Hence, each individual in a given social subnetwork will receive indirect influence linked to his context. Under these influences, some individuals (in blue on Fig. 2) can become obese and others not (in green on Fig. 2). We can now simulate this model of the social contagion mechanisms through which the disease can propagate from individuals to individuals or from environmental sources over populations, individuals changing of state like in biological regulatory networks for which many theoretical and numerical tools have been recently developed (Demongeot et al. 2009a, b, 2010, 2011, 2012, 2013a, b, c, 2014, 2015).

We have developed LIVENET®, a software to represent the person, their environment, and their evolution in the framework of their social network. This system allows you to track their physical condition with BMI or BAI (body adiposity index, cf. Dauphinot et al. 2009), eating habits (amount of food, type of food), physical activity (by counting weekly sedentary hours as well as physical activity hours), and social environment (including family and friends). In this software, each individual can answer a questionnaire in his smartphone or computer, which allows obtaining information from individuals and then about their relating environment. The system allows also to study the behavior "homophilic", i.e., to describe social relations established between people with similar attributes and the corresponding dynamics of both the individuals and the networks. On Fig. 2c, we see the scholar network of a class in a French secondary school, red nodes corresponding to overweight or obese students and blue nodes to normal students (based on BMI). The size of the nodes represents their in-degree (number of arrows entering in a node of the network). We can see the nodes most

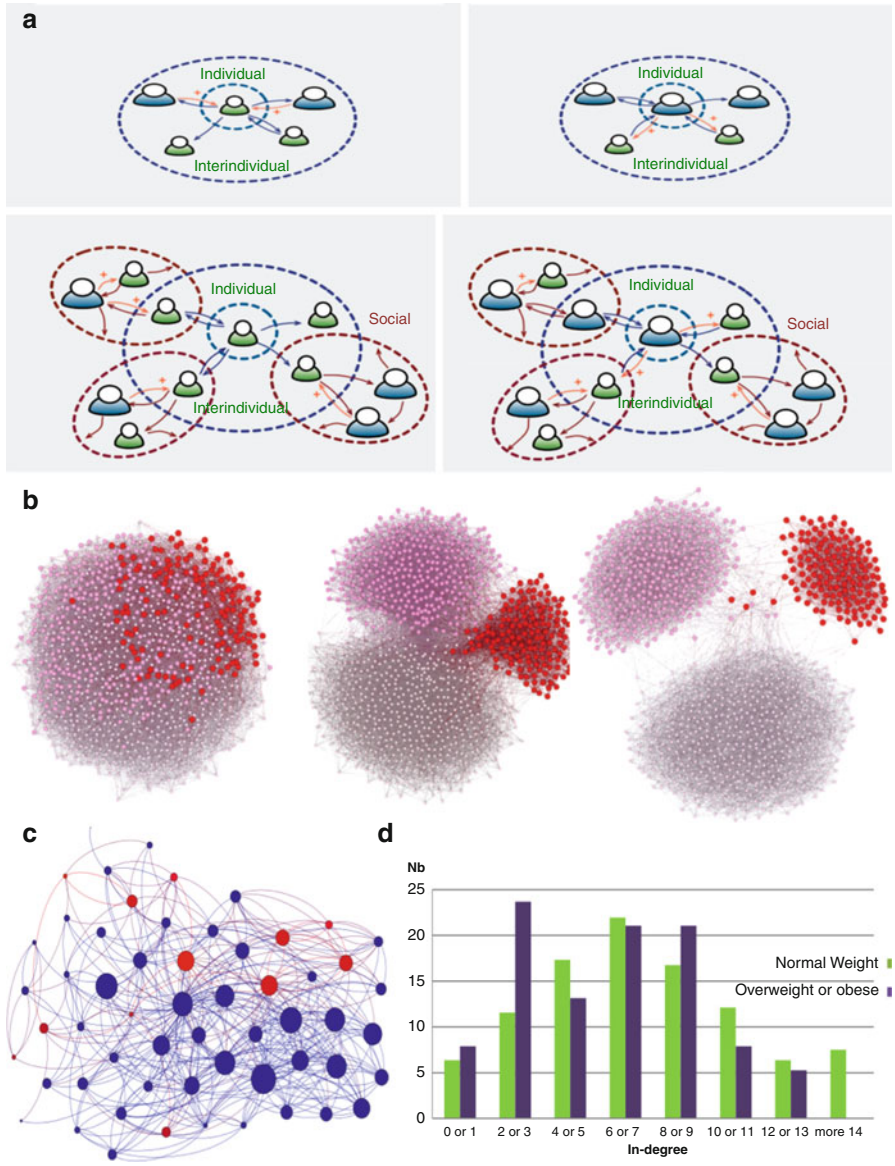

Fig. 2 (**a**) Interindividual relationships between obese (in *blue*) and nonobese people (in *green*) in a social context. (**b**) Dynamics with a progressive clusterization (from *left* to *right*) inside a small-world-directed network with initial proportion of obese individuals in *red* (14.5 %), overweight in *pink* (31.9 %,), and normal in *white* (53.6 %) with 0.25 tolerance and connection probability of the version 1. (**c**) Real network (similar to the empirical type II network) in a class of a French high school, with overweight and obese in *red* and normal scholars in *blue*, the size of the ellipses representing them being proportional to their in-degree (number of their neighbors). (**d**) Distribution of the values of in-degree for overweight and obese (*violet*) and normal (*green*) scholars from four classes of the studied high school

connected have normal weight and nodes with fewer connections have obesity or overweight. This kind of visualization allows us to detect changes in social relationships (creating new relations or loosing interactions). With this system, we can characterize real-time individuals in their environment and see, for example, on Fig. 2d, that the distribution of the in-degree

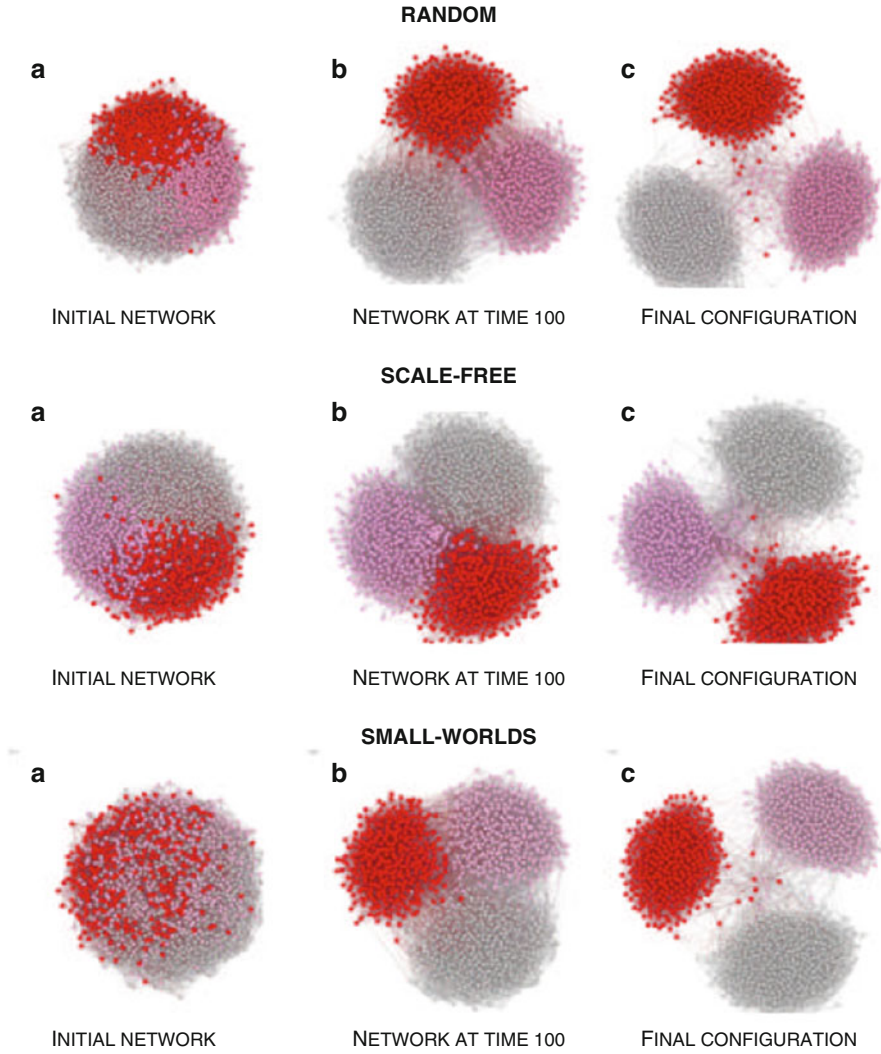

Fig. 3 Initial, intermediate, and final configurations for architectures and initial distribution of states of section "Social Network Framework," with tolerance equal to 0.25 and connection probability of version 3

inside the whole population of scholars is unimodal for overweight and obese and bimodal for normal, which is due to the classical gender effect on size and weight for normal individuals and to the disappearance of this sexual influence on growth in the case of abnormal weight.

2.3 Equilibrium Configurations

Under the homophilic rule, the networks are converging until an equilibrium configuration of both links of the interaction graph architecture and node states, independently of the initial architecture and initial state distribution (Fig. 3). By using the simulation engine of the social network described in section "Homophilic Hebbian Graphs," we can study the speed of convergence to this equilibrium for all the topologies proposed. The relaxation time to the steady state (related to speed of convergence to equilibrium) depends on the network topology (Fig. 4c). The shape of the initial and final "in-degree" distributions is about the same after applying the homophilic dynamics,

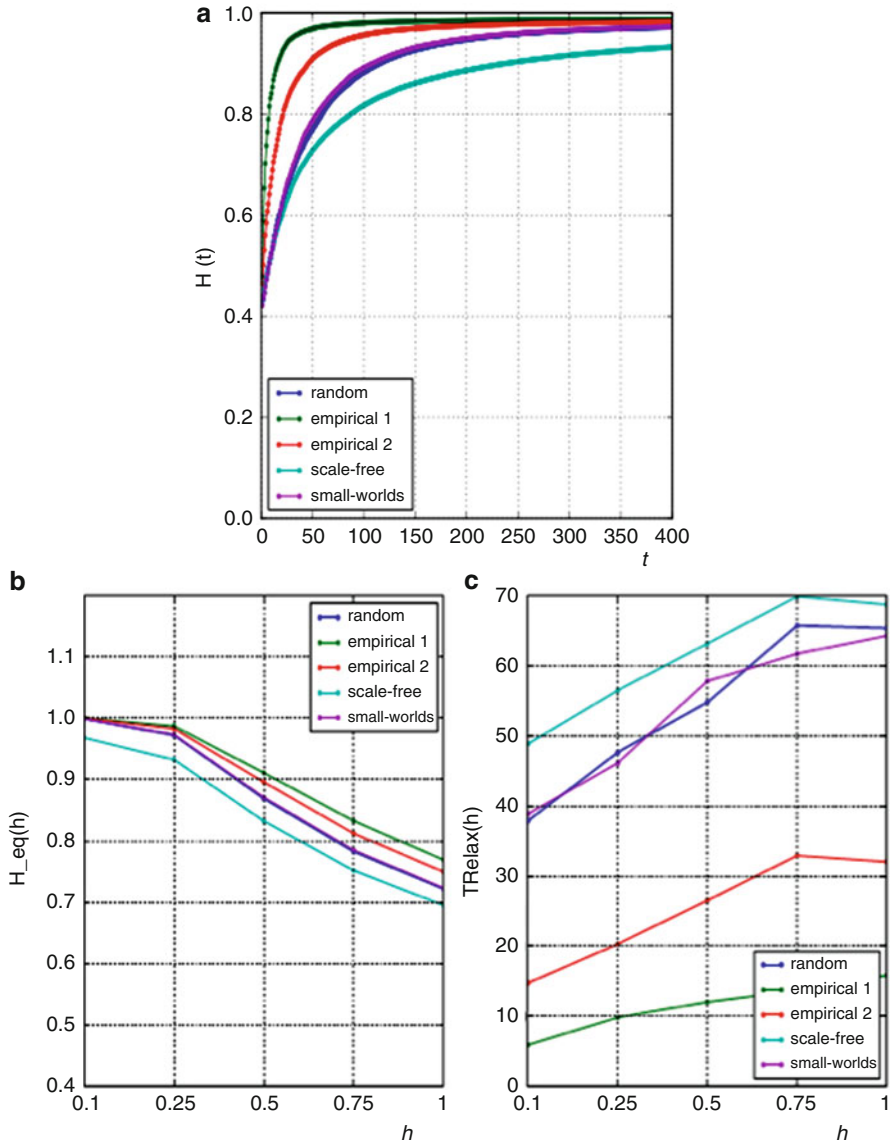

Fig. 4 (**a**) Evolution of the homophily coefficient (equal to $\sum_{x=S,W,O} L_{x,x}/L$) at equilibrium as function of time t, with tolerance equal to 0.25 and connection probability of the version 2. (**b**) Evolution of the homophily coefficient at equilibrium as function of the mean tolerance h. (**c**) Evolution of the relaxation time to equilibrium as function of the mean tolerance h

but we can show that paradoxically in the small-world initial topology, the mean clustering coefficient diminishes, but the marginal clustering coefficient calculated by states increases (this phenomenon being due to the modification of the state distribution). The final value of the homophily coefficient $\mathrm{H} = \sum_{x=S,W,O} L_{x,x}/L$ depends weakly on the topology (Fig. 4a, b). The final configuration of the network has always the homophily maximum, the three groups of the final segregation depending on the topology (Fig. 3).

2.4 Examples of Dynamics of Obesity

Homophily as defined above suggests that individuals tend to interact with those who resemble them in terms of alimentary education and behavior, and the structure of the social fabric is involved in the increase and current development of obesity (Baranova et al. 2005; Demetrius et al. 2010a; Demetrius and Tuszynski 2010b). By using the simulation rules of section "Homophilic Hebbian Graphs," we can compare the simulated graphs with real graphs. The approach described above has highlighted the necessity to integrate randomness at each scale to better understand the evolution of the obesity pathology, e.g., in Fig. 4, the connectivity of the real social network of Fig. 2c representing the obesity spread corresponds better to the homophilic empirical network type II version 2 (the qualitative differences between versions being small), than in the other architectures: random, scale-free, small-world, or empirical type I.

3 Serious Games Design and Setting

In order to prevent the obesity spread through the social networks, we propose to use educative tools called serious games. The general objectives of such serious games are (Talbot 2011; McCallum 2012):

- Acquire progressively self-care skills, taking into account the experience of the disease management by the patient himself.
- Relieve symptoms, by self-monitoring and maintaining sensors.
- Adjust the dose of medication.
- Change the lifestyle (diet balance, adapted physical activity program, etc.).
- Prevent and detect early avoidable complications.
- Involve familial helpers and professional caregivers in the management of the disease.
- Acquire coping skills based on the development of the engagement, empowerment, and accountability by the patient himself (Joubert et al. 2007).
- Capitalize treasury skills, in areas of weight control, diet, and exercise.
- Know the disease and get self-confidence.
- Know how to manage emotions and control stress.
- Develop creative and critical behavior concerning his disease.
- Favor the discussion with other patients suffering from the same disease in order to exchange about the recent therapies and lifestyles influencing the evolution of the disease.

The life cycle of the development of a health serious game is the following:

1. Validation by patients and by a medical committee of a prioritization (in time) in the development of the serious game, namely:
   (a) In the case of diabetic retinitis, explanation of the genesis of the microcirculatory disease and presentation of its impact through functional tests about capacity of visual illusions
   (b) Presentation of the metabolic and endocrine mechanisms behind type II diabetes
   (c) Information on physical activity, dietary recommendations, and biofeedback on their practice
   (d) Information on drug therapy and biofeedback on its observance
   (e) Building tests of compliance of type II diabetic patients
2. Use of the end-user patient to write the general specifications of the game
3. Creating the game scenario
4. Developing the game prototype
5. Assesment final of the game in routine
6. Rewriting the game 2 years after the initial prototyping phase in order to take into account all the observations of the end user and of his helpers and also to introduce the most recent techniques coming from a field in constant development

We will present in the following three different serious games using the software Unity®.

3.1 Nutrition Serious Game

We have first studied the state of the art constituted of different already developed serious games like:

(a) "L'affaire Birman" is designed by an association of type 1 diabetics and the endocrinology-diabetology department of the University Hospital of Caen and is accessible on a web site (Glucifer 2015).
(b) The "Diabeo" application is designed to help type 1 diabetic patients to manage their disease on a daily basis (Diabeo 2015). It provides to the patient a support to real-time calculation of doses of slow and fast insulin, depending on his diet and physical activity, as prescribed by his doctor. Using self-learning techniques, a patient can, for example, learn the best behavior in case of hypo- or hyperglycemia before and after meals, Diabeo offering to revise upwards or downwards his doses. The purpose of Diabeo is to strengthen the doctor/patient relationship with automatic transmission of glycemia results. An automatic analysis tool is integrated for alerting the patient, his familial helpers, and professional caregivers in case of abnormalities (e.g., hypoglycemia). Nineteen different alert messages have been defined.
(c) The "Sophia" system is dedicated to diabetic patients giving information about their disease. It is created by the French National "Assurance Maladie," which intends now to implement the system in the framework of a serious game (Sophia 2015).
(d) The application "Escape from Diab" is a serious game that emphasizes the virtues for the patient of preventive diet and adequate physical activity (Escape from Diab 2015).
(e) Sometimes the serious games are aimed at practitioners, like "InsuOnline," a game for education of primary care physicians on the initiation and adjustment of insulin treatment of diabetes, which was designed to be (a) educationally adequate, (b) self-motivating and attractive, and (c) informative, e.g., by reminding them about the most recent procedures of glycemic surveillance and insulin injection (InsuOnline 2015).
(f) The "Power Defense" game is for the two types of diabetes therapeutic education. It gives a good information on diet and appropriate physical activity that teaches and helps diabetic patient practice (Power Defense 2015).

The risk of a bad alimentation, too rich in carbohydrates, during the phase of early type II diabetes, is to increase the imbalance of insulin control and cause a preprandial coma, due to a poor utilization of glycogen. It is therefore appropriate to advise the diabetic patient about the use of carbohydrates, avoiding snacking and an excessive load of fast sugars. A healthy diet, balancing carbohydrate intake for an energy balance corresponding to a given physical activity, is recommended in the game: the player disposes of several menus he composes entirely in his own way, and a virtual coach reminds him during the game food mistakes he made and advises other behaviors, virtuous this time, corresponding to a nutrition adapted to his diabetic condition (Fig. 5). Depending on the quality of the patient's responses, progressive exercises are proposed as well as the opportunity to build a collection of tailored menus for all periods of the year and all sedentary conditions or physical activities motivating the patient and allowing him to avoid accidents of hypo- or hyperglycemic types. Two levels of the game are proposed, the first for the starting diabetic patient, who ignores the mechanism of the disease and the consequences of a bad nutrition, and the second for the complicated diabetic patient, which takes into account the complications already installed (like retinitis or nephropathy) proposing more than dietary advises, an actual combined adapted alimentation and physical activity (AAPA) diminishing the effects of the evolution of the disease to the complications observed and described by the patient (Wijers 2009; Kahol 2011; Rizzo et al. 2011; Shaw et al. 2014).

Fig. 5 Nutrition game showing the comments of the coach about the energy and glycemic charges (*top left*) and dietetic content (*bottom left*) of menus chosen by the patient (*top right*), leading to exercises about the real dietetic value of some ingredients (*bottom right*)

3.2 Vision Serious Game

Very few examples of serious games are testing visual acuity and still less the capacity to perceive visual illusions (Yoshino et al. 2006). But it is important to explain to a diabetic patient what is occurring progressively in his retina, provoking the diabetic retinitis: to understand deeply this complication, we must present evolutive scenarios about the progressive disappearance (due to a loss of interactions between retinal cells caused by a defect in the microvessels) of the lateral inhibition phenomenon, where excitable cells are activated at short range and inhibited at medium range (Demongeot et al. 2009b). The simulation of this phenomenon allows, for example, to understand the visual illusions, like the Hermann illusion (Fig. 6). It is easy to see, if the retina retains the integrity of its cellular interactions, in particular the lateral inhibition, white (resp. gray) squares at the edges of small (resp. large) white lines, obtained by continuation from the four corners of the surrounding squares.

Depending on the degree of retinal disease due to the disappearance first of the rods and second of the cones due to the loss of a cone growth factor coming from the rods (Léveillard and Sahel 2010) in diabetic retinitis, causing the loss of lateral inhibition, the conservation of the Hermann illusion can be quantified by the liminal value of the distance between the edges of the structure. Similarly, other illusions of Fig. 6 can all be related to the integrity of lateral inhibition, and their disappearance can be quantified by parameters on the geometry of the items offered (Optical illusions 2009; Tayyab et al. 2009). Repeated tests about illusions in biofeedback conditions at home are a means of prevention and alarm for the establishment of the earlier treatment possible, for example, gene therapy to restore the cone growth factors (like p53, GDNF, RdCVF, etc.), which seem to be the most promising (Léveillard and Sahel 2010). The serious game devoted to the vision aims to detect early defects in the perception of visual illusions by the type II diabetic patient.

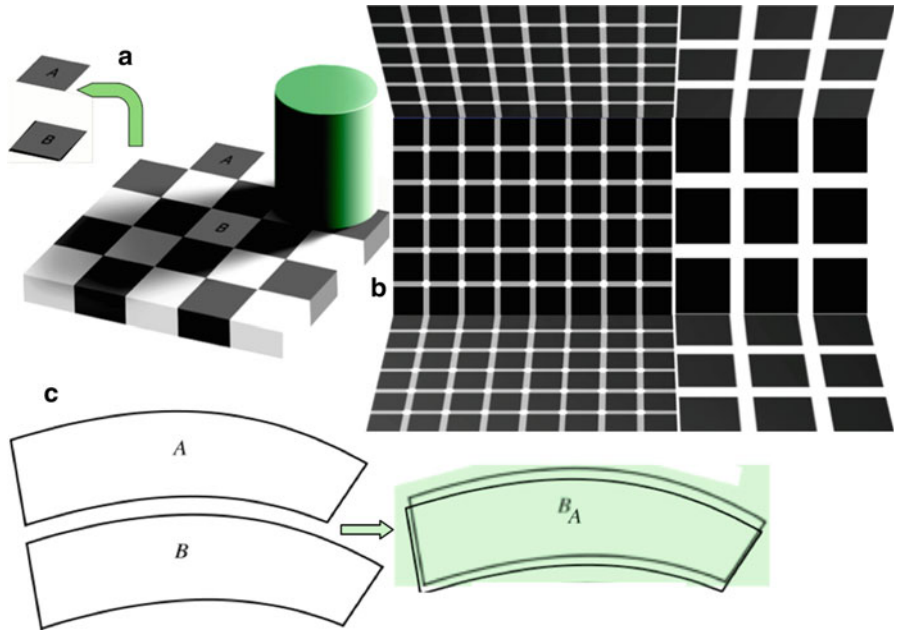

Fig. 6 (**a**) Vision game searching for the sensitivity threshold of perception of Exchequer visual illusion due to an artifactual difference of gray due to the shadowing of *B* square. (**b**) Hermann and Bergen illusions due to an artifactual perception of *white* or *gray* at the intersection of *white* lines. (**c**) Jastrow illusion due to an artifactual difference in length between circular bands *A* and *B* (*bottom*)

We will present now successively six sub-games concerning different aspects of the vision, based on different features of the perception and allowing the measure of threshold psychophysical variables related to the visual illusion recognition. We give in the following only some examples of such variables (cf. Bach 2015 for more illusions):

1. *Geometric illusions*
   - 1.1 Fraser's illusion; threshold variable: black and white square side giving a nonparallelism feeling (Fig. 7e)
   - 1.2 "Curved square" illusion; threshold variable: number of concentric circles giving the perception of curvature of the square sides (Fig. 7f)
   - 1.3 Jastrow's illusion; threshold variable: shift of circular bands giving the sensation of different lengths for the bands (Fig. 6c)
   - 1.4 Poggendorff's illusion; threshold variable: thickness of the vertical band giving the impression of no continuation of the oblique line (Fig. 7a)
2. *Contrast illusions*
   - 2.1 Hermann's illusion; threshold variable: relative thickness of the black and white lines giving the feeling to have white or gray squares at their intersections (Fig. 7b)
   - 2.2 Bergen's illusion; threshold variable: size of the black squares with rounded corners with critical value causing the vision of blurring spots at the intersections of white lines (Fig. 6b)
   - 2.3 "Simultaneous contrast" illusion; threshold variable: gray level of the periphery of the central square chosen on a grayscale to annulate the feeling of difference of gray inside the central squares (Fig. 7c). The same with a gradient of gray on the periphery giving the feeling of a counter-gradient inside the central band (Fig. 7d)
   - 2.4 Exchequer illusion; threshold variable: the gray level of squares A and B chosen on a grayscale to describe the perceived gap between the gray levels of these squares (Fig. 6a)

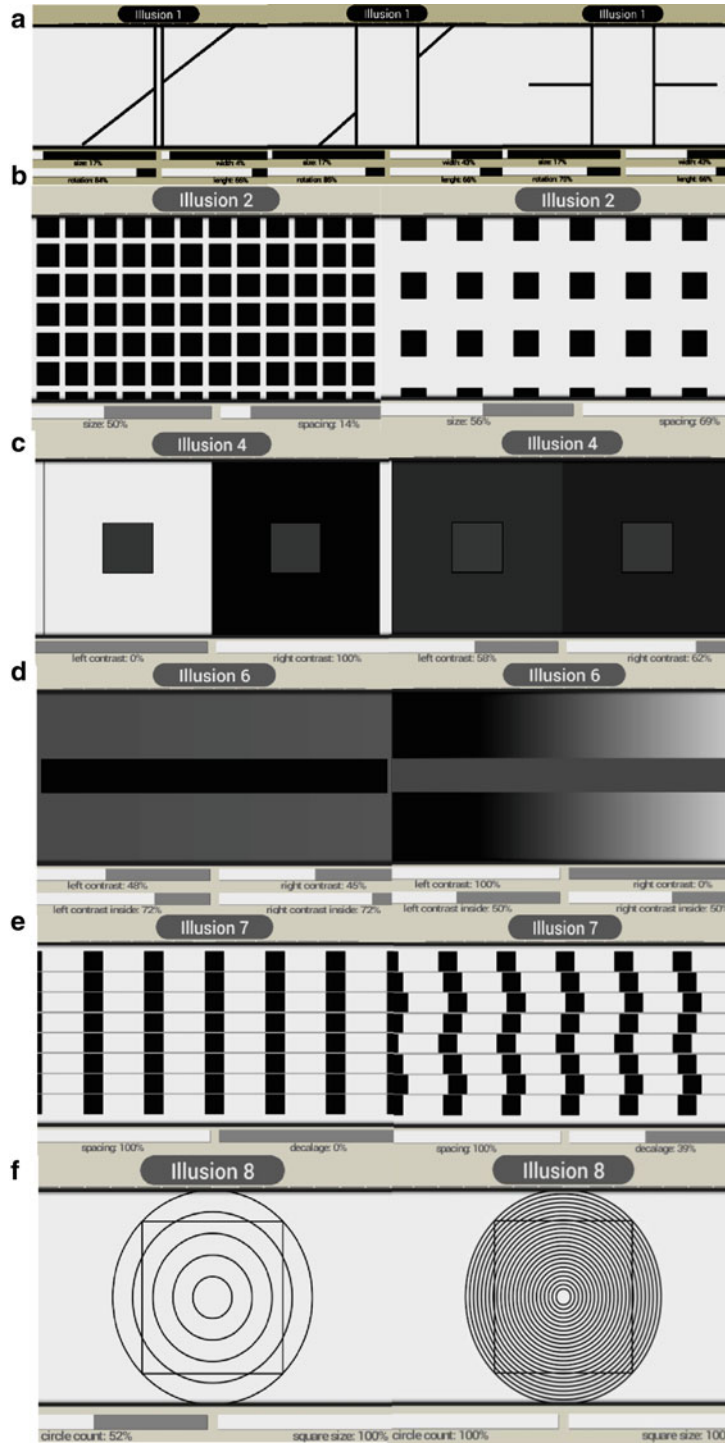

Fig. 7 Different visual illusions with correcting procedures: (**a**) Poggendorff's illusion with feeling of no continuation of the oblique line. (**b**) Hermann's illusion with feeling to have *white* or *gray* squares at their intersections. (**c**) "Simultaneous contrast" illusion with feeling of difference of *gray* inside central squares. (**d**) Same with a *gray* gradient on the periphery with feeling of a counter-gradient inside the central band. (**e**) Fraser's illusion giving a nonparallelism feeling. (**f**) "Curved square" illusion with perception of curvature of the square sides

3. *Contour illusions*
   - 3.1 Ehrenstein's illusion; threshold variables: radius value of the virtual circles and number of afferent rays causing viewing circles
   - 3.2 Kanizsa 2D illusion; threshold variable: value of the distance between peripheral black vertices and search for its critical value causing the feeling to view a 2D triangle
   - 3.3 Kanizsa 3D illusion; threshold variable: value of the distance between concentric black squares and search for the critical value causing the feeling to view a 3D pyramid (Demongeot et al. 2009b)
   - 3.4 "Square that tracks itself" illusion; threshold variable: binary variable, diameter of the light-gray dots giving the impression to be the vertices of a virtual square
4. *Motion illusions*
   - 4.1 "Rotating cylinders" illusion; threshold variable: value of the size of the blue ellipses and research for the critical value causing first the feeling that cylinders rotate
   - 4.2 "Rotating circles" illusion; threshold variable: value of the radius of tricolor circles and search for the critical value causing first the circles rotation
   - 4.3 "Floating disk" illusion; threshold variable: distance to the screen which displays or not floating
   - 4.4 "Double rotation black" illusion; threshold variable: distance to screen displaying or not rotating

The other types of illusions are persistence illusions like "French flag" and "moving pink points" illusions and cognitive illusions like Schroeder's scale and Necker's cube illusions (cf. Bach 2015).

3.3 Locomotion Serious Game

The feedback information of the locomotion serious game is provided by a smart sock made of a textile from Texisense® sensitive to pressure of the foot on the ground (Texisense 2015) and able to record pathologic analgetic postures on the foot sole, due to the attempt to avoid walking on the diabetic foot sores (Vuillerme et al. 2007; Chenu et al. 2012). The patient is invited to walk and run with the smart sock, and his successive positions on the foot sole are recorded (see Fig. 8). An extension of the game compares the bad positions of the foot with the bone defects (coming from a pathologic trabecular reconstruction caused by the bad pressures of the foot on the ground due to pathologic positions during an analgetic walk avoiding the sore pain) thanks to a 3D osteodensitometry of the foot bones, notably the calcaneum. The three bricks of the game already completed consist to record pressure data at the level of the foot sole, basin, and shoulders with the help of smart socks done with the sensitive textile Texisense®, as well as the restitution of these data on various devices of the patient:

1. *Basin and shoulder data*

   The smart fabric can be placed in the form of a pressure-sensing mat; on a wheelchair, an armchair, or a bed; or optionally at ground level, where it continuously records and displays (in case of alert) some pressure data at critical levels for the genesis of ulcers (including shoulders, iliac crest, and sacrum).

   These data are monitored especially in a person by decubitus (hence rarely standing or walking) or working in a sitting posture. The loss (due to vascular complications of type II diabetes) of pressure-sensitive organs indeed often causes the local anoxia of the peripheral tissues, due to the constant position of the patient on the same side; the alert (usually nonconscious) is given by four varieties of cutaneous corpuscles that are pressure sensitive, three dermal and one epidermal. The first varieties are encapsulated near nerve endings: Meissner (superficial dermal), Pacini (median dermal), and Ruffini (deep dermal) corpuscles. The latter variety corresponds to free nerve endings associated with the Merkel cells, which arrive until the epidermis. The type II diabetes keeps intact and functional the nociceptive sensors of the cutaneous pain due to pressure, called mechanical nociceptors and

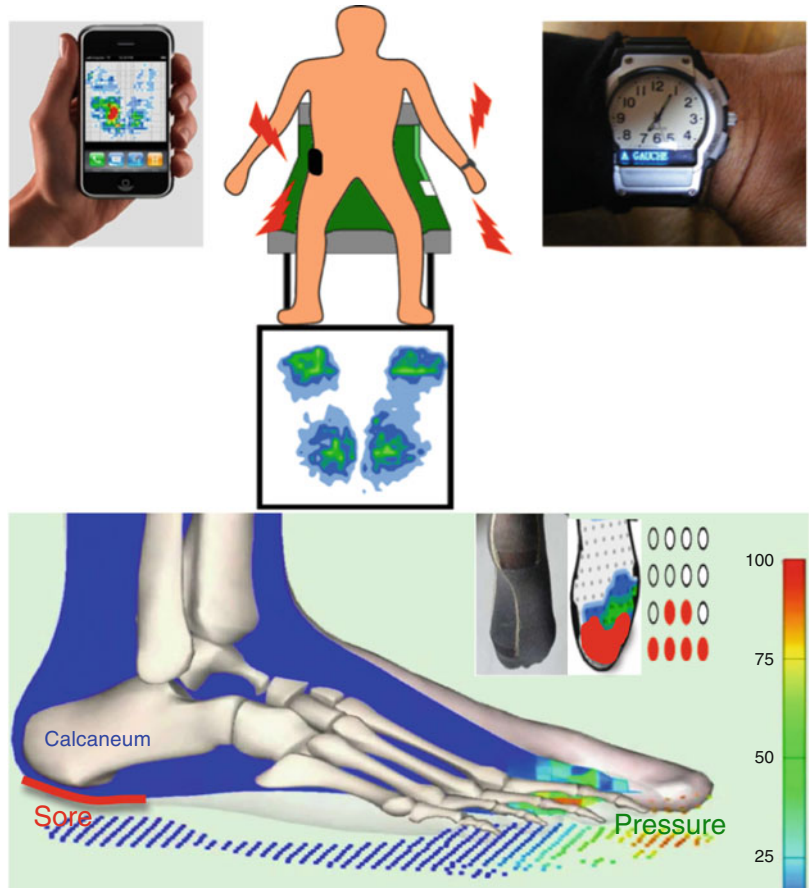

Fig. 8 Locomotion game showing the pressure on feet recorded with a smart textile from Texisense® through different media (*top*) and the information taken by smart sock and sole (*upper* thumbnail) matched on a ultrasonic image of foot bones (*bottom*)

located in the skin, muscles, and joints. The analgetic response often leads to a vicious circle of postures that gradually induce, to escape the pain, other ulcerative locations in the zones of antalgic avoidance.

2. *Foot sole data*

   The plantar pressure data are recorded by the smart sock Texisense® (cf. Texisense 2015, and Fig. 8 thumbnail). As for the basin, the analgetic avoidance of an ulcer on the heel can cause a permanent steppage causing secondarily a forefoot ulcer.

3. *Pressure data integration and restitution*

   The pressure card is presented (Fig. 8 bottom), with the critical areas in red (corresponding to a compression for a time exceeding the threshold of anoxia) on a smartphone, a watch, a screen placed on the wheelchair, etc. (Fleury et al. 2013; Franco et al. 2013a). The initial alert is audible or vibrating, and in case of blindness or deafness, information can be given on the palate, tongue, or teeth in the form of non-painful electrical stimuli or vibrations (Vuillerme et al. 2007).

4 Coupling Between Surveillance in Social Networks and Serious Games

The coupling between the actimetry, i.e., the surveillance of the successive tasks in different rooms of the house or outside (Demongeot et al. 2002, 2008; Franco et al. 2010, 2013b; Mokhtari et al. 2012; Meeks et al. 2014), and therapeutic education consists in:

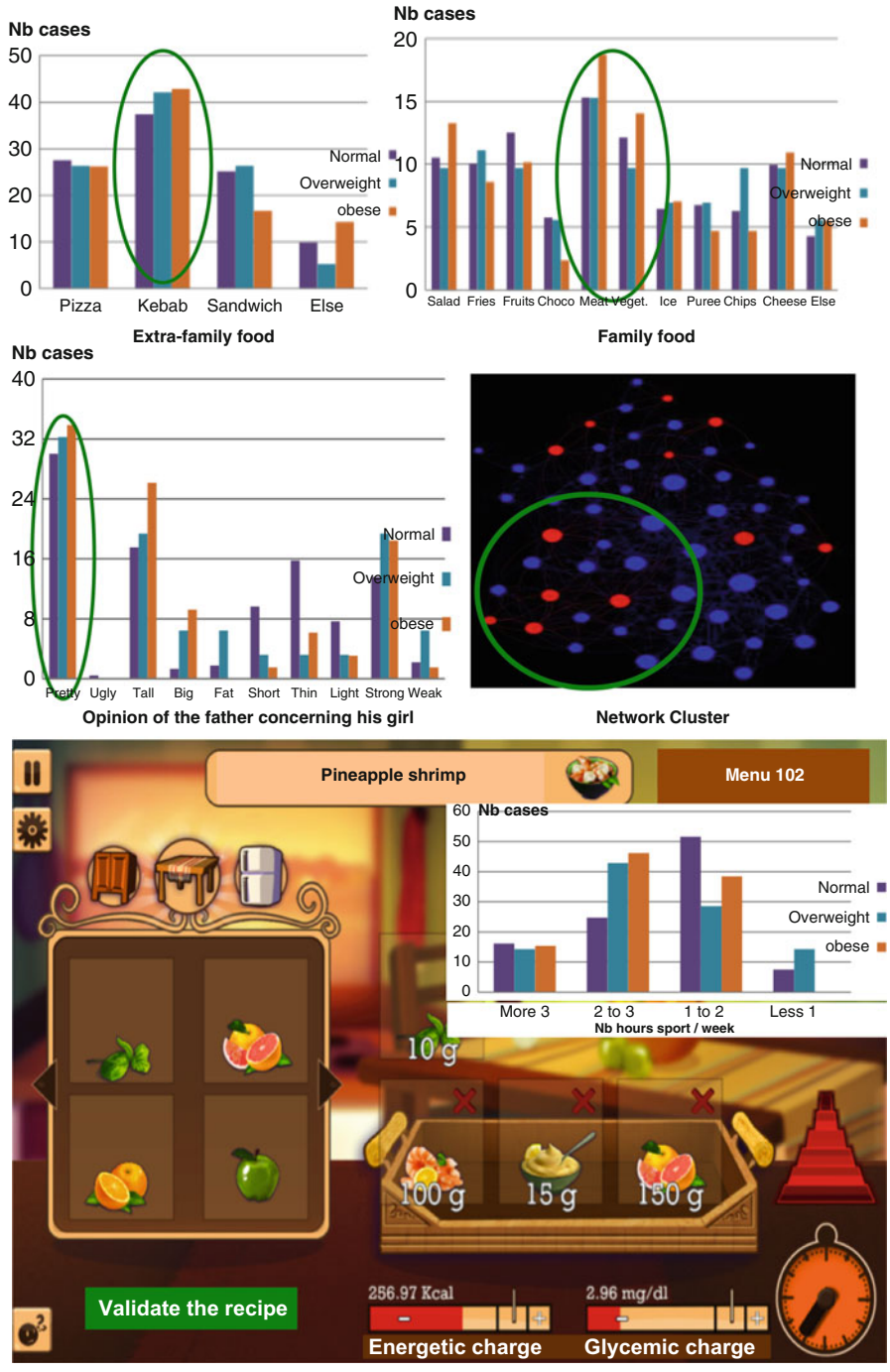

Fig. 9 *Top*: histograms showing the distribution inside a scholar network (3rd class) among extra- (*left*) and intrafamilial food choices (*right*). *Middle*: opinion of the father about his girl (*left*) inside a subcluster identified (in *green*) inside the network using k-means (*right*). *Bottom*: personalization of the nutrition game using the knowledge about the sport practice inside the *green* cluster

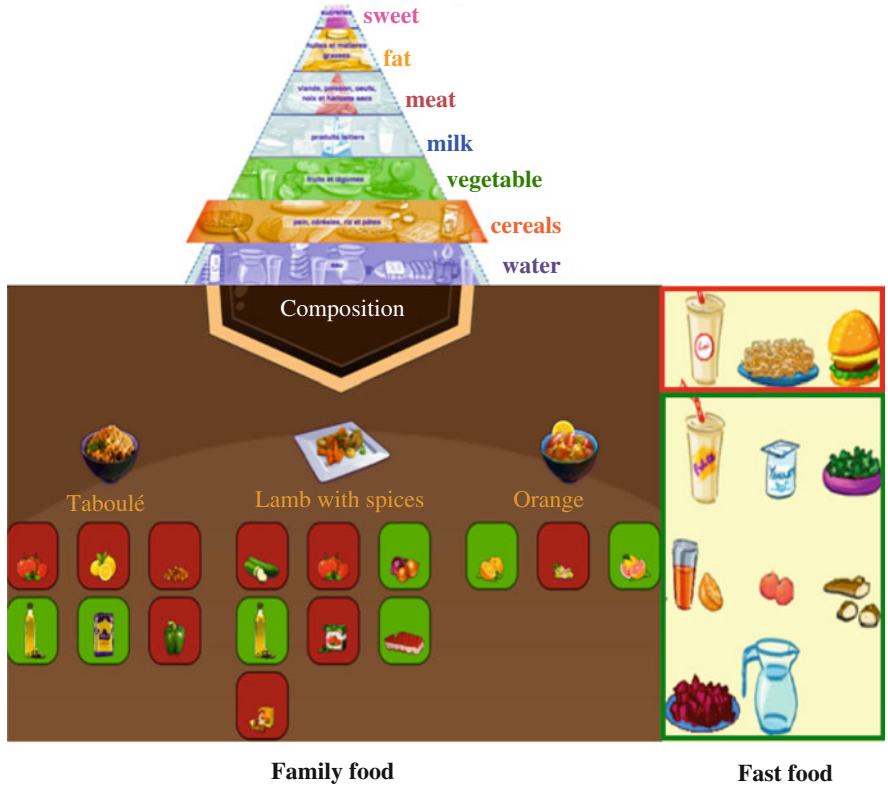

Fig. 10 Explanation given by the nutrition game about the choice of intra- (*bottom left*) and extrafamilial food (*bottom right*) showing in *green* good ingredients and in *red* ingredients missed and their global decomposition inside the dietary pyramid (*top*)

– Reinforcing the reliability of the subjective data requested during the game by objective data from sources of information external to the patient, for example, data from an infrared or RFID localizer (e.g., giving the exact number of hours dedicated to sport as in Fig. 9 bottom), can be compared to the program of the daily activities provided by the patient for calculating the energy and glucose loads needed.
– Delivering any alarms to authorized persons, located in the place of performance of activities.

Customizing a serious game in therapeutic education requires a good knowledge of the person in his familial and social environment. For example, the knowledge of its food heritage or that of his friends in their educational, friendly, or professional environment allows adjusting menu proposals if family food and extra-family diet include lots of meat (Fig. 9 top): even if the opinion of the relatives considers that there is no risk of obesity (Fig. 9 middle), the game will advise eating proteins coming rather from fishes and plants and monitor this alimentation thanks to a food pyramid adapted to the individual (Fig. 10).

5 Conclusion

We have presented in this chapter simulations of the homophilic dynamics of the social network explaining the obesity spread. In order to improve this study, a theoretical estimation of the speed of convergence to the equilibrium

configuration could be made, as well as the consideration of the robustness of the process: does only one or more equilibrium states exist, and if yes, are other "attractors" only fixed states or possibly periodic configurations? Which network parameters are critical, i.e., at which parameter perturbation (provoking a change in the number or nature of attractors) is sensitive to the dynamics? Which perturbation of the initial configuration of the social network leads to a change of attraction (or stability) basin? All these problems will be addressed in a future work.

Concerning the serious games, they have been developed in the framework of national French and Chilean projects, the research aiming to improve the chronic patient engagement, empowerment, and accountability through an interactive system based on these new therapeutic education techniques. Improvements can be made in these games, leading in the future to the inclusion of social elements of human environment of the patient to refine the game and, hence, reduce the duration of the period of learning. Eventually, a continuum should exist between the individual medical case file and the exchange internet facility within the framework of a social network of people suffering from the same disease, taking into account the transmission of synergistic or antagonistic eating habits in the population of persons involved in the pathological sequence "overweight/obesity/type II diabetes." The long-term use of an education and prevention method will develop in the patient's feelings of empowerment, accountability, and engagement in his own treatment and efforts to push the latest possible the occurrence of complications of its initial chronic pathology. The appropriation, involvement, and implication in the tool improvement by the patients themselves, for example, in an associative framework, should provide a product well accepted, effective and scalable, and regarded as the product of creativity of a community of patients, rather than a new software "parachuted" by the medical community, away from the real needs of the end user, who suffers from a constantly evolving progression of his specific pathology.

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Part IV

Pathophysiology

Principles of Energy Homeostasis

18

Rexford S. Ahima

Contents

Abstract

Mammals have evolved complex mechanisms to obtain energy from food; store excess energy in the forms of glycogen, fat, and protein; and utilize energy efficiently for vital functions. Obesity develops when energy intake exceeds energy expenditure. While obesity treatment is mostly focused on reducing food intake, studies suggest that increasing energy expenditure through physical activity and adaptive thermogenesis is an important strategy for weight loss and maintenance of health. This chapter will describe fundamental concepts of bioenergetics and provide a framework for understanding the pathogenesis and treatment of metabolic syndrome.

Keywords

Obesity • Diet • Energy intake • Energy expenditure • ATP • Thermogenesis • Physical activity

1 Introduction

Energy metabolism is controlled by genetic and environmental factors which affect energy intake and energy expenditure (Fig. 1a). Energy balance is attained when energy intake is equal to energy expenditure. When energy intake exceeds energy expenditure, a state of positive energy balance occurs, and this leads to obesity, a condition characterized by increased body weight, especially fat,

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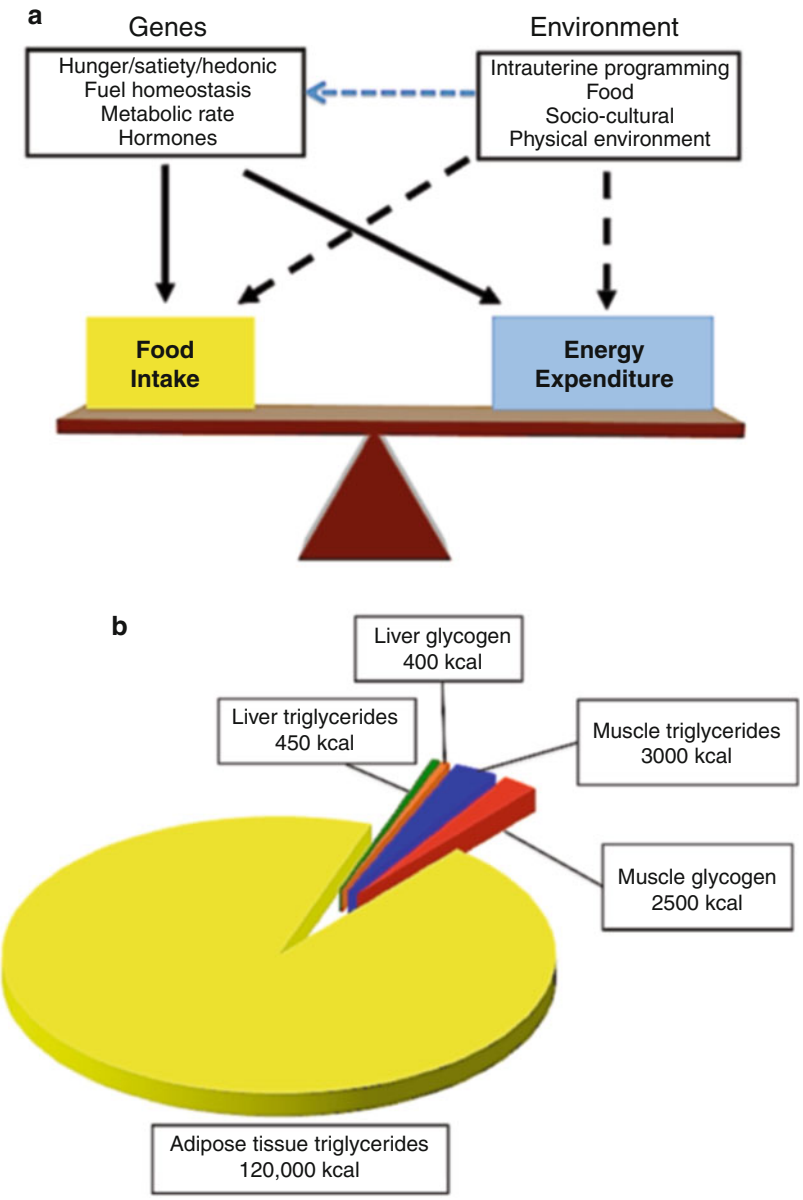

Fig. 1 (**a**) Energy homeostasis. Genetic and environmental factors affect food intake and energy expenditure. Energy balance is achieved when energy intake is equal to expenditure. Obesity is a state of positive energy balance in which the excess energy is stored mainly as fat. (**b**) Body energy stores of a lean 70 kg man

in adipose tissue and other organs. A state of negative energy balance ensues when energy intake in markedly reduced in relation to energy expenditure. There is profound individual variability in the time to attain energy balance and the patterns of weight gain and weight loss. Over the past two decades, we have gained substantial insights into the genetic, epigenetic, and environmental factors favoring overeating, obesity, and metabolic syndrome (Leibel et al. 1995; Redman et al. 2009). It is difficult to lose weight and maintain weight loss over long periods due to metabolic, behavioral, neuroendocrine, and autonomic responses that promote weight regain and maintain energy stores in adipose tissue (Leibel et al. 1995; Redman et al. 2009; Ahima 2011). Multiple neuronal and hormonal signals oppose the state of weight reduction and predispose

toward positive energy storage. For example, the fall in leptin counteracts weight loss by stimulating appetite and decreasing energy expenditure (Ahima 2011). Hyperinsulinemia promotes energy storage in the forms of glycogen, fat, and protein (Leibel et al. 1995; Redman et al. 2009). Important inferences about the pathogenesis and treatment of obesity and metabolic syndrome can be drawn from fundamental concepts of energy metabolism.

2 Energy Intake

Energy needed for metabolic and physiological functions is derived from the chemical energy bound in macronutrient components of food, i.e., carbohydrates, fats, proteins, and ethanol. Food digestion is facilitated by cooking, chewing, mixing with saliva, gastric movements, and enzymes which blend the food into chyme (Spiller 1994; Elia and Cummings 2007). In the upper intestine, the chyme is digested further to produce glucose, fatty acids, and amino acids which are absorbed (Spiller 1994; Elia and Cummings 2007). The chemical energy in nutrients is released and converted into heat, mechanical, and other forms of energy. Fats and carbohydrates are the main sources of dietary energy (Human energy requirements: report of a joint FAO/WHO/UNU Expert Consultation 2005; Joint 2007). Proteins are also an important source of energy, especially when total dietary energy intake is limited (Human energy requirements: report of a joint FAO/WHO/UNU Expert Consultation 2005; Joint 2007). Ethanol is often overlooked as a source of energy in food, but its contribution to total energy intake is significant in people who regularly consume alcoholic beverages (Human energy requirements: report of a joint FAO/WHO/UNU Expert Consultation 2005).

The unit of energy in the International System of Units is the joule (J), which is the energy expended when 1 kg is moved 1 meter by a force of 1 Newton (Joint 2007). The conversion factors for joules and calories are 1 kJ = 0.239 kcal and 1 kcal = 4.184 kJ. The *ingested energy* (IE) or gross energy (GE) is the maximum amount of energy measured after complete combustion to carbon dioxide and water in a bomb calorimeter. Incomplete digestion of food in the small intestine, and fermentation of unabsorbed carbohydrate in the colon, results in the loss of *fecal energy* (FE) and *gaseous energy* (GaE). Short-chain fatty acids are formed in the intestine, some of which are absorbed and available as energy. Some energy is lost as *urinary energy* (UE) in the form of urea and other nitrogenous waste compounds derived from incomplete catabolism of protein. Food energy remaining after accounting for these losses is known as *metabolizable energy* (ME), most of which is available for the production of ATP. Some of the ME is utilized during metabolic processes associated with digestion, absorption, and intermediary metabolism of food and can be measured as heat production referred to as *diet-induced thermogenesis* (DIT) or *thermic effect of food* (TEF). The *net metabolizable energy* (NME) is obtained by subtracting the energy lost to microbial fermentation and DIT from the ME.

The ME was classically defined as the food energy available for heat production and recently defined as the amount of energy available for whole body (total) heat production in a state of nitrogen and energy balance (Joint 2007). The NME is defined on the basis of the ATP-producing capacity of food instead of the total heat-producing capacity. Strictly, the NME refers to the food energy available for body functions requiring ATP. The measurement of *food energy content* is by chemical analysis or estimated from food composition tables. The Atwater general factor system of food energy is based on the heat of combustion of protein, fat, and carbohydrate, corrected for energy losses via digestion, absorption, and urinary excretion. The ME values are 17 kJ/g (4.0 kcal/g) for protein, 37 kJ/g (9.0 kcal/g) for fat, 17 kJ/g (4.0 kcal/g) for carbohydrates, and 29 kJ/g (7.0 kcal/g) for ethanol (Human energy requirements: report of a joint FAO/WHO/UNU Expert Consultation 2005; Joint 2007).

Dietary recommendations must meet energy requirements in addition to providing all essential nutrients necessary for attainment and maintenance of optimal health and physiological functions. The daily human energy requirement is estimated from the measurement of energy expenditure plus the extra energy needed for growth, pregnancy, and lactation. A state of *energy balance* is attained when the dietary energy intake is equal to total energy expenditure. A person is considered to be in a *steady state* when the energy balance is maintained over a long period. Recommended food intake, referred to as *daily requirement* or *recommended daily intake*, represents an average of energy needs over a certain number of days and does not indicate exactly how much energy should be consumed daily. Energy requirements are estimated from data from group of individuals of the same gender, age, BMI, and *physical activity level* (PAL) (Human energy requirements: report of a joint FAO/WHO/UNU Expert Consultation 2005; Joint 2007). However, there may be individual variations due to differences in lifestyle and other factors that alter energy requirements within a population (Human energy requirements: report of a joint FAO/WHO/UNU Expert Consultation 2005; Joint 2007).

The *food energy density* is defined as the amount of energy contained in a gram of food. *Very low energy density foods* contain less than 0.6 calories/gram, e.g., lettuce, apple, tomato, strawberry, broccoli, grapefruit, nonfat milk, carrot, and vegetable soup. *Low energy density foods* contain 0.6–1.5 calories/gram, e.g., oatmeal, whole milk, beans, banana, broiled fish, fat-free yogurt, baked potato, and cooked whole grain rice. *Medium energy density foods* contain 1.5–4 calories/gram, e.g., egg, roast chicken, bagel, white bread, ham, cream cheese, raisin, pretzel, cake with frosting, and cheddar cheese. *High energy density foods* contain more than 4 calories/gram, e.g., mayonnaise dressing, chocolate chip cookies, potato chips, bacon, butter, and peanut butter. Low energy density foods have a high content of water, complex carbohydrate, and fiber content, while the high energy density foods have a low content of water and fiber content and a content of high sugar and fat.

3 Energy Expenditure

Basal metabolism. This refers to the energy required to maintain the functions essential for life, such as the maintenance of cellular structure, metabolic pathways, temperature, cardiorespiratory, and brain functions (Rolfe and Brown 1997; Bosy-Westphal et al. 2004; Rising et al. 1992; Bogardus et al. 1986; Johnstone et al. 2005). The Basal Metabolic Rate (BMR), also known as the Standard Metabolic Rate, is the rate of energy expenditure measured under standard conditions that include being awake in the supine position after 10–12 h of overnight fasting, 8 h of physical rest, a state of mental relaxation, and thermoneutral conditions, i.e., an environmental temperature that does not elicit heat generation or dissipation. The BMR is the largest component of energy expenditure and represents 45–70 % of the daily total energy expenditure (TEE). The BMR is heritable, correlated with body size, body composition, sex, age, and sympathetic nervous system (SNS) activity (Rising et al. 1992; Bogardus et al. 1986; Johnstone et al. 2005; Bouchard et al. 1989; Saad et al. 1991; Spraul et al. 1993). The Fat-Free Mass (FFM) accounts for two-thirds of the BMR variance between individuals (Bosy-Westphal et al. 2003; Keys et al. 1973). Men have higher BMR compared to women, and aging is associated with a decline in BMR, and these differences are attributable to FFM (Bosy-Westphal et al. 2003; Keys et al. 1973). The BMR can be estimated based on age, sex, and weight (Table 1).

In contrast to the BMR, the Resting Metabolic Rate (RMR) measures the amount of energy used in a relaxed, but not a postabsorptive state, and requires the subject to be in a thermoneutral environment (Weststrate 1993). The less stringent criteria make the RMR more practical than BMR for clinical and research studies.

Energy expenditure related to feeding. Eating requires energy for ingestion and digestion of food and for absorption, transport, interconversion, oxidation, and storage of nutrients. These processes increase oxygen consumption and heat

Table 1 Estimates of Basal Metabolic Rate from body weight

Age (*Years*)	BMR: MJ/day	BMR: kcal/day
Males		
<3	0.249 kg − 0.127	59.512 kg − 30.4
3–10	0.095 kg + 2.110	22.706 kg + 504.3
10–18	0.074 kg + 2.754	17.686 kg + 658.2
18–30	0.063 kg + 2.896	15.057 kg + 692.2
30–60	0.048 kg + 3.653	11.472 kg + 873.1
>60	0.049 kg + 2.459	11.711 kg + 587.7
Females		
<3	0.244 kg − 0.130	58.317 kg − 31.1
3–10	0.085 kg + 2.033	20.315 kg + 485.9
10–18	0.056 kg + 2.898	13.384 kg + 692.6
18–30	0.062 kg + 2.036	14.818 kg + 486.6
30–60	0.034 kg + 3.538	8.126 kg + 845.6
>60	0.038 kg + 2.755	9.082 kg + 658.5

production and are known by various terms such as *thermic effect of food* (TEF), *diet-induced thermogenesis (DIT)*, and *specific dynamic action (SDA)* (Tataranni et al. 1995; Brundin et al. 1992). The TEF is dependent on the dietary composition and may account for about 10 % of the TEE in a person eating a mixed diet.

Adaptive thermogenesis. This refers to heat production in response to ambient temperature. Cold exposure induces non-shivering thermogenesis in brown adipose tissue and shivering thermogenesis in skeletal muscle. Non-shivering thermogenesis is a major thermoregulatory mechanism against cold exposure in rodents, and it is mediated through activation of SNS activity and generation of heat by uncoupling protein (UCP)-1 (Golozoubova et al. 2001). As discussed later, browning of adipose tissue occurs in humans and plays an important role is adaptive thermogenesis and pathogenesis of obesity.

Physical activity. This is the most variable component of TEE. Physical activity may be divided into *obligatory* and *discretionary* activities. Obligatory activities include work, other daily activities such as self-care, caring for the family and other home activities, going to school, and other demands imposed by the economic, social, and cultural environment. Discretionary activities include exercise for fitness and health and other optional but desirable activities for social interaction. The physical activity level (PAL) can be estimated from the 24-h TEE and BMR ratio (PAL = TEE/BMR) (Joint 2007). A sedentary or light activity person has a PAL of 1.40–1.69, a moderately active or active person has a PAL of 1.70–1.99, and a very active person has a PAL of 2.0–2.4.

Growth, pregnancy, and lactation. The energy required for growth comprises of energy needed for the synthesis of growing tissues and energy deposited in growth tissues. The energy cost of growth is about 35 % of TEE in the first 3 months of age, falls to 5 % at 12 months and 3 % in the second year, remains at 1–2 % until mid-adolescence, and is minimal in the late teenage years (Joint 2007). During pregnancy, energy is needed for growth of the fetus, placenta, and maternal tissues, such as the uterus, breasts, and fat stores, as well as meeting the demands of maternal metabolism at rest and during physical activity. The energy cost of lactation comprises of energy required to produce and secrete breast milk. In addition to increasing their food intake, lactating women derive part of the higher energy requirement from fat stores accumulated during pregnancy.

3.1 Measurement of Energy Expenditure

The concept that energy expenditure is related to chemical combustion was proposed by Lavoisier (Green and Zande 1981). Energy expenditure can be measured by *direct calorimetry*. The subject is housed in a testing chamber, and the non-evaporative heat loss is measured from the temperature gradient across the walls of an insulated chamber, and evaporative heat loss is measured in the water vapor in the test chamber. The total heat loss is measured as the sum of evaporative and non-evaporative loss. *Direct calorimetry* is accurate, but it requires a specialized testing facility (Jequier et al. 1987).

Indirect calorimetry is based on the principle that the combustion of food to generate energy requires oxygen consumption. *Indirect*

calorimetry estimates the energy expenditure from the rates of respiratory gas exchange and nitrogen excretion (Livesey and Elia 1988; Ravussin et al. 1986). The heat produced by the utilization of oxygen varies according to the contents of carbohydrate, fat, and protein. Indirect calorimetry is often used to measure BMR or RMR for hours using a ventilation hood or for days in a respiratory chamber. A constant supply of fresh air is provided to the subject, and the respiratory gas exchange is measured by analyzing the air inflow and outflow and the flow rate. Oxygen consumption, carbon dioxide production, and urinary nitrogen excretion are measured. Energy expenditure = MR (kcal/day) = 3.941 VO_2 (L/day) + 1.106 VCO_2 (L/day) – 2.17 N Urine (g/day), where MR = metabolic rate, VO_2 = oxygen consumption, VCO_2 = carbon dioxide production, and N Urine = nitrogen excreted in urine. The urinary nitrogen derived from incomplete combustion of protein is small, and it is estimated to be 12 g/day (0.5 g/h). The ratio of VCO_2 and VO_2 is known as the respiratory quotient (RQ) or respiratory exchange ratio (RER) and ranges from 0.7 to1.0. The RQ is 1 when carbohydrate is the sole fuel being oxidized and 0.7 when fat is the sole fuel being oxidized. The proportion of energy utilized from carbohydrate or fat can be estimated using standard equations (Livesey and Elia 1988; Ravussin et al. 1986).

The *doubly labeled water* technique enables the TEE to be measured under free-living conditions (Schoeller 1999; Ravussin et al. 1991; Speakman 1998). A single oral dose of water enriched in deuterium (^{2}H) and ^{18}oxygen (^{18}O) is given orally to label the body water. After equilibrium is reached in 3–6 h, ^{18}O is lost as $CO^{18}O$ and $H_2{}^{18}O$, and deuterium is lost in water. ^{18}O and ^{2}H enrichment is measured by isotope ratio mass spectrometry in the urine or saliva. Carbon dioxide production rate is based on the difference in turnover rates between the oxygen and hydrogen labels. The difference between the slopes for the log-transformed disappearance rates of ^{2}H and ^{18}O is proportional to the amount of carbon dioxide produced. Based on a 24-h respiratory quotient value of 0.85, the oxygen consumption and TEE values are calculated (Schoeller 1999; Ravussin et al. 1991; Speakman 1998).

Assessment of body movement using *accelerometry* is a popular method for measuring physical activity (Plasqui et al. 2013). Accelerometers can measure body movement and provide information about physical activity patterns over long periods. Recent advancements in sensor technologies have enabled the development of accelerometers with different capabilities. Piezoresistive or piezo-capacitive sensors differentiate between physical activity intensity and postures. In order to capture physical activity patterns, the monitoring needs to be done over several days and weeks. Detection of specific types of activities may require a multiple sensor system (Plasqui et al. 2013). It is noteworthy that accelerometers do not measure energy expenditure; therefore, the data may need to be compared to energy expenditure measured by the doubly labeled water method.

The TEE can be estimated by *factorial calculations* based on the time and energy cost of habitual activities (Joint 2007) (Table 2). Factorial calculations combine the energy spent while sleeping, resting, working, and doing social or discretionary household and leisure activities, and the energy expenditure estimate is based on the time allocated to each activity and the corresponding energy cost.

4 Energy Partitioning

Most of the energy in the body is stored as fat in adipose tissue (Fig. 1b). Figure 2 shows the weights and energy expenditure of key metabolic organs that contribute to the total energy expenditure. Various organs are involved in the production, storage, and utilization of energy (Schulz and Schoeller 1994; Redman et al. 2009; Rosenbaum et al. 2005; Flatt et al. 1985; Smith et al. 2000; Hill et al. 1991; Frayn 2002) (Fig. 3). The liver is the main distributor of energy to other organs and maintains blood glucose levels within a narrow range in response to intermittent food intake. The liver also produces urea and other nitrogenous

Table 2 Factorial calculations of total energy expenditure

Main daily activities	Time allocation (h)	Energy cost[a] (PAR)	Time × energy cost	Mean PAL[b] (multiple of 24-h BMR)
Sedentary or light activity lifestyle				
Sleeping	8	1	8.0	
Personal care (dressing, bathing)	1	2.3	2.3	
Eating	1	1.5	1.5	
Cooking	1	2.1	2.1	
Sitting (e.g., office work, selling produce, tending shop)	8	1.5	12.0	
General household work	1	2.8	2.8	
Driving car to and from work	1	2.0	2.0	
Walking at varying paces without a load	1	3.2	3.2	
Light leisure activities (e.g., watching TV, chatting)	2	1.4	2.8	
Total	**24**		**36.7**	**36.7/24 = 1.53**
Active or moderately active lifestyle				
Sleeping	8	1	8.0	
Personal care (dressing, bathing)	1	2.3	2.3	
Eating	1	1.5	1.5	
Standing, carrying light loads (e.g., waiting on tables, arranging merchandise)[c]	8	2.2	17.6	
Commuting to and from work on the bus	1	1.2	1.2	
Walking at varying paces without a load	1	3.2	3.2	
Low intensity aerobic exercise	1	4.2	4.2	
Light leisure activities (e.g., watching TV, chatting)	3	1.4	4.2	
Total	**24**		**42.2**	**42.2/24 = 1.76**
Vigorous or vigorously active lifestyle				
Sleeping	8	1	8.0	
Personal care (dressing, bathing)	1	2.3	2.3	
Eating	1	1.4	1.4	
Cooking	1	2.1	2.1	
Non-mechanized strenuous work (e.g., agricultural work-planting, weeding, gathering)	6	4.1	24.6	
Collecting water and wood	1	4.4	4.4	
Non-mechanized domestic chores (sweeping, washing clothes and dishes by hand)	1	2.3	2.3	
Walking at varying paces without a load	1	3.2	3.2	
Miscellaneous light leisure activities	4	1.4	5.6	
Total	**24**		**53.9**	**53.9/24 = 2.25**

[a]Energy costs of activities expressed as multiples of the BMR or PAR
[b]PAL = physical activity level or energy requirement expressed as a multiple of 24-hour BMR
[c]Composite of the energy cost of standing, walking slowly, and serving meals or carrying a light load

waste products. After a carbohydrate-rich meal, glucose enters hepatocytes via GLUT2, and the glucose is phosphorylated by glucokinase to form glucose 6-phosphate (G6-P). Glucokinase has a higher Km for glucose, 10 mM, than other hexokinase isozymes, which allows hepatocytes to continue phosphorylating glucose when the blood glucose concentration is very high after eating. Conversely, the high Km of glucokinase limits glucose phosphorylation when the blood

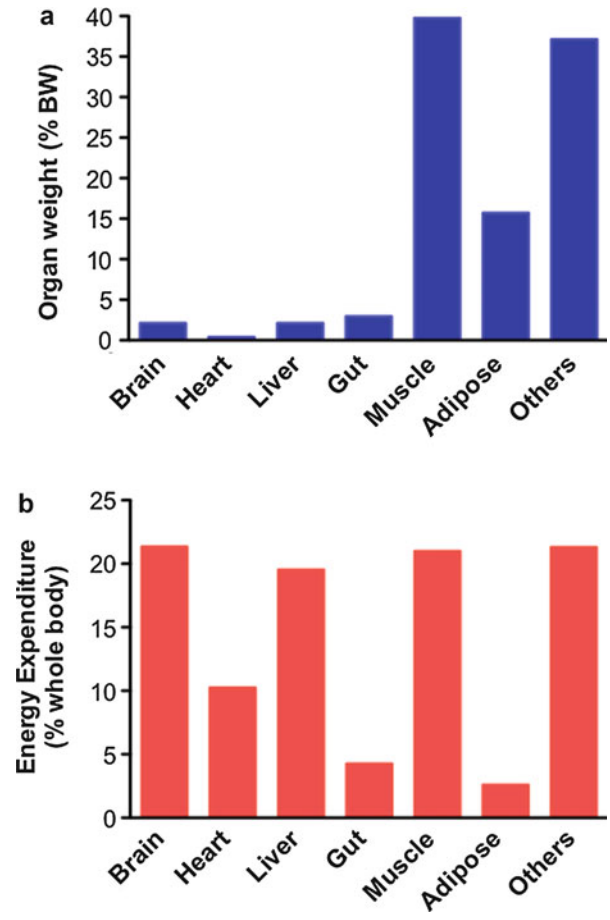

Fig. 2 (**a**) Organ weight (% body weight) and (**b**) organ energy expenditure (% whole body energy expenditure) in a healthy adult (Adapted from Kummitha et al. 2014. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited)

glucose concentration is low during fasting, thereby preventing the liver from consuming glucose. During fasting, G6-P is dephosphorylated by G6-Pase to supply blood glucose to the brain and other tissues. Some of the G6-P undergoes glycolysis to form pyruvate, decarboxylated to form acetyl-CoA, which is then oxidized by the citric acid cycle to produce ATP. Acetyl-CoA also serves as a precursor of fatty acids, used for triglyceride, phospholipid, and cholesterol synthesis. G6-P can also enter the pentose phosphate pathway, producing NADPH for the synthesis of fatty acids and cholesterol and D-ribose 5-phosphate, a precursor for nucleotides.

Amino acids entering hepatocytes are used as precursors for protein synthesis or exported to other organs. Amino acids are transaminated, deaminated, and degraded in hepatocytes to produce pyruvate and other intermediates in the citric acid cycle. Ammonia released from amino acid catabolism is excreted as urea. Pyruvate generated from amino acids is converted to glucose and glycogen via gluconeogenesis, or to acetyl-CoA to be oxidized via the citric acid cycle and oxidative phosphorylation to produce ATP or converted to lipids. During the period between meals, a small amount of muscle protein is degraded to amino acids, which donate their amino groups via transamination to pyruvate, producing alanine, which is transported to the liver and deaminated into pyruvate, which is then converted to glucose via gluconeogenesis.

The liver plays an important role in lipid metabolism. Triglycerides are synthesized de novo or from the esterification of glycerol and fatty acyl-CoA. Fatty acids are the primary fuel for oxidative metabolism in hepatocytes, generating acetyl-CoA and NADH. Acetyl-CoA is

a

Metabolic Pathways	Brain	Heart	Skeletal Muscle	GI Tract	Liver	Adipose Tissue
Gluconeogenesis I, II, III (PYR→GAP,GAP→G6P, G6P→GLC)					■	
Glycogen synthesis (GLY→G6P)	■	■	■		■	
Glycogenolysis (G6P→GLY)	■	■	■		■	
Fatty acid synthesis (ACoA→FFA)					■	
Fatty acid oxidation (FFA→ACoA)		■	■		■	■
Lipolysis (TG→FFA+GLR)		■	■	■	■	■
TG synthesis (FFA+GRP→TG)		■	■	■	■	■
Glycerol phosphorylation (GLR→GRP)		■	■		■	
GAP reduction (GAP→GRP)						■
GRP oxidation (GRP→GAP)					■	
Alanine breakdown (ALA→PYR)					■	
Alanine synthesis (PYR→ALA)			■			
Protein breakdown (Protein→ALA)			■			

b

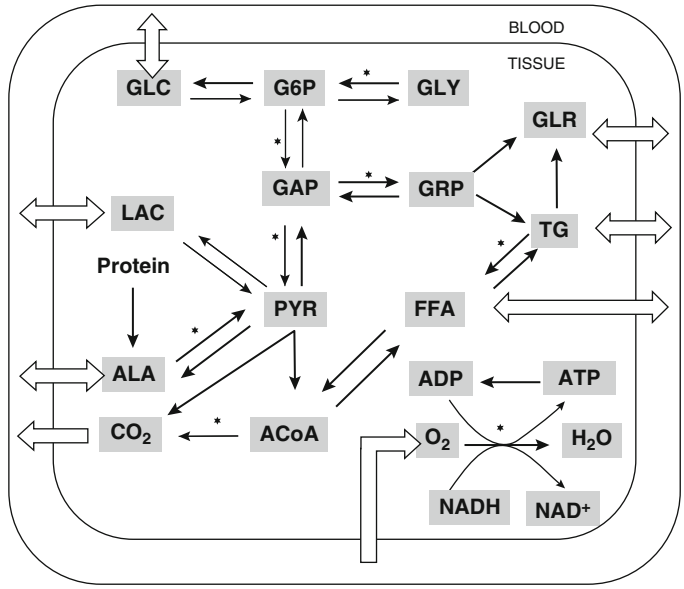

Fig. 3 (**a**). Organ-specific pathways for energy metabolism. Gray panels indicate the existence of a particular metabolic pathway (**b**). Cellular metabolism of carbohydrate, fat, and amino acid. Abbreviations: *ADP* adenosine diphosphate, *ATP* adenosine triphosphate, *ACoA* acetyl-CoA, *AA* amino acids, *GLC* glucose, *G6P* glucose-6-phosphate, *GAP* glyceraldehyde-3-phosphate, *GLR* glycerol, *GRP* glycerol-3-phosphate, *GLY* glycogen, *FFA* free fatty acid, *LAC* lactate, *PYR* pyruvate, *TG* triglycerides (Adapted from Kummitha et al. 2014. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited)

oxidized via the citric acid cycle to produce ATP, and the excess acetyl-CoA is converted to acetoacetate and beta-hydroxybutyrate. These ketones are important fuels for the heart and brain during prolonged fasting. Acetyl-CoA derived from fatty acids is used for the synthesis of cholesterol, needed for membrane assembly, and for the synthesis of steroid hormones and bile salts. Fatty acids are also converted to phospholipids and triglycerides, which are exported via lipoproteins to adipose tissue for storage. Nonesterified fatty acids are bound to serum albumin and transported to the heart and skeletal muscles to be used as fuel.

White adipose tissue (WAT) is the main energy storage organ and comprises 15–20 % of the mass of a normal adult (Fig. 1b). Adipocytes interact with the brain, liver, skeletal muscles, heart, and other organs. During periods of high carbohydrate intake, adipocytes are capable of converting glucose into fatty acids and fatty acids to triglycerides. However, most of the triglycerides stored in human adipocytes are derived from the VLDL exported from liver and chylomicrons from the intestinal tract. When energy demand rises, adipocyte lipases release free fatty acids from triglycerides which are transported to skeletal muscles and heart. Epinephrine stimulates adipocyte lipolysis via hormone-sensitive lipase (HSL), while insulin inhibits lipolysis. Most of the fatty acids generated by triacylglycerol lipase in adipocytes are re-esterified to triglycerides by glycerol kinase which uses glycerol phosphate derived mainly from pyruvate via glyceroneogenesis.

Skeletal muscle performs mechanical work necessary for maintaining body posture, breathing, and locomotion. Type I (slow-twitch; red) myofiber has low tension, is highly resistant to fatigue, and produces ATP via oxidative phosphorylation. Red muscle fiber is very rich in mitochondria and blood supply. Type II (fast-twitch; white) myofiber has fewer mitochondria than red muscle, is less vascular, generates greater tension and faster contraction, and is quicker to fatigue. Resting muscle uses mostly free fatty acids from adipose tissue and ketone bodies from the liver. These fuels are oxidized and degraded into acetyl-CoA, which enters the citric acid cycle for oxidative phosphorylation and ATP production. Moderately active muscle uses glucose in addition to fatty acids and ketones. The glucose is converted to pyruvate via glycolysis and then to acetyl-CoA and oxidized via the citric acid cycle. Maximum contraction of fast-twitch muscle rapidly depletes ATP, and this cannot be replenished by aerobic respiration. Glycogen stored in muscle is broken down to produce lactate, but the amount of glycogen in skeletal muscle is small and cannot sustain glycolysis during prolonged exercise. Thus, skeletal muscle also generates phosphocreatine to provide energy. After exercise, the lactate is transported from muscle to liver, and glucose is produced via gluconeogenesis and transported back to muscle to replenish the glycogen stores.

The brain has a very active oxidative metabolism, accounting for about 20 % of oxygen consumption. The brain uses glucose as its main fuel, but it can also use fatty acids and ketones during starvation. The liver is the main source of glucose for the brain. Neurons metabolize glucose via glycolysis and the citric acid cycle, and this provides most of the ATP needed to establish and maintain the membrane electrical potential and also generate action potentials during neurotransmission.

5 Hormones Mediating Energy Homeostasis

The effects of gut hormones, adipokines, and other circulating factors involved in energy metabolism are described in other chapters. The blood glucose concentration is maintained within a narrow range around 4.5 mM. During feeding, insulin stimulates glucose uptake by muscle and adipose tissue and stimulates the synthesis of glycogen and triglycerides from glucose. Excess triglycerides are exported from the liver as VLDL. Insulin stimulates triglyceride synthesis in adipocytes from fatty acids released from the VLDL. During fasting, glucagon and epinephrine levels are increased and stimulate glycogenolysis by activating glycogen phosphorylase and inactivating glycogen synthase. As fasting is prolonged, glucagon inhibits glucose breakdown

via glycolysis in the liver and stimulates glucose synthesis by gluconeogenesis by reducing the concentration of fructose 2,6-bisphosphate, an allosteric inhibitor of fructose 1,6-bisphosphatase and an activator of phosphofructokinase. Glucagon inhibits pyruvate kinase, leading to accumulation of phosphoenolpyruvate, which drives gluconeogenesis. Glucagon also stimulates the synthesis of phosphoenolpyruvate carboxykinase (PEPCK) which promotes gluconeogenesis. Ultimately, these effects of glucagon culminate in an increase in hepatic glucose output to supply glucose to the brain and other vital organs. During prolonged fasting, the fall in insulin and rise in glucagon and epinephrine levels trigger a switch from carbohydrate-based to fat-based metabolism. Epinephrine stimulates acetyl-CoA production via fatty acid oxidation and promotes the formation of ketones which are exported from the liver to heart, skeletal muscle, and brain to be used as energy substrates.

The conversion of cortisol to active or inactive metabolites has profound effects on carbohydrate, fat, and protein metabolism. Plasma cortisol is increased during starvation, acute infection, and in response to other stressors and stimulates glucose production, lipolysis, and proteolysis. In contrast to glucagon and epinephrine, cortisol acts relatively slowly through nuclear transcriptional mechanisms to control energy metabolism.

6 Brown Adipose Thermogenesis

Oxidative metabolism occurs within mitochondria through the citric acid cycle and electron transport chain (Green and Zande 1981). Oxygen is consumed, water and carbon dioxide are produced, and the ATP generated is used for various cellular functions, including the maintenance of Na^+/K^+ and Ca^{2+} pumps. H^+, Na^+, K^+, and Ca^{2+} leak across membrane channels along electrochemical gradients, and the H^+ leak dissipates free energy in the form of heat and decreases the amount of ATP generated per molecule of oxygen split by the electron transport chain (Harper et al. 2008). The *uncoupling* of oxidative phosphorylation is very prominent in brown adipose tissue (BAT) and is mediated by UCP1, a 32 kDa protein located in the inner mitochondrial transmembrane of brown adipocytes, which allows protons to reenter the mitochondrial matrix from the inner membrane space. BAT uses glucose and fatty acids as fuel, and the heat is liberated by H^+ rushing down its electrochemical gradient. BAT plays a critical role in thermogenesis in rodents (Golozoubova et al. 2001; Enerback et al. 1997; Kontani et al. 2005; Feldmann et al. 2009). UCP1-deficient mice are hypersensitive to cold temperature and prone to obesity, whereas UCP1 expression in WAT results prevents obesity (Enerback et al. 1997; Kontani et al. 2005; Feldmann et al. 2009; Kopecky et al. 1995).

BAT is located in the interscapular region of neonates, and it has been detected in the cervical and supraclavicular regions of adults, using ^{18}F-FDG-PET-CT scans and histological analysis of fat biopsies (Cypess et al. 2009; Virtanen et al. 2009; van Marken Lichtenbelt et al. 2009; Saito et al. 2009; Zingaretti et al. 2009). BAT activity is increased in response to cold exposure, β_3-adrenergic agonist, and ephedrine and results in weight loss (Astrup 1986; Weyer et al. 1998; Astrup et al. 1985; Shekelle et al. 2003; Baba et al. 2007). Other factors implicated in the browning of adipose tissue include thyroid hormone, bile acids, leptin, melanocortin-4-receptor agonists, and FGF-21 (Harms and Seale 2013).

7 Muscle Thermogenesis

Skeletal muscle plays an important role in thermogenesis (Wijers et al. 2008; Vybiral et al. 2000; van Ooijen et al. 2005; Rosenbaum et al. 2005). Fidgeting and other non-exercise activities dissipate heat and prevent obesity (Zurlo et al. 1992; Levine et al. 1999; Johannsen and Ravussin 2008). Shivering thermogenesis occurs in skeletal muscle in response to cold exposure (Wijers et al. 2008; van Ooijen et al. 2005). Chronic exercise increases the expression of genes involved in mitochondrial respiration and fatty acid oxidation, which protect against obesity, diabetes, and hyperlipidemia (Vybiral et al. 2000). Cold exposure also promotes a switch from white

(glycolytic) to red (oxidative) myofibers by inducing the expression of nuclear co-activator PGC1α, which is also induced in brown fat in response to cold (Puigserver et al. 1998; Lin et al. 2002).

Another mechanism for skeletal muscle thermogenesis is linked to the control of ATP turnover and Ca^{2+} gradient by the sarcoplasmic reticulum Ca^{2+} ATPase (SERCA) (Bal et al. 2012; Maurya et al. 2015). Ca^{2+} promotes heat production from ATP hydrolysis during muscle relaxation or sustained contraction. The heat energy is released when the Ca^{2+} is pumped back into the sarcoplasmic reticulum by SERCA. Cold exposure induces the expression and activity of SERCA1 in skeletal muscle to increase muscle oxidative metabolism and heat production. Normally, the opening of sodium channels leads to the release of Ca^{2+} into the cytoplasm from sources outside the cell and the sarcoplasmic reticulum through ryanodine receptor (RyR). The RyR-mediated Ca^{2+} leak is an important mechanism for SERCA-activated heat production (Bal et al. 2012; Maurya et al. 2015). Sarcolipin interacts with SERCA in the presence of Ca^{2+}, leading to uncoupling of the SERCA pump (Bal et al. 2012). Mice lacking sarcolipin develop diet-induced obesity, confirming an important role of this pathway in muscle thermogenesis and energy homeostasis (Bal et al. 2012).

8 Energy Dysregulation in Obesity

The worldwide increase in obesity and metabolic syndrome is attributed to overconsumption of food, especially energy-dense foods rich in fat and sugar. The excess energy is deposited mainly as fat in adipose tissue, as well as in the liver, muscle, pancreatic beta-cells, and other tissues. Ectopic fat deposition (steatosis) leads to insulin resistance, oxidative injury, inflammation, and other changes that predispose to type 2 diabetes and greater cardiovascular risk. Food restriction is the main strategy for obesity treatment, but this alone is often unsuccessful due to an adaptive reduction in energy expenditure, increased hunger, and other physiological and behavioral responses that oppose weight loss (Weyer et al. 2000; Sims et al. 1973; Larson et al. 1995; Tataranni et al. 1997). Discoveries in molecular genetics, in addition to population and laboratory studies, have enriched our knowledge of mechanisms underlying obesity and related diseases. Pathway analyses provide strong support for genetic loci related to CNS circuits and molecules related to energy metabolism and glucose homeostasis (Loos and Bouchard 2008; Loos et al. 2008; Locke et al. 2015).

Some studies have demonstrated associations of RMR, TEF, RQ, or SNS activity with weight gain or weight loss (Saad et al. 1991; Spraul et al. 1993; Flatt et al. 1985; Smith et al. 2000; Hill et al. 1991; Ravussin et al. 1988; Astrup et al. 1999; Amatruda et al. 1993; Tataranni et al. 1997). A seminal experiment by Bouchard et al. (Bouchard et al. 1990) showed that monozygotic twins who were overfed displayed similar gains in body weight and fat between each twin pair, indicating a strong genetic influence on energy metabolism. It is possible that genetic factors predispose toward obesity by affecting multiple factors, such as food digestion, absorption, availability of metabolizable energy (ME), TEF, and mitochondrial energy metabolism. Reduced physical activity is often cited as a cause of obesity, but the evidence is debatable. Some studies have suggested that the increasing obesity trend parallels the sedentary lifestyle in various populations (Swinburn et al. 2011; Caleyachetty et al. 2015). Non-exercise physical activity may prevent the development of obesity (Villablanca et al. 2015). Reduced physical activity may predispose to sarcopenia, insulin resistance, and metabolic syndrome, especially among older people (Kim and Choi 2015; Batsis et al. 2014). However, other researchers have found no major changes in physical activity to explain the increasing trend of obesity (Westerterp and Speakman 2008). It has been proposed that energy balance may be easier to achieve at a higher level of energy expenditure (Hill et al. 2012). Above a threshold physical activity level, the energy intake and energy expenditure are very sensitive to changes in each other within the "regulated zone" of energy balance (Hill et al. 2012). In

contrast, the energy intake and expenditure are weakly sensitive to changes in each other in the "unregulated zone" below the physical activity threshold, and this promotes overeating and weight regain following caloric restriction (Hill et al. 2012).

9 Conclusions

The mechanisms of energy metabolism respond more robustly to negative energy balance than to positive energy balance. The energy balance concept predicts that it would be easier to prevent the transition from a normal to obese weight than to produce a sustained weight loss in an obese person (Eckel et al. 2011). This concept offers a rational biological basis for the implementation of obesity prevention programs, aimed at promoting healthier food choices, increasing energy expenditure through physical activity in individuals and among the wider population, and developing cognitive skills and behaviors to sustain long-term healthy weight (Eckel et al. 2011). Obesity prevention demands changes in the "built environment" and a transformation of societal perceptions and practices regarding the causes and treatment of obesity and related diseases.

A better understanding of the principles of bioenergetics will facilitate new preventive and treatment approaches for obesity and metabolic diseases. Novel technologies to precisely measure energy intake, expenditure, and storage under free-living conditions will help in the development of accurate diagnostic tools and a better stratification of metabolic syndrome risk. Bioenergetic pathways of the gastrointestinal tract, liver, brown fat, white fat, skeletal muscle, and other tissues need to be thoroughly investigated to determine their contributions to whole body metabolism and how these pathways can be targeted specifically and safely for therapeutic purposes.

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10 Cross-References

- ▶ Body Composition Assessment
- ▶ Carbohydrate, Fat, and Protein Metabolism in Obesity
- ▶ Diet and Obesity (Macronutrients, Micronutrients, Nutritional Biochemistry)
- ▶ Genetics of Obesity
- ▶ Myokines and Metabolism
- ▶ Overview of Metabolic Syndrome
- ▶ Sarcopenic Obesity
- ▶ The Built Environment and Obesity

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Carbohydrate, Fat, and Protein Metabolism in Obesity

19

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Contents

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Abstract

Macronutrient metabolism is essential for transferring energy contained in food to usable forms of cellular energy. The balance between energy fuels flowing to cells and being released as cellular work will determine the body size. In the last decades, energy homeostasis has been challenged by an overwhelming macronutrient availability that imposes a need for further expansion of adipose mass. The capacity to handle such higher energy and macronutrient fluxes will determine metabolic disturbances (e.g., insulin resistance) at tissue and whole organism level. Herein, we reviewed carbohydrate, fat, and protein metabolism with special emphasis to the comparison between lean and obese individuals.

Keywords

Fuel oxidation • Energy balance • Fuel partitioning • Cellular work • Energy transfer

1 Introduction

All forms of life require exogenous energy supply and the biochemical machinery for transforming fuels to usable forms of cellular energy. This energy is required to sustain multiple processes that are pivotal for survival of living organisms, including the maintenance of electrochemical gradients, macromolecule synthesis and breakdown, and thermogenesis, among many others (Rolfe and Brown 1997). Energy resides in the carbon-hydrogen bonds of carbohydrate, fat, and protein and only can be used by cells after being transferred to suitable energy carriers. In the mitochondria, a sequence of complex reactions removes hydrogen atoms (i.e., dehydrogenation) from energy substrates. The energy contained in the resulting transmembrane proton (H^+) gradient is ultimately transferred to cellular energy carrier molecules (i.e., phosphorylated adenosine nucleosides).

Thermodynamically, obesity pathogenesis requires a chronic positive energy balance in which exogenous energy supply surpasses body energy expenditure. The most notorious biological consequence of this energy unbalance is the expansion of *white adipose tissue* (WAT). This adaptation allows massive amounts of metabolic energy accumulate as *triacylglycerols* (TAG). Every time that body energy balance is shifted, a new homeostatic level is set between exogenous and endogenous energy fluxes. Thus, obese subjects have increased energy turnover, which is due to higher body mass rather than to higher physical activity-dependent energy expenditure. These individuals often develop insulin resistance, a condition in which insulin action is abnormal. Because of the pivotal roles of *insulin* on macronutrient metabolism regulation, insulin resistance may determine impaired carbohydrate, lipid, and protein metabolism. In turn, altered macronutrient metabolism may eventually lead to insulin resistance. Herein, we offer a condensed analysis of macronutrient metabolism with focus on aspects that appear to be especially relevant for the understanding of obesity-related metabolic disorders such as insulin resistance.

2 Role of Energy Homeostasis Regulation on Obesity Pathogenesis

The maintenance of stable body mass and composition requires that cumulative energy intake over a long period of time (days to weeks) matches cumulative energy demand, resulting in null *energy balance*. Upon these conditions, net macronutrient storage is also null, and thus, whole-body mass and composition are constant. Therefore, null energy balance necessarily derives from that the average proportion of macronutrient oxidized (*respiratory quotient*, RQ) equals the proportion of dietary macronutrients available for oxidation (*food quotient*, FQ) over a period (Hill et al. 1991; Westerterp 1993).

Nonetheless, long-term energy flux stability is the integrated result of the intra- and inter-day fluctuations in both energy/macronutrient intake and energy expenditure that lead to either slightly

positive or negative energy/macronutrient balance. Such short-term variations in the energy balance are buffered by rapid adjustment of carbohydrate and protein oxidation and fat storage (Abbott et al. 1988). Thus, states of negative energy balance, in which the energy intake is lower than its demand, are mostly compensated by net fatty acid release from fat stores that cope energy deficit. Conversely, positive energy balance states, in which energy intake is greater than its demand, lead to net fatty acid storage in adipose tissue (Frayn 2002). Carbohydrate and protein oxidation follows their respective fluctuations in carbohydrate and protein dietary availability (Abbott et al. 1988). These aforementioned concepts have critical implications for understanding of obesity, where particular modifications in macronutrient balance without significant changes in energy balance have no impact on body weight.

A number of mechanisms have evolved to compensate restricted energy intake, including increased *appetite* and lower metabolic rate (Prentice et al. 1991). When negative energy balance extends for longer periods, metabolic adaptation includes increased *energy efficiency* in order to prevent further weight loss (Rosenbaum et al. 2005; Redman et al. 2009; Goldsmith et al. 2010). On the contrary, increased energy intake normally results in suppression of appetite and eventual reduction in the efficiency of energy production (Stock 1999). Interestingly, *metabolic adaptation* to energy availability appears to be more efficient in preventing energy depletion than in preventing body weight gain.

Thus, in individuals that gain weight, the finely tuned interplay of metabolic and behavioral adaptations aimed to ensure appropriate balance between energy supply, storage, and utilization is overwhelmed by constant macronutrient surplus. The nature and identity of external (e.g., food availability and composition, social and environmental cues) and internal (e.g., genetic and epigenetic background, physiological and pathological determinants) factors sustaining long-lasting positive energy balance are still puzzling the scientific community (Speakman 2013).

Obesogenic environment undoubtedly plays a role. For instance, Swinburn et al. estimated that most of the positive energy gap and excess body weight over the past three decades can be entirely accounted by the higher food energy availability (Swinburn et al. 2009). Decreased energy expenditure may also contribute to positive energy balance. Few decades ago, it was postulated that basal energy expenditure (i.e., the minimal energy needed for vital functions) was lower in obese versus lean individuals, suggesting that decreased energy utilization contributes to the obese phenotype. Nowadays, it is accepted that these findings must be interpreted under the concept that the relationship between body mass (in kg) and *metabolic rate* (kcal per day) is *allometric* (i.e., metabolic rate and body mass do not change in direct proportion) (Poehlman and Toth 1995). As a consequence of this fact, metabolic rate ($kcal \cdot kg^{-1}$) of obese individuals will expectedly be lower than that of leaner individuals (Tschop et al. 2012; Speakman et al. 2013). Concordantly, proper analysis of lean versus obese individuals has consistently showed similar metabolic rates between them, which suggests that cellular energy homeostasis is not significantly influenced by obesity.

Nevertheless, most of the comparisons of the energy expenditure between lean and obese individuals have been reported in the literature taking into account their differential body mass and composition. It is known that organ mass, particularly of high metabolic rate organs (the liver, brain, and heart), significantly influences whole-body metabolic rate (Wang et al. 2001; Javed et al. 2010; Muller et al. 2013). In addition, individual *organ size* does not proportionally correlate with whole-body mass (Muller et al. 2011). This aspect can be particularly relevant in the well-described, but otherwise not well-understood, metabolic adaptation in response to weight loss (Bosy-Westphal et al. 2009). Therefore, analysis of metabolic rate by taking into account organ size between lean and obese as well as in response to changes in whole-body energy flux is required for a better understanding of the mechanisms linking chronic energy unbalance and obesity.

3 Carbohydrate Metabolism in Obesity

3.1 Overview of Glucose Metabolism

Carbohydrate is normally the main source of dietary energy for humans, and glucose is the major energy substrate for cells. Red blood cells lack *mitochondria* and thus depend exclusively on *glucose* for energy provision. Similarly, although due to other mechanisms, the brain and renal medulla also rely primarily on glucose as their energy source. Indeed, the sole brain, due to its high metabolic rate [~20 % of whole-body basal metabolic rate (Rolfe and Brown 1997)], requires ~100 g per day of glucose (A Report of the Panel on Macronutrients et al. 2002).

Dietary carbohydrate and glucose intake fluctuate over 24 h, being null during the sleeping time and episodic over the awaking period. On the other hand, cells have continuous glucose requirements. This metabolic conundrum is compensated by a complex neuroendocrine regulatory system that provides constant glucose supply while prevents *hyperglycemia* after meals and *hypoglycemia* over the fasting periods (Mizgier et al. 2014).

After a standard glucose load in healthy humans, ~70 % and ~20 % of this glucose are taken up by peripheral (mainly skeletal muscle) and splanchnic (mainly liver) tissues, respectively (Ferrannini et al. 1985). This efficient glucose uptake buffers the massive increase in blood glucose levels that otherwise dietary glucose will impose. In fact, both insulin-dependent and insulin-independent glucose uptake (Baron et al. 1988) in coordination with increased *glucose oxidation* and *glycogen* synthesis prevents postprandial hyperglycemia. Thus, high blood glucose concentration is the main driver of hepatic glucose uptake (Ferrannini et al. 1985), while hyperinsulinemia is the main promotor of *glucose uptake* and utilization in the skeletal muscle (Ferrannini et al. 1985; Baron et al. 1988). Postprandial suppression of hepatic *glucose production* is also a major mechanism to prevent hyperglycemia and maintaining glycemia within a physiological range (Ferrannini et al. 1985; Bonuccelli et al. 2009).

In contrast, under conditions of null exogenous glucose supply, the concentration gradient of glucose between the extra- and intracellular compartments is sustained by the ability of the liver to release glucose into circulation. This process is accomplished through hydrolysis of hepatic glycogen and the conversion of specific metabolites (lactate, pyruvate, glycerol, and some amino acids) to glucose (Brosnan 1999). Concomitantly, other tissues such as skeletal muscle spares glucose by adapting its energy demand to alternative energy substrates (e.g., fatty acids) (Cahill 2006).

Finally, energy sufficiency at cellular, organ, and whole-body level is achieved after adapting fuel oxidation to fuel availability, a process known as *metabolic flexibility* (Galgani et al. 2008b). In this metabolic scenario, insulin plays a pivotal role in determining fuel partitioning, so dietary macronutrient availability matches their oxidation rate.

3.2 Glucose Uptake/ Phosphorylation

Glucose uptake occurs through facilitated transport in a process involving 14 *glucose transporter* (GLUT) isoforms (Thorens and Mueckler 2010). *GLUT1* is expressed ubiquitously and is constitutively located in plasma membrane. *GLUT2* is present in the *pancreatic beta* (β) *cells*, hepatocytes, and basolateral membrane of intestinal and kidney epithelial cells. Its high capacity for glucose transport allows translocation of glucose between the extra- and intracellular compartments depending on glucose concentration gradient. GLUT2 also mediates the efflux of glucose from the liver into the circulation under conditions of limited exogenous glucose supply. *GLUT3* is expressed in the brain and has high affinity for glucose. This feature allows it to provide a relatively constant glucose supply to the neurons, even upon low extracellular glucose concentration. *GLUT4* is found in striated myocytes as

well as in adipocytes and is largely responsible for insulin-stimulated glucose uptake in those cells. In addition, GLUT4 translocation from the cytosol to the plasma membrane is also stimulated by muscle contraction, and this seems to be driven by a decrease in cellular oxygen concentration (Egan and Zierath 2013).

To prevent the outflow of newly incorporated glucose, this sugar is rapidly phosphorylated. This is an ATP-dependent reaction catalyzed by *hexokinases*. The isoform found in the liver (type 4 hexokinase, glucokinase) has relatively low affinity for glucose, with a K_m that doubles the fasting blood glucose concentration (~5 mM). This kinetic feature allows hepatocytes to phosphorylate glucose that massively comes from intestine after meals. Once glucose is converted to glucose-6-phosphate (G6P), it has two major metabolic fates: (i) glycolytic oxidation to *pyruvate* and further conversion to *lactate* (anaerobic condition) or oxidation to acetyl-CoA (aerobic condition) and (ii) conversion to glucose-1-phosphate (G1P), the precursor of glycogen synthesis.

Under non-insulin-stimulated conditions (e.g., overnight fasting), circulating glucose is mostly taken up by nonskeletal muscle tissues (e.g., central nervous system), with about 20 % being cleared up by the skeletal muscle (Baron et al. 1988). Interestingly, both lean and obese individuals have similar glucose clearance rates (Kelley et al. 1999a), which is consistent with the observation that most of the glucose uptake in *fasting* conditions relies on insulin-independent mechanisms. Concordantly, the transport of a non-metabolizable glucose analog (3-*O*-methylglucose) (Dohm et al. 1988) and the content of G6P (Allenberg et al. 1988) were similar in muscle biopsies from lean and obese donors.

Under insulin-stimulated conditions, Bonadonna et al. compared glucose uptake at different insulin doses (4–400 $mU \cdot m^{-2} \cdot min^{-1}$) in lean and obese volunteers by the glucose clamp procedure (Bonadonna et al. 1990). They found that insulin dose-response curve was right shifted in obese when compared with lean individuals indicating impaired insulin action. Laakso et al. (Laakso et al. 1990) reported that the most important contributor to the decreased whole-body glucose uptake in obese patients was the diminished insulin-stimulated glucose clearance by skeletal muscle. At the molecular level, insulin-stimulated *GLUT4 translocation* is quantitatively lower in insulin-resistant obese individuals versus their normal counterparts, which is consistent with the impaired insulin-stimulated *glucose transport* detected in muscle biopsies of obese versus lean subjects (Dohm et al. 1988; Goodyear et al. 1995).

In response to a dietary challenge (i.e., ingestion of a fixed glucose dose or a mixed meal) and in contrast to the *glucose clamp* method, on which a fixed insulin dose is infused and the administered glucose is continuously adjusted so euglycemia is maintained, whole-body glucose uptake mostly depends on the capacity of pancreatic beta (β) cells to release as much insulin as required to compensate any eventual defect on insulin action in tissues. Thus, in obese individuals with normal beta (β)-cell function, hyperinsulinemia might well be sufficient to compensate the defect in peripheral insulin action and maintain normal glucose uptake (Fig. 1). However, contrary to this prediction, (Baron et al. 1990) found that both whole-body and skeletal muscle glucose uptake were both reduced after an oral glucose dose (1 g per kg body weight) in obese when compared with lean individuals (Laakso et al. 1990).

3.3 Glycolysis and Oxidation

The *glycolytic* processing of one mole of G6P yields two moles of pyruvate and two moles of ATP (net production). In turn, pyruvate can be converted to lactate through the action of *lactate dehydrogenase* or oxidized to acetyl-CoA through the action of the mitochondrial *pyruvate dehydrogenase* complex (PDH). In the mitochondria, acetyl-CoA is integrated in the *tricarboxylic acid* (TCA) cycle, and its oxidation results in the release of CO_2 and the generation of reducing equivalents (NADH and $FADH_2$). The energy contained in these molecules is used to build an

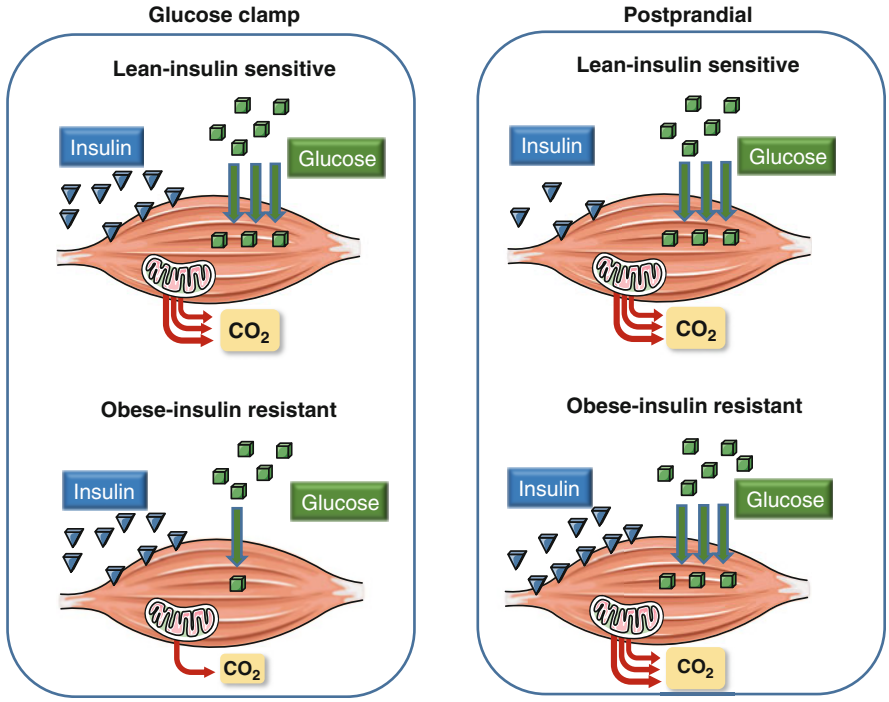

Fig. 1 The figure represents glucose uptake in lean, insulin-sensitive and obese, insulin-resistant individuals under two insulin-stimulated conditions: glucose clamp (supraphysiological) and postprandial (physiological). In the glucose clamp, insulin-stimulated glucose uptake is by definition impaired in insulin-resistant versus insulin-sensitive subjects. This leads to diminished intracellular glucose utilization and glucose oxidation (CO_2 production). Instead, in the postprandial condition, circulating insulin concentration eventually compensates any defective tissue insulin action, which might even prevent the decrease in glucose uptake and further glucose oxidation. Thus, during the glucose clamp condition, insulin resistance is manifested by decreased glucose uptake and oxidation at a similar circulating glucose and insulin concentration. In turn, in the postprandial condition, insulin resistance is mainly characterized by hyperinsulinemia with eventually normal glucose utilization

H^+ gradient across the internal membrane of the mitochondria and ultimately drive mitochondrial ATP synthesis.

There is a plethora of studies aimed to assess whole-body and skeletal muscle glucose oxidation as well as the ratio between glucose-to-fat oxidation in obese patients in comparison with lean individuals (Galgani et al. 2008b). Most of these studies have been conducted in fasted individuals, which is hardly distinguishable whether the reported differences among obese and lean subjects correspond to intrinsic metabolic alterations of obesity or are merely result from inaccurate control of previous dietary and metabolic conditions. Interestingly, when macronutrient intake and energy balance were carefully controlled, fasting respiratory quotient, measured in a *respiratory chamber* for 48 h, was similar in obese and lean subjects (Weyer et al. 2001).

Regarding *postprandial* conditions, we assessed whole-body glycolysis and glucose oxidation rates in insulin-sensitive and insulin-resistant individuals, defined by the glucose clamp technique (Galgani and Ravussin 2012). In this study, the insulin-resistant group also resulted to be heavier than the insulin-sensitive group (29 ± 4 [SD] vs. 25 ± 4 $kg \cdot m^{-2}$, respectively). Despite these contrasting characteristics, whole-body glycolysis and glucose oxidation over 4 h of ingesting a standard oral glucose dose were similar between groups. In line with this finding, no differences in the oxidative disposal of glucose and other macronutrients in obese compared to lean subjects were observed

over an 8-h feeding protocol (Owen et al. 1992). Using a more prolonged feeding paradigm (96 h), McDevitt et al. (McDevitt et al. 2000) delivered a hypercaloric diet (50 % excess energy over individuals' energy requirements) to lean and obese volunteers and monitor them in a whole-body metabolic chamber. Interestingly, both groups showed a similar capacity to handle energy excess, with macronutrient oxidative disposal remaining similar between groups.

Whole-body glucose oxidation has also been assessed during *euglycemic-hyperinsulinemic clamp* conditions, where the extent at which RQ increases upon insulin stimulation is used as a marker of metabolic flexibility (Galgani et al. 2008b). It has been reported that insulin resistance is accompanied by an impaired ability to increase whole-body and muscle-specific glucose oxidation in the clamping, indicating metabolic inflexibility (Kelley et al. 1999b; Galgani et al. 2008a) (Fig. 1). On the other hand, improvement of *insulin sensitivity*, for example, after weight loss, is paralleled by enhanced metabolic flexibility (Kelley et al. 1999a; Galgani et al. 2008a). Traditionally, these findings have been considered a feature of intrinsic cellular defects, mostly at the mitochondrial level, owing to reduced ability to switch off lipid oxidation and simultaneously switch on glucose oxidation in the transition from fasting to insulin-stimulated conditions (Muoio 2014).

An alternative explanation for the impaired capacity to raise glucose oxidation over lipid oxidation that insulin-resistant individuals exhibit in the glucose clamping is that this phenomenon results from the lower intracellular glucose availability of these individuals in comparison with insulin-sensitive subjects (Galgani et al. 2008a) (Fig. 1). Indeed, when insulin-stimulated glucose disposal rate was taken into account, the increase in the RQ remained equivalent in obese, nondiabetic vs. obese, type 2 diabetic patients. In addition, similar metabolic flexibility after correcting for insulin-stimulated glucose disposal rate was also observed when obese, type 2 diabetic patients were studied before and after a one-year weight loss intervention (Galgani et al. 2008a).

Another aspect deserving further analysis is the observation that obese vs. lean individuals show relatively elevated blood lactate levels (Lovejoy et al. 1990, 1992). In fact, obesity and insulin resistance are both independently associated with increased *lactacidemia* (Galgani et al. 2013; Adeva-Andany et al. 2014). Furthermore, direct assessment of lactate turnover showed increased conversion of lactate to glucose and from glucose to lactate in obese vs. lean children (Stunff and Bougneres 1996). The pathophysiological relevance of this finding and its mechanistic basis remain unclear. At the molecular level, the ability to convert pyruvate to lactate or acetyl-CoA is pivotal for cellular metabolic flexibility. In this regard, an animal model having defective PDH activity (by hyperacetylation of PDH E1 alpha (α) subunit) has impaired metabolic flexibility, reduced glucose oxidation, enhanced lactate production, and higher fatty acid oxidation even in the fed state (Jing et al. 2013). Future studies should focus in investigating the molecular basis of metabolic inflexibility as well as its pathophysiological meaning.

3.4 Glucose Storage

Conversion of *G6P* to *G1P* is mediated through *phosphoglucomutase*. G1P is then converted to uridine diphosphate (UDP) glucose and finally bounded to a growing glycogen polymer. Insulin stimulates glycogen synthesis by relieving the inhibition that *glycogen synthase kinase 3* exerts on *glycogen synthase*. Also, insulin-mediated GLUT4 translocation to plasma membrane results in higher glucose flux and thus higher availability of the substrates for glycogen synthase action (Yki-Jarvinen et al. 1987). Glycogen is synthesized by both the liver and skeletal muscle. The former has a higher content per gram of wet tissue, whereas the latter has a greater contribution to total body glycogen because of its larger contribution to the body mass (~50 % of fat-free mass in adult individuals).

Hepatic glycogen has a systemic role because it contributes to sustain hepatic glucose production and normoglycemia during periods of fasting.

In contrast, skeletal muscle glycogen mostly sustains local ATP production during contraction. Under conditions of limited exogenous glucose supply, glycogen is hydrolyzed in order to increase G6P supply, which is then converted to glucose by action of *glucose-6-phosphatase* in the liver. G6P cannot be converted to glucose in skeletal muscle because it lacks glucose-6-phosphatase, so G6P is metabolized to pyruvate. It has been reported that obese individuals have decreased glycogen synthase activity under fasting conditions, although muscle glycogen content remained unaltered (Allenberg et al. 1988).

Under glucose clamp conditions, *non-oxidative glucose disposal*, mostly dependent on glycogen synthesis, is decreased in obese when compared with lean individuals (Young et al. 1988), possibly owed to decreased intracellular glucose availability and lower insulin-dependent *glycogen synthase* activity (Cline et al. 1999; Hojlund et al. 2009). However, under feeding conditions, whole-body non-oxidative glucose disposal was similar in lean and obese females studied for 96 h in a whole-body metabolic chamber (McDevitt et al. 2000).

3.5 Hepatic Glucose Production

Hepatic cells can produce glucose out of two different mechanisms: (i) *glycogenolysis*, i.e., hydrolysis of stored glycogen, and (ii) *gluconeogenesis*, i.e., de novo glucose production out of nonsugar precursors. Conditions of limited exogenous glucose supply are characterized by low blood insulin-to-glucagon ratio. This hormonal milieu promotes glycogenolysis as well as gluconeogenesis. Biochemically, gluconeogenesis follows the reverse glycolytic flux, although some reactions are exclusive for glycolysis (i.e., glucose phosphorylation and the synthesis of fructose-6-phosphate and phosphoenolpyruvate). Thus, gluconeogenesis requires specific energy-demanding enzymes to convert precursors such as pyruvate, alanine, lactate, and glycerol to glucose.

Increased basal (fasting) hepatic glucose production as well as impaired ability of insulin to suppress this process is observed in obese individuals (Bonadonna et al. 1990). Epidemiological studies have consistently found a direct correlation between abdominal obesity and insulin resistance and its systemic consequences, the so-called metabolic syndrome. However, at the tissue level, intrahepatic rather visceral fat associates with impaired hepatic glucose control (Fabbrini et al. 2009). These findings suggest that the metabolic dysfunction of the liver, more than any other intra-abdominal organ, is central in the pathogenesis of insulin resistance. In concordance with this hypothesis, the surgical removal of *visceral adipose tissue* appeared to have little impact on insulin sensitivity in humans (Fabbrini et al. 2010; Dunn et al. 2012; Lima et al. 2013). The fact that less than 20 % of portal vein *free fatty acids* (FFA) comes from visceral fat in lean and obese humans while ~10 % of the total FFA found in peripheral blood circulation is derived from visceral fat challenges any causative role of visceral fat on metabolic disturbances (Nielsen et al. 2004).

3.6 De Novo Lipogenesis

Although the main metabolic fates of glucose are oxidation or glycogen synthesis, under special metabolic circumstances, glucose can also be converted into palmitate, the main product of endogenous fatty acid synthesis pathway. Oxidation of acetyl-CoA in the mitochondria originates citrate, a TCA intermediary. Under conditions of excess glucose supply, citrate leaves the mitochondria and is converted to acetyl-CoA and oxaloacetate by the action of citrate lyase in the cytosol. Acetyl-CoA is then carboxylated to *malonyl-CoA* in a reaction stimulated by insulin and catalyzed by acetyl-CoA carboxylase. Malonyl-CoA is the substrate of fatty acid synthase that generates palmitate in a multistep sequence of NADPH-dependent reactions. Therefore, *de novo lipogenesis* (DNL) only occurs when cellular energy status is high (e.g., it requires of NADPH) and excess glucose is largely available.

Decades ago, it was postulated that DNL was partially responsible for increased adiposity of

obese patients, by converting carbohydrate excess in fat, particularly in those individuals eating *high-carbohydrate diets*. Acheson et al. (Acheson et al. 1988) evaluated the RQ of individuals consuming large amounts of glucose (500 g per day) and found that RQ values above 1.00 were transitorily observed, indicating that net DNL was minimal after short-term carbohydrate overfeeding.

Later studies based on the stable isotopic labeling of metabolic substrates aimed to quantify in vivo hepatic *very low-density lipoprotein* (VLDL) secretion as a marker of hepatic DNL. Using this approach, McDevitt et al. (2001) evaluated hepatic DNL after 4 days of overfeeding in lean and obese females in response to 50 % surplus of energy as glucose or sucrose. They found that hepatic DNL was stimulated at a similar extent in lean and obese individuals regardless of carbohydrate type. Total hepatic DNL ranged between 0.7 and 4.5 $g \cdot day^{-1}$, equivalent to less than 3 % of the carbohydrate energy supply and less than 2 % of the total energy balance. Additional studies performed over shorter periods of time concluded that hepatic DNL is a process of minor metabolic relevance in humans (Hellerstein et al. 1996) and highlighted the potential role of adipose tissue in this process (Aarsland and Wolfe 1998). Thus, adipose tissue DNL was approached by deuterium incorporation in fatty acids and gene expression analysis of *lipogenic* enzymes in lean and obese individuals (Guo et al. 2000; Minehira et al. 2004). Overall, those studies showed that carbohydrate feeding did not stimulate adipose tissue DNL or expression of lipogenic enzymes at a greater extent in obese when compared with lean participants.

These findings can be interpreted under the consideration that fatty acids are largely available in human diets, and then there is no need for lipid synthesis from an alternative precursor. In addition, when carbohydrate is provided at a level below total energy needs, DNL does not play a metabolically relevant role. By contrast, the contribution of hepatic DNL to the total fatty acid pool in subjects with *nonalcoholic fatty liver disease*, a frequent condition in obese subjects with insulin resistance, appears significant as discussed below.

3.7 Fructose Metabolism and Obesity

Fructose is also a hexose abundant in human diet, although its presence in foods is mostly restricted to sucrose, honey, and fruits. Lately, with the introduction of a corn-derived product (*high-fructose corn syrup*) to many processed foods, fructose consumption has been drastically increased, especially in societies with elevated consumption of industrialized food stuffs (Bray and Popkin 2014). This situation has renewed the interest in fructose metabolism, in particular, its effect on human metabolic disease.

Fructose metabolism is unique in many aspects. For instance, fructose is primarily metabolized in the liver; therefore, its blood concentration is minimally increased after ingestion. Once inside hepatic cells, fructose is phosphorylated to *fructose-1-phosphate* through *fructokinase*, and two metabolites are generated: (i) dihydroxyacetone phosphate, which is a glycolytic intermediate, and (ii) glyceraldehyde, which can be converted to glycolytic intermediates. Because fructokinase is not subjected to allosteric control by cellular energy status, dihydroxyacetone and glyceraldehyde production will proceed according to fructose availability. Thus, fructose is quickly oxidized and spares glucose and fatty acids as energy fuels. In addition, it provides precursors for TAG synthesis.

In line with these particular metabolic properties, elevated blood TAG concentration and exacerbated visceral and *ectopic fat* accumulation were detected in humans fed with large doses of fructose versus glucose for several weeks (>100 g per day) (Stanhope and Havel 2009; Stanhope et al. 2009). However, fructose can also speed up hepatic glucose metabolism because fructose-1-phosphate prevents the inhibition of hexokinase, which leads to enhanced glycolytic disposal and hepatic insulin sensitivity (Hawkins et al. 2002). Indeed, some authors have reported that small doses of fructose consumed in a meal (~20 g) may have beneficial impact on glycemic control (Sievenpiper et al. 2012).

The role of fructose on human metabolic regulation and disease remains highly controversial,

with some authors proposing that dietary fructose is intrinsically harmful for humans (Bray and Popkin 2014), whereas others postulate that energy overconsumption is the major factor leading to metabolic disturbances, regardless of the energy source (Kahn and Sievenpiper 2014).

4 Fat Metabolism in Obesity

4.1 Overview of Fat Metabolism

Fats are integral components of all cellular systems and fulfill energetic, structural, and regulatory roles. Fatty acids and *cholesterol* are the most abundant dietary lipids. Dietary fatty acids are mostly found as TAG in WAT, which is able to store a vast amount of energy (~7,000 kcal/kg). Because of its ability to buffer short- and long-term fluctuations in calorie intake, WAT is a major evolutionary adaptation against starvation in vertebrates. WAT also secretes a variety of endocrine factors, called *adipokines*, which integrate whole-body energy balance, feeding behavior, basal metabolic rate, insulin sensitivity, and vascular function. WAT also regulates fertility, mating selection, offspring growth, immune function, and even bone accrual (Norgan 1997; Trujillo and Scherer 2006).

Fatty acid oxidation fulfills 25–45 % of daily energy needs in humans, which in an average healthy adult represents about 60–110 g of fat per day. Unlike fatty acids, cholesterol cannot be oxidized for energy production and can only be converted to derivative sterols, steroids, and biliary acids for disposal. Abnormal lipid accumulation in non-adipose tissues, such as blood, muscle, and the liver, is a frequent abnormality in obesity, and it is possibly connected with the insulin resistance present in these individuals (McGarry 2002).

Dietary TAG is hydrolyzed in the lumen of small intestine by *pancreatic lipase*, and the released fatty acids are absorbed and reesterified by enterocytes into TAG. Small intestine incorporates this TAG and other lipid nutrients and vitamins in *chylomicrons*, which ultimately reach systemic circulation. Upon extracellular hydrolysis mediated by *lipoprotein lipase* (LPL), chylomicrons deliver their lipid load mostly to the WAT, skeletal muscle, and heart. Finally, chylomicron remnants are cleared by the liver. In turn, hepatocytes incorporate TAG into secreted VLDL, which can then be hydrolyzed by LPL and the released FFA taken up by WAT and muscle.

LPL is located on the endothelial surface of WAT capillaries and is potently regulated by insulin. Circulating as well as LPL-released FFA are internalized by a number of binding proteins present in the plasma membrane of adipocytes, including the scavenger receptor *FAT/CD36* and members of *fatty acid transport protein* (FATP) family (Hajri and Abumrad 2002). Importantly, whereas FAT/CD36 is abundant in adipose tissue and skeletal muscle, it is expressed at very low levels in the adult liver. Inside the cell, fatty acids are rapidly esterified with coenzyme A (CoA) by the action of *acyl-CoA synthetase*. Acyl-CoAs are then esterified to glycerol-3-phosphate backbone for glycerolipid and glycerophospholipid synthesis in a series of reactions catalyzed by acyltransferases and phosphatases. In the muscle and liver, acyl-CoAs are mainly destined to mitochondrial beta (β)-oxidation for ATP synthesis. In the *brown adipose tissue*, acyl-CoAs are burnt out for heat generation upon cold and/or adrenergic stimulation (Ravussin and Galgani 2011). Fatty acids can also be esterified to sphingosine to form *ceramide*. Some of these lipids (e.g., *diacylglycerol*, DAG, and ceramide) are well-characterized second messengers in signaling pathways and have been consistently implicated in the pathogenesis of insulin resistance (Coen and Goodpaster 2012).

In fasted individuals, circulating FFA are the main source for the synthesis of hepatic TAG, and they constitute the bulk of fatty acids incorporated in TAG of secreted VLDL particles (Parks et al. 1999). In addition, low insulin-to-counter-regulatory hormone ratio triggers intracellular lipolysis of TAG in adipocyte *lipid droplets*. FFA are released to the extracellular space and circulate bound to plasma proteins, mostly albumin. Then, FFA are taken up in non-adipose tissues for reesterification, oxidation, or hepatic conversion to ketone bodies.

At the transcriptional level, endogenous fatty acid and TAG synthesis are mostly regulated by *sterol regulatory element-binding protein* (*SREBP*) *1c*, *carbohydrate-responsive element-binding protein* (*ChREBP*), and *peroxisomal proliferator-activated receptor* (*PPAR*) *gamma* (*γ*). Although SREBP1c, ChREBP, and PPAR gamma (γ) have extensively overlapped control of gene expression of enzymes involved in lipogenesis, they diverge on their primary regulatory stimuli, suggesting cooperative rather than redundant physiological roles. In fact, while SREBP1c is regulated by insulin, ChREBP is responsive to glucose, and PPAR gamma (γ) appears to be directly regulated by fatty acids.

PPAR gamma (γ) is the only lipogenic transcriptional regulator that is currently targeted by drugs approved for clinical use. In fact, *thiazolidinediones* (*pioglitazone* and *rosiglitazone*) are effective insulin sensitizers used in type 2 diabetic patients. Ironically, PPAR gamma (γ) endogenous ligand still remains unknown. It is possible that some of proposed lipid ligands identified in in vitro assays (polyunsaturated fatty acids and prostanoids) correspond to physiological agonist/antagonist of this nuclear receptor; however, the support for this assertion is circumstantial. By contrast, 1-palmitoyl-2-oleoyl-*sn*-glycerol-3-phosphocholine was recently identified as the endogenous ligand of PPAR alpha (α) isoform in the liver of mouse (Chakravarthy et al. 2009).

Whereas all these three transcriptional regulators are expressed in the human adipose tissue, only SREBP1c and ChREBP are present in the normal liver. By contrast, upon steatotic conditions, hepatic PPAR gamma (γ) is increased at the mRNA and protein level (Browning and Horton 2004). It is plausible that PPAR gamma (γ) ectopic expression further contributes to the excessive TAG accumulation and abnormal gene expression observed in *nonalcoholic fatty liver disease* (Gavrilova et al. 2003; Matsusue et al. 2003). The extent at which these metabolic pathways proceed will determine tissue lipid balance and insulin action on critical tissues such as the liver and skeletal muscle.

4.2 Fatty Acid Uptake

After extracellular LPL-mediated hydrolysis of TAG, resulting FFA are taken up by tissues through FATPs that facilitate fatty acid influx from extra- to intracellular compartment (Bonen et al. 2007). Then, fatty acids bind to cytosolic fatty acid-binding proteins for intracellular transport and utilization (Glatz et al. 2010). At the physiological level, both LPL and FAT/CD36 are critical determinants of fatty acid uptake. Mice with specific overexpression of LPL in the skeletal muscle show reduced levels of circulating TAG along with increased muscle fatty acid uptake and augmented *peroxisomal* and mitochondrial proliferation. Importantly, these metabolic changes were accompanied by progressive myopathy (Levak-Frank et al. 1995), indicating cellular toxicity triggered by excessive tissue lipid accumulation. Although FFA (Levak-Frank et al. 1995) and TAG (Hoefler et al. 1997) levels were increased in skeletal muscle of these mice, the effect of muscle LPL overexpression on insulin resistance remains uncertain as animals with different genetic backgrounds have divergent phenotypes (Jensen et al. 1997; Ferreira et al. 2001; Voshol et al. 2001). In addition, specific liver or muscle LPL overexpression led to elevated intrahepatic or intramuscular TAG contents as well as accumulation of *long-chain acyl-CoAs*, DAG, and ceramides. In addition, these three lipid species were directly correlated with tissue-specific insulin resistance (Kim et al. 2001).

FAT/CD36 may also determine tissue lipid load as suggested from a mouse knockout model (Hajri and Abumrad 2002), which shows reduced VLDL clearance and muscle fatty acid uptake while increased plasma TAG levels. Noteworthy, FAT/CD36 deficiency determined reduced muscle TAG content and increased *DAG-to-TAG* ratio (Coburn et al. 2000; Goudriaan et al. 2005). Such changes were associated with improved skeletal muscle insulin sensitivity but, unexpectedly, impaired hepatic insulin sensitivity (Goudriaan et al. 2003). Conversely, skeletal muscle-specific FAT/CD36 overexpression elevated plasma glucose and insulin concentrations,

which suggests impaired insulin-dependent glucose homeostasis (Ibrahimi et al. 1999).

In humans, the assessment of tissue fatty acid uptake has been restricted to skeletal muscle and adipose tissues. In vitro determinations performed in giant sarcolemmal vesicles have suggested that obese and type 2 diabetic patients have increased fatty acid uptake as well as increased membrane-associated FAT/CD36 and intramuscular TAG content (Bonen et al. 2004). However, gene expression analysis of muscle FATP has showed inconsistent results in both lean and obese individuals (Simoneau et al. 1999; Bonen et al. 2004; Pelsers et al. 2007). On the other hand, in vivo studies found similar skeletal muscle fatty acid uptake rate in fasted and insulin-stimulated lean and obese subjects (Kelley et al. 1999a).

4.3 Fatty Acid Oxidation

Fatty acids are the main metabolic fuel for oxidation in the transition from fed to fasted condition. Fatty acid oxidation is regulated at three enzyme-mediated steps: (i) fatty acid activation to acyl-CoA in cytosol, (ii) acyl-carnitine translocation to the mitochondrial matrix (catalyzed by *carnitine palmitoyltransferase* [*CPT*] *1*), and (iii) mitochondrial beta (β)-oxidation through four sequential enzymatic reactions.

Impaired fatty acid oxidation attributed to mitochondrial abnormalities has been postulated as a major driver of muscle and hepatic fat accumulation leading to insulin resistance (Kelley and Mandarino 2000; Shulman 2014). In line with this hypothesis, Kim et al. found reduced palmitate (CPT1-dependent) and *palmitoyl-carnitine* (CPT1-independent) oxidation as well as lower CPT1 activity in muscle biopsies from obese versus lean donors (Kim et al. 2000). In vivo human studies have only partially corroborated this finding (Galgani et al. 2008b). On the other hand, experimental inhibition of in vivo fatty acid oxidation through administration of *etomoxir* (a drug that decreases CPT1 activity) led to expectedly higher glucose-to-fat oxidation ratio, which was accompanied by higher sarcolemmal GLUT4 content and lower circulating glucose, indicative of enhanced insulin sensitivity. In turn, etomoxir-treated mice had increased muscle TAG and DAG content in parallel with improved insulin-stimulated GLUT4 translocation (Timmers et al. 2012). Taken together, these findings suggest that reduced fat oxidation does not necessarily impair insulin sensitivity by itself.

4.4 Fatty Acid Turnover

Fatty acids are stored as TAG in lipid droplets, which are dynamic structures that appear to regulate intracellular fatty acid trafficking (Walther and Farese 2012). Thus, the signaling cascade mediating lipolysis converges in the elevation of intracellular cAMP and activation of protein kinase A. This enzyme phosphorylates lipid droplet-associated protein perilipin to allow *adipose TAG lipase* (ATGL, also known as patatin-like phospholipase domain-containing protein 2 and desnutrin) to physically interact with the lipid droplet surface and hydrolyze TAG in the *sn*-1 position (Zimmermann et al. 2004). Resulting *sn*-2,3 DAG is subsequently hydrolyzed by hormone-sensitive lipase and monoacylglycerol lipase (Walther and Farese 2012; Badin et al. 2013).

The balance between glycerolipid synthesis and intracellular lipolysis ultimately determines tissue lipid balance as well as the synthesis of lipid intermediates (Badin et al. 2013). Thus, the increase in lipolytic rates led to higher fatty acid availability as well as de novo ceramide synthesis in a muscle cell line overexpressing ATGL (Liu et al. 2007). Alternatively, incomplete TAG hydrolysis might also favor DAG accumulation (Badin et al. 2011).

The relevance of fatty acid turnover is highlighted by studies showing that whole-body adiposity associates directly with *intramyocellular lipid* content, but not with muscle content of DAG or ceramide (Moro et al. 2009). Thus, muscle-specific lipid metabolism is a determinant of muscle fatty acid turnover that is independent of total body adiposity level. In this regard, the

DAG-to-TAG hydrolase activity ratio (an index of incomplete TAG hydrolysis) seems to be lower in obese individuals, which is accompanied by increased muscle ceramide and DAG content as well as impaired insulin sensitivity (Itani et al. 2002; Moro et al. 2009).

4.5 Consequences of Altered Tissue Lipid Balance

Obesity is characterized by increased WAT mass at the subcutaneous and intra-abdominal level. As mentioned above, obese people commonly have augmented tissue lipid accumulation in the liver, skeletal muscle, and heart (Shulman 2014). It appears that elevated fat content in ectopic versus eutopic (i.e., WAT) location is more deleterious for whole-body and tissue metabolic homeostasis. In fact, clinical and experimental observations suggest that excessive fat accumulation in non-adipose cells is causative of insulin resistance in obese individuals (Krssak et al. 1999; McGarry 2002; Virtue and Vidal-Puig 2008; Moro et al. 2009). Upon this hypothesis, chronic caloric overload results in a series of pathologic changes in the WAT, including exaggerated *hypertrophy* of adipocytes, activated immune cells infiltration, abnormal vascular supply, and fibrotic extracellular matrix (Rutkowski et al. 2015). This pathologically remodeled adipose tissue lacks the ability to fully expand and thus leaks fatty acids toward cells and tissues that are not adapted to store massive amounts of these molecules (Rutkowski et al. 2015).

In support of this hypothesis, type 2 diabetic patients have increased intramyocellular TAG content (Anastasiou et al. 2009; Nielsen et al. 2010) as well as postprandial hepatic and skeletal muscle fat storage (Ravikumar et al. 2005). These findings are in line with the observation that intrahepatic fat correlates with impaired glucose tolerance, systemic insulin resistance, and increased circulating levels of enlarged VLDL particles (Despres 1998; Adiels et al. 2006; Fabbrini et al. 2009).

Interventions that decrease ectopic tissue lipid load are usually associated with improved insulin sensitivity, further supporting the role of excessive lipid levels in insulin resistance pathogenesis. For instance, thiazolidinediones reduce plasma FFA concentration and liver TAG content while enhancing insulin-stimulated glucose disposal rate in type 2 diabetic subjects (Mayerson et al. 2002; Promrat et al. 2004). Importantly, the role of *exercise*, a well-established insulin-sensitizing tool, on intramuscular TAG remains controversial. Some studies have shown that physical training decreases intramyocellular TAG (Bergman et al. 1999), whereas others found the opposite result (Hoppeler et al. 1985). What seems to be consistent is that the increased intramyocellular lipid content normally observed in endurance-trained *athletes* does not associate with impaired muscle insulin sensitivity, and this phenomenon has been referred as the athlete's paradox (Goodpaster et al. 2001).

Ectopic fat accumulation is also instrumental to explain why lipodystrophic patients, who have severe paucity of adipose tissue mass, show severe insulin resistance. These individuals are characterized by substantial accumulation of lipids in the liver and skeletal muscle (Gan et al. 2002; Simha et al. 2003). Remarkably, *leptin*, the most potent insulin sensitizer for patients with generalized lipodystrophy, also decreases lipid overload in the liver and skeletal muscle (Oral et al. 2002; Simha et al. 2003).

5 Protein Metabolism in Obesity

5.1 Overview of Protein Metabolism

Proteins are heterogeneous macromolecules with a broad range of molecular mass, structure, and functions. All the biological properties of proteins are determined by their unique sequence of amino acids. Amino acids are organic structures containing at least one atom of *nitrogen*. Essential amino acids, i.e., those that cannot be synthesized in human cells, and nitrogen must be obtained from diet to match amino acid requirement for protein synthesis.

Dietary *amino acids* as well as those derived from endogenous protein hydrolysis are significant energy substrates for humans, normally corresponding to 10–20 % (70–100 g per day) of total energy needs. As a by-product of amino acid oxidation, nitrogen is lost in urine, mainly in the form of *urea*, implying that amino acids undergoing oxidation must be replaced by dietary amino acids. Thus, the balance between protein degradation (mainly assessed by nitrogen loss in urine), synthesis, and intake is critical for preserving whole-body lean mass.

Dietary amino acids reach the liver via portal vein, and a significant proportion is retained by hepatic tissue. Interestingly, *branched-chain amino acids* (BCAA), i.e., *valine*, *leucine*, and *isoleucine*, are poorly metabolized by hepatocytes and are preferentially channeled to skeletal muscle for energy production as well as conversion into *alanine* and *glutamine*. These two latter amino acids are then released from muscle and taken up by the liver and other tissues for further utilization.

Amino acid turnover is dependent on the level of energy sufficiency that determines the extent at which amino acids are spared as energy source including the balance between protein synthesis and degradation. Insulin is a key regulator of this balance, although its effect depends on circulating insulin concentration. Thus, low circulating insulin concentration (similar to observed in insulin-sensitive fasted individuals) in the presence of elevated amino acid supply stimulates muscle protein synthesis without affecting skeletal muscle protein breakdown (Greenhaff et al. 2008). However, increasing blood insulin concentration does not further enhance protein synthesis, while it strongly suppresses protein degradation (Greenhaff et al. 2008).

At the molecular level, insulin increases AKT (also referred as PKB) activity, which then relieves the inhibition over *mammalian target of rapamycin* (mTOR). As a consequence, the activity of eukaryotic initiation factor-binding protein 1 (4E-BP1) and ribosomal protein S6 kinase (p70S6K) increases leading ultimately to higher protein synthesis. Insulin also decreases protein degradation by inhibiting *proteasome* activity (Chondrogianni et al. 2014).

5.2 Protein Turnover in Obesity

Theoretically, obesity-related hyperinsulinemia should promote protein accretion unless defective insulin action also extends to amino acid utilization. However, empirical demonstration of this proposition has resulted inconclusive. In fact, many studies have been carried out to compare whole-body and tissue-specific amino acid metabolism between lean and obese individuals. Some of these studies found that, in fasting condition, obese patients have increased protein degradation in comparison with lean individuals (Nair et al. 1983; Bruce et al. 1990; Welle et al. 1992; Chevalier et al. 2005); however, several other studies did not confirm that finding (Luzi et al. 1996; Solini et al. 1997; Guillet et al. 2009). Upon insulin stimulation, obese subjects have either impaired (Jensen and Haymond 1991; Luzi et al. 1996) or unchanged (Caballero and Wurtman 1991; Welle et al. 1994; Solini et al. 1997; Chevalier et al. 2005) suppression of protein degradation.

Regarding protein synthesis, similar controversial results also exist (Luzi et al. 1996; Solini et al. 1997; Chevalier et al. 2005, 2006; Guillet et al. 2009). Therefore, it is uncertain what role plays insulin resistance in amino acid and protein metabolism. Differences in study design (e.g., adjustment in protein kinetic by body size, relative versus absolute expression, insulin dose, duration, etc.) as well as in subject characteristics including *body fat distribution* (Jensen and Haymond 1991; Solini et al. 1997) can partly explain the lack of consistency across studies. Alternatively, insulin regulation of glucose and amino acid metabolism may not lie on the same molecular pathways or insulin dose-response kinetic.

5.3 Branched-Chain Amino Acids (BCAA) and Obesity

For over 50 years, it has been known that circulating BCAA concentration is elevated in human obesity (Newgard 2012). Even more, there is evidence suggesting that increased blood BCAA is

an independent risk factor for insulin resistance (McCormack et al. 2013) and *type 2 diabetes* (Wang et al. 2011); however, a mechanistic explanation of these findings is elusive (Lynch and Adams 2014). Importantly, Everman et al. recently challenged the notion that BCAA may actually be a causal determinant of insulin resistance. Thus, they found that a short-term infusion of BCAA in healthy individuals did not change insulin sensitivity (Everman et al. 2015). Still the question why blood BCAA is increased in obesity and what is its pathophysiological relevance remain unsolved. One possible explanation comes from the fact that most of dietary BCAA reach peripheral circulation, which prompts the idea that increased protein intake in obese individuals may lead to higher circulating BCAA. Indeed, there is a tight direct correlation between BCAA intake and blood BCAA concentration (Meguid et al. 1986a, b).

Impaired tissue clearance of circulating BCAA might also play a role. In this regard, decreased content of enzymes involved in the oxidation of BCAA in skeletal muscle biopsies of obese donors has been reported at the protein (Lefort et al. 2010) and the mRNA levels (Lackey et al. 2013). Furthermore, the content of *mitochondrial BCAA aminotransferase* and *branched-chain keto acid dehydrogenase subunit E1* (two important catabolic enzymes of BCAA) was increased after *gastric bypass*-induced weight loss in the WAT of obese individuals, and this was paralleled by a reduction in circulating BCAA concentration (She et al. 2007). Although the possible contribution of WAT to whole-body BCAA metabolism seems minor (Lackey et al. 2013), these studies suggest that high blood BCAA concentration in obesity may not just be a consequence of higher food/protein intake.

6 Concluding Remarks

Obesity is the result of a chronic mismatch between energy intake and expenditure. This unbalance challenges the capacity of the body to properly handle and dispose glucose and lipid macronutrients. Over the time, positive energy balance leads to a new steady state, set at a higher energy flux levels, in which macronutrient overflow matches macronutrient oxidation. Why when individuals reach this new steady state cannot resolve the metabolic disturbance associated with excessive adiposity remains unknown.

It is possible that abnormally high steady-state energy flux, attributed to increased body size rather than to elevated physical activity, might itself determine metabolic stress. On the other hand, tissue-specific metabolic disturbances may be undetectable when a whole-body approach is utilized. On this regard, the fact that whole-body macronutrient oxidative and non-oxidative disposal under physiological conditions (e.g., in the transition from fasting to feeding conditions or over a 24-h period) is fairly similar in lean and obese individuals may underscore subtle tissue-specific macronutrient unbalances.

It is very likely that our common notion of obesity as a single metabolic entity may be wrong. In fact, it has lately been described two types of obese individuals: the metabolically healthy and unhealthy obese (Samocha-Bonet et al. 2014). The identification of tissue, cellular, and molecular determinants of metabolic adaptation to high-energy fluxes will require the expansion of our capabilities to study in vivo tissue metabolic dynamics. It will be critical to identify the key biological features that promote metabolic stress during overfeeding and weight gain and understand the mechanisms underlying interindividual variation in the adaptation to overfeeding. Answering these questions should accelerate our comprehension of obesity-related metabolic disorders.

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Brain Regulation of Feeding and Energy Homeostasis

20

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Abstract

In the past decades, it has become clear that the brain plays a key role in the control of feeding and energy homeostasis. These are complex systems that require the integration of diverse physiological components, from sensing energy demands and storage to behavioral responses, motor function, and reflex adjustments. Studies in different organisms from worms to flies and rodents to humans have identified key molecular pathways, conserved genes, and neural circuits crucial for the understanding of the control of distinct components of energy homeostasis. Among them, the brain plays a fundamental role in food intake (e.g., meal frequency and size), energy expenditure, body weight and body composition, feeding behavior, satiety, reward or hedonic consumption, and glucose homeostasis. Although the brain function in metabolic control has been explored for almost a century, the discovery of leptin and its cognate receptor in the mid-1990s and advances in molecular and genetic tools propelled the field toward an unprecedented development. In this chapter, we will highlight the main findings in recent years using these scientific tools with emphasis on the brain pathways and circuitry associated with the control of the metabolic function.

Keywords

Hypothalamus • Neuroendocrinology • Autonomic nervous system • Melanocortin • Lateral parabrachial nucleus • Paraventricular nucleus of the hypothalamus • Arcuate nucleus • Mesolimbic dopaminergic system

1 Introduction

The fundamental role of the central nervous system (CNS) in the regulation of feeding and energy homeostasis has been known for decades. Clinical observations in patients with Fröhlich's syndrome (adiposogenital dystrophy) displaying excessive subcutaneous fat due to adenopituitary tumors gave rise to an important debate on the relative contributions of the pituitary gland versus the overlying hypothalamus in the genesis of the metabolic aspects of the syndrome (Fröhlich 1901). While Fröhlich, Crowe, and Cushing supported the importance of the pituitary gland in the adiposity, Aschner, a few years later, demonstrated that removal of the pituitary gland alone did not affect adiposity in dogs, suggesting that damage of the hypothalamus was the main cause of the obese phenotype seen in Fröhlich's syndrome (Crowe et al. 1910; Aschner 1912; Elmquist et al. 1999). With the development of experimental tools to lesion restricted areas of the brain, Hetherington and Ranson reinforced Aschner's findings and proposed a crucial role for the hypothalamus in food intake and body weight regulation (Hetherington and Ranson 1940). They observed that bilateral lesions of the medial hypothalamus of rats (without disturbing the pituitary gland) produced a profound increase in body weight and adiposity. On the other hand, lesions of the lateral hypothalamic area induced hypophagia leading to death by starvation, in some cases (Anand and Brobeck 1951). Together, these observations gave rise to the classic "dual center" model proposed by Stellar in 1954, comprised of a "satiety center" (i.e., the ventromedial nucleus of the hypothalamus, the VMH) and a "feeding center" (i.e., the lateral hypothalamic area, the LHA) (Stellar 1954).

These ideas were later revised with the development of more refined and precise techniques. For example, small electrolytic or excitotoxic lesions of the VMH and adjacent areas, knife cuts of projecting fibers, and subdiaphragmatic vagotomy challenged the concept of the VMH as the satiety center (King 2006; Gold 1973; Cox and Powley 1981). Concurrently, others questioned the interpretation of data from lesions of the LHA due to the potential interruption of the medial forebrain bundle (which contains the ascending dopaminergic system), which might cause movement disorders or other behavioral changes (Stricker and Verbalis 1990; Bernardis and Bellinger 1996).

The discovery of the adipocyte-derived hormone leptin and its cognate receptor (LepRb) in the mid-1990s, together with the development of

new molecular and genetic tools, has permitted the identification of chemically defined neuronal populations associated with specific physiological components of energy homeostasis and the molecular dissection of relevant neural circuits (Zhang et al. 1994; Tartaglia et al. 1995; Chua et al. 1996; Lee et al. 1999; Myers and Leibel 2015).

As a starting point, the neural control of metabolic function recapitulates the basic organizational principles of the CNS in general. The sensory (*input*) arm perceives and conveys information on nutritional state and energy stores to specific brain nuclei (*integrative centers*) that integrate multiple physiological signals and orchestrate a coordinated response via the motor (*output*) arm. The sensory arm relies on hormones, peptides, and other signals from peripheral organs and tissues that function as "metabolic cues." In this chapter, we will summarize what we have learned in the past decade or so with the use of animal models and genetic tools. We will give special emphasis to the brain circuitry unraveled by studies performed in rodents, the preclinical animal model of choice in the field.

2 Sensing Metabolic Cues: Humoral and Neural Components

The sensory (input) arm of the neural control of the metabolic function may be subdivided in humoral and neural components, according to the route used by the metabolic cues to access the CNS. Most of these signals enter the CNS via the hypothalamus (mostly humoral signals) and brain stem (humoral and neural signals).

2.1 Humoral Components

Most metabolic cues derived from peripheral tissues are released into the circulation and directly act in specific hypothalamic and brain stem nuclei to control food intake, energy expenditure, and glucose homeostasis. Among them, hormones secreted by adipocytes (e.g., leptin), endocrine pancreas (e.g., insulin), and gut (e.g., ghrelin) have been widely investigated in the context of the neural control of the metabolic function.

Leptin, encoded by the *Lep/LEP* gene (previously called *ob* for obese), is primarily synthesized and secreted by white adipose tissue (Zhang et al. 1994). During negative energy balance, the fall in leptin levels represents a key signal for the neuroendocrine adaptations prompted by states of energy insufficiency (Flier 1998; Chan and Mantzoros 2005; Ahima et al. 2000; Casanueva and Dieguez 1999). These adaptive responses include decreased locomotor activity and thermogenesis, increased appetite and motivation for food, inhibition of the thyroid and reproductive axes, and activation of the adrenal axis (Ahima 2006). Leptin acts via LepRb (encoded by the *Lepr/LEPR* gene), which is highly expressed in several regions of the hypothalamus, including the arcuate nucleus (Arc), the VMH, the dorsomedial nucleus (DMH), and the LHA. In the brain stem, the ventral tegmental area (VTA), the periaqueductal gray matter, the lateral parabrachial nucleus (lPBN), and the nucleus of the solitary tract (NTS) also express LepRb (Tartaglia et al. 1995; Chua et al. 1996; Mercer et al. 1996; Fei et al. 1997; Elmquist et al. 1998a; Scott et al. 2009; Myers et al. 2009).

Insulin, produced by the pancreatic β cells, is crucial for the control of blood glucose; it stimulates glucose uptake by peripheral organs including liver, muscle, and adipose tissue (Weyer et al. 1999; Biddinger and Kahn 2006). Glucose uptake by neurons and glia is mediated by insulin-insensitive glucose transporters; hence, the acquisition and use of glucose by the brain are independent of insulin action (McEwen and Reagan 2004; Banks et al. 2012). Insulin receptors are widespread in the CNS, however, and growing evidence supports a role for brain insulin action in the control of energy balance (along with peripheral glucose homeostasis). For example, mice with neuronal deletion of insulin receptor display increased adiposity and higher susceptibility to obesogenic diet (Plum et al. 2006; Kleinridders et al. 2014; Bruning et al. 2000).

Ghrelin is primarily produced and released by endocrine cells of the stomach and small intestine

(Kojima et al. 1999). It was initially described as a potent growth hormone (GH) secretagogue, acting via the GH secretagogue receptor (GHSR). Soon after its discovery, several laboratories reported that peripheral or central injections of ghrelin potently stimulate food intake and decrease energy expenditure, leading to weight gain (Nakazato et al. 2001). Ghrelin is also an important modulator of glucose homeostasis. Loss-of-function mutations in the ghrelin gene (*Ghrl*) increase glucose-stimulated insulin secretion, as well as insulin sensitivity (Sun et al. 2006). Similarly, ghrelin infusion reduces insulin sensitivity and increases glucose levels. Some of ghrelin's actions may be mediated by direct effects in pancreatic islets (Dezaki et al. 2006), but many lines of evidence demonstrate major roles for GHSR in the brain (Nogueiras et al. 2008). GHSR is abundant in the Arc and VMH, as well as relevant brain stem sites, including the VTA, lPBN, and NTS (Nakazato et al. 2001; Zigman et al. 2006).

To exert their effects, circulating hormones must pass the blood–brain barrier (BBB) to access their receptors in the brain parenchyma. The BBB is composed of closely adjoined endothelial cells, glia, and (in some areas) tanycytes. It is present in the entire brain with the exception of small areas located adjacent to the cerebral ventricles, called circumventricular organs (CVOs). The CVOs contain fenestrated blood vessels that allow diffusion and interchange of bigger molecules (peptides and hormones) between the brain parenchyma and the bloodstream, presumably without the need for active transport across the BBB (Ganong 2000; Johnson and Gross 1993; Broadwell and Brightman 1976). Among the seven well-described CVOs, the median eminence and the area postrema are of particular interest here, given their proximity to metabolic sensing neurons in the Arc and the NTS, respectively. These are sites where metabolic signals may passively penetrate the brain and bind to receptors. Alternatively, hormones in the circulation may cross the BBB by two mechanisms: (a) via lipid-mediated free diffusion or (b) via carrier- or receptor-mediated active transport. Most of the metabolic hormones (e.g., leptin, insulin, and ghrelin) have BBB transporters that permit access to deep structures in the brain, not just CVO-adjacent regions (Banks et al. 1996, 2012; Balland et al. 2014; Banks 2008).

2.2 Neural Components: Visceral Inputs

The CNS control of energy homeostasis also relies on information conveyed by visceral inputs. Sensory information is generated in each segment of the alimentary tract, from food taste, temperature, and texture in the mouth to mechanical and chemical signals in the stomach and intestine. These signals are conveyed by several cranial nerves carrying different modalities of sensory inputs. The upper segments of the alimentary tract (mouth and tongue) convey gustatory inputs (taste signals) to the rostral subdivision of the NTS via the facial (VII) and glossopharyngeal (IX) cranial nerves; the mid- and lower segments (pharynx, larynx, esophagus, stomach, and intestine, as well as the liver and the portal vein) transmit mechanical and chemical inputs to the intermediary and caudal subdivisions of the NTS via the vagus (cranial nerve X). The different modalities of sensory inputs convey distinct information to the brain. For example, while gustatory inputs are associated with food selection and hedonic responses, mechano- and chemoreceptors signal nutritional content. In this regard, the vagus nerve is the primary neural component in the transmission of visceral inputs to the CNS (Chung and Andrea 2011; Pavlov and Tracey 2012).

The vagus nerve is comprised of afferent (sensory) and efferent (motor) fibers. The afferent vagal branch is organized as a typical sensory nerve, i.e., pseudounipolar neurons with cell bodies located in a ganglion outside the CNS, the nodose ganglion (aka inferior ganglion of the vagus nerve (Fig. 1)). Vagal dendrites, which contain specialized receptors, are distributed in a topographic manner along the mid- and lower segments of the alimentary tract. The mechanoreceptors are concentrated in the pharynx, esophagus, and stomach, and the chemoreceptors are

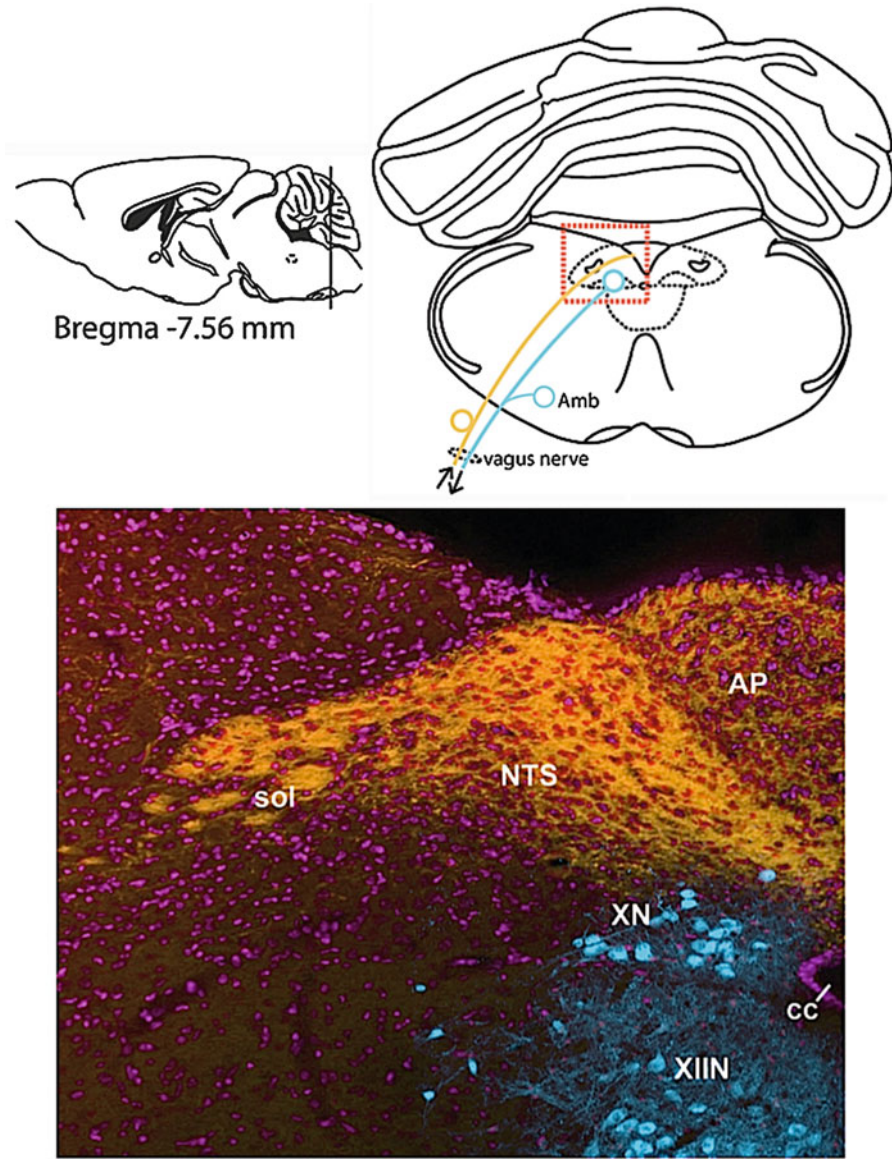

Fig. 1 Sensory and motor arms of the vagus nerve (*XN*). Sensory terminals innervate the area postrema (*AP*) and the nucleus of the solitary tract (*NTS*, pseudocolor *yellow*, using Nav1.8 reporter mice). Motor neurons in the motor nucleus of the vagus nerve (*DMV*) are represented in *blue* (choline acetyltransferase/ChAT-reporter mice). This image was kindly provided by Dr. Laurent Gautron from the University of Texas Southwestern Medical Center, Dallas, Texas, USA

more abundant in the stomach, liver, and intestine (Berthoud 2002). The mechanoreceptors are found throughout the myenteric plexus and external smooth muscle layers. In the stomach, they sense gastric distension and provide signals that promote satiation (Fox et al. 2001). The chemoreceptors are distributed in the mucosal and submucosal layers of the gastrointestinal (GI) tract and in the liver and portal vein; these may sense changes in glucose, amino acids, and fatty acids. The chemoreceptor cells are also responsive to peptides produced in the GI mucosa in response to food intake, including ghrelin, cholecystokinin (CCK), amylin, peptide YY, and

glucagon-like peptide-1 (GLP-1) among others in response to food intake (Berthoud 2002; Chaudhri et al. 2008). The viscerosensory inputs (via the vagus nerve) and humoral signals (via the area postrema) reach the CNS via direct actions upon NTS neurons. This neuronal relay functions as the primary brain stem entry site in metabolic regulation.

3 Brain Stem Pathways: Transducing Visceral and Humoral Inputs

Many humoral and neural signals of energy balance, including a variety of gut-derived signals, converge on the NTS (Fig. 2; Grill and Hayes 2012; Myers and Olson 2014). In addition to receiving the vagally encoded information from gut distension, a variety of humorally conveyed signals (including gut peptides, such as amylin and CCK) activate cells in the area postrema that project onto an overlapping set of neurons in the medial NTS; medial NTS responses contribute to short-term satiety. Additionally, many of the neurons in the medial NTS that receive vagal and area postrema-derived information also express LepRb and respond to leptin (Huo et al. 2008). Leptin augments the response of these cells to gut peptide- and vagally encoded signals, thus amplifying the effects of feeding on these satiety-promoting circuits (Huo et al. 2008; Morton et al. 2005).

The gut- and nutrient-responsive neurons of the medial NTS contain a variety of neurotransmitters; most are glutamatergic, but many also contain neuropeptide transmitters including proopiomelanocortin (POMC)-derived peptides, CCK, and GLP-1 (Huo et al. 2008; Garfield et al. 2012). Subpopulations of these cells express the transcription factor Phox2B, and Phox2b-Cre-mediated deletion of LepRb interferes with satiety signaling, as does virally mediated suppression of

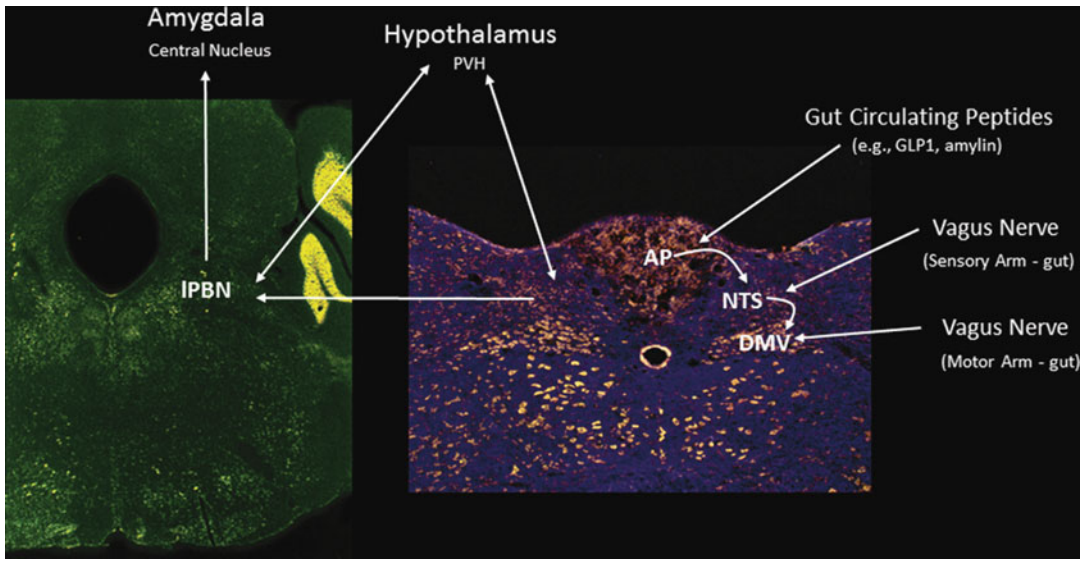

Fig. 2 Flow of information in the hindbrain. The area postrema (AP), a circumventricular organ that has direct access to the circulation, receives information about feeding status by sensing gut peptides (e.g., GLP1 and amylin). These cells project to the nucleus of the solitary tract (*NTS*), where the area postrema-derived information is integrated with information conveyed by vagal sensory afferents from the gut. This integrated information is not only passed to the dorsal motor nucleus of the vagus nerve (*DMV*) to stimulate vagal motor neurons efferent to the gut (controlling peristalsis, etc.) but is also passed forward to the lateral parabrachial nucleus (*lPBN*), an important center for anorexia, and to a variety of hypothalamic sites, including the paraventricular nucleus (*PVH*). Hypothalamic sites also project to the lPBN and NTS. The output of these nuclei promotes satiety. A subset of lPBN neurons projects to the central nucleus of the amygdala (CeA) to mediate a powerful anorectic signal

NTS LepRb expression (Aponte et al. 2011). Medial NTS neurons project to a variety of regions, including the adjacent dorsal motor nucleus of the vagus (DMV) – where they mediate gut reflexes that alter peristalsis, etc. (Grill and Hayes 2012). Medial NTS cells also project to the lPBN, where they synapse on neurons that contain calcitonin gene-related peptide (CGRP), among others (Wu et al. 2012). lPBN CGRP neurons project to the central nucleus of the amygdala to promote anorexia. Medial NTS neurons also make direct projections into more rostral areas, including hypothalamic sites (such as the paraventricular nucleus of the hypothalamus, the PVH), the amygdala, and the thalamus.

Importantly, in addition to roles played by brain stem nuclei in conveying gut- and nutrient-derived information rostrally, the NTS and lPBN receive information from hypothalamic structures and play an important role in mediating the control of food intake by these sites (Grill and Hayes 2012; Myers and Olson 2014). Both the NTS and lPBN receive direct inputs from the hypothalamus – especially from the PVH and the Arc nuclei; the lPBN plays prominent roles in the control of food intake by cells in both of these areas. Indeed, the lPBN also plays important roles in the anorexia associated with gut sickness-derived signals, as well as normal satiety signals.

4 Hypothalamic Systems that Control Energy Balance

4.1 Overall Organization

Many of the neural systems that control energy balance lie in the hypothalamus. Like the brain stem (and unlike more recently developed brain areas such as the neocortex and hippocampus), the hypothalamus is not organized in a laminar manner but rather consists of clusters of neuronal soma (nuclei). The cells within each nucleus connect to other cells in the same region and/or other nuclei to generate an integrated signal, which is then passed to output nuclei that ultimately relay the signal to motor neurons that control autonomic and endocrine systems or influence feeding behavior. While each of these nuclei contains heterogeneous (and even oppositely acting) types of neurons, the neurons of each nucleus often control related functions. While many hypothalamic nuclei contribute to the control of energy balance at some level, several of these nuclei play defined and especially important roles.

Within the medial region, the Arc, which lies immediately above the median eminence, enjoys rapid access to circulating factors (see Humoral Components discussed above) that mediate important signals of energy balance (Myers and Olson 2014). The Arc makes strong reciprocal connections with the dorsomedial nucleus of the hypothalamus (DMH), which integrates the Arc-derived signals with information (e.g., circadian cues, body temperature) from other hypothalamic regions (Fig. 3). The Arc and DMH each also make strong reciprocal connections with the PVH, which lies anterior to these other structures. As noted above, the PVH also receives direct input from the brain stem. The PVH represents a crucial output nucleus for the hypothalamus: PVH efferents to the brain stem and spinal cord control autonomic function, projections to the median eminence and posterior pituitary control endocrine function, and projections to the brain stem regulate feeding.

The VMH, especially the dorsomedial VMH (dmVMH, which mediates most of the energy balance function of the VMH), though nestled between the anterior portions of the Arc and DMH, makes relatively few connections with these two nuclei but rather projects to rostral and brain stem regions associated with autonomic function (e.g., the bed nucleus of the stria terminalis and the periaqueductal gray matter) (Canteras et al. 1994). Lateral to the Arc, VMH, and DMH lies a more loosely defined structure, the lateral hypothalamic area (LHA), through which course projections among several limbic regions rostral and caudal to the hypothalamus. The LHA contains many cell bodies, as well; many of these receive metabolic signals and project to the midbrain (including the dopaminergic ventral tegmental area or VTA) or to rostral limbic regions (such as the nucleus accumbens). The

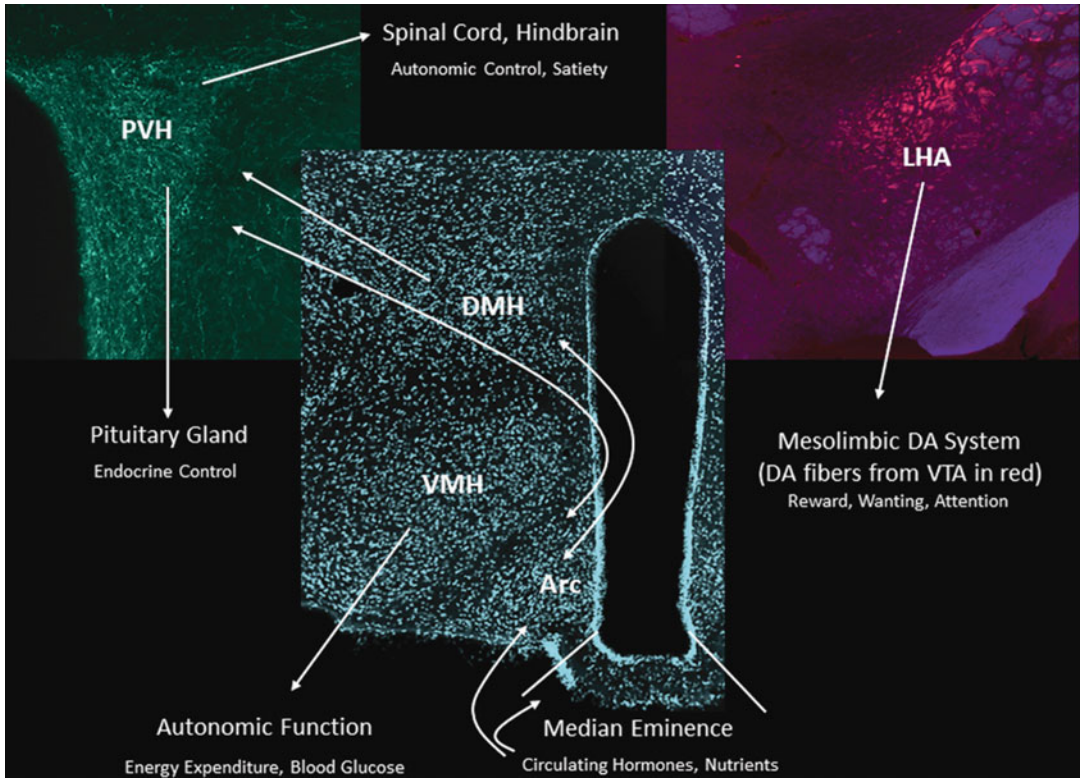

Fig. 3 Flow of information in the hypothalamus and roles of hypothalamic nuclei. The arcuate nucleus (*Arc*), which is located directly above the median eminence, has the most direct exposure to circulating hormones and nutrients and is enriched in receptors for these substances. Arc neurons, including the important POMC and AgRP neurons that comprise the inception site of the hypothalamic melanocortin system, project densely to the dorsomedial hypothalamic nucleus (DMH, where information is integrated with circadian, temperature, and other inputs) and to the paraventricular nucleus of the hypothalamus (PVH, the major output nucleus for the medial hypothalamus). The DMH makes reciprocal connections with the Arc and PVH. Projections from the PVH target the median eminence and pituitary gland for the regulation of endocrine function, the spinal cord to control sympathetic nervous system (*SNS*) function, and the hindbrain to modulate satiety. The ventromedial hypothalamic nucleus (*VMH*) senses glucose, along with some hormones that are sensed by the Arc, and projects to forebrain and hindbrain regions that control autonomic function, thereby controlling energy expenditure and blood glucose levels. The lateral hypothalamic area (*LHA*) contains many types of neurons that project into areas associated with attention, reward, and wanting, such as the mesolimbic dopamine system. The LHA represents a major conduit from hypothalamic homeostatic circuits into the brain's motivational circuitry

LHA represents a major conduit linking the hypothalamus to the mesolimbic dopamine system and other circuits that control motivation (Opland et al. 2010).

4.2 Arcuate Nucleus

The Arc in rodents (tuberal nucleus in humans) is located in the medioventral portion of the hypothalamus surrounding the third ventricle and intimately connected to the median eminence and hypophyseal portal vascular system by the infundibular stalk. It contains a heterogeneous group of projection neurons producing proopiomelanocortin (POMC), agouti-related peptide (AgRP), or Kisspeptin, hypophysiotropic neurons producing growth-hormone-releasing hormone (GHRH), somatostatin, or dopamine, plus glial-like tanycytes (in addition to astrocytes and microglia). A Golgi impregnation study showed that the majority of Arc neurons are bipolar with two major, relatively

aspiny dendrites (van den Pol and Cassidy 1982). Tanycyte cell bodies are located in the ventral-most ependymal lining of the third ventricle and elaborate their characteristic arching projections laterally and ventrally (Langlet 2014). The median eminence is one of the circumventricular organs with fenestrated capillaries and therefore provides neurons of the Arc with relatively unfettered access to circulating hormones, cytokines, nutrients, and metabolites. Modulation of tanycytes by peripheral signals, including leptin, appears to be capable of further opening the blood–brain barrier to allow access of circulating factors deeper into the Arc parenchyma (Balland et al. 2014; Mullier et al. 2010).

Neuropeptidergic neurons of the Arc, including those that contain POMC and somatostatin, are among the earliest differentiated neurons of the CNS, at E10.5 in the mouse. The homeodomain transcription factor Isl1 has recently been shown to be essential for the specification of POMC neuron identity and transcription of the *Pomc* gene by its interaction with two distinct neural-specific enhancers (Lam et al. 2015; Nasif et al. 2015). Similarly, the homeodomain transcription factor Bsx has been implicated in transcription of the *Agrp* gene (Sakkou et al. 2007). The early POMC-positive neurons in the developing Arc appear to be intermediate progenitors that ultimately give rise to mature POMC neurons, as well as subpopulations of mature AgRP and Kisspeptin neurons (Padilla et al. 2010; Sanz et al. 2015). Another defining feature of the developing Arc is the trophic action of the postnatal surge in leptin secretion to stimulate neural projections from the Arc to other hypothalamic nuclei (Bouret et al. 2004). There is increasing evidence that the epithelial lining of the third ventricle contains a stem cell population that together with tanycytes is capable of generating newly born and differentiated Arc neurons in the adult mouse brain (Kokoeva et al. 2007; McNay et al. 2012; Lee et al. 2012), although the physiological significance of these discoveries remains to be fully defined. Excitingly, recent reports have outlined the in vitro conditions essential to generate differentiated cells representative of the full range of Arc neurons from either human ES (embryonic stem) cells or IPSC (induced puripotential stem cells) cells (Merkle et al. 2015; Wang et al. 2015a). These groundbreaking findings will likely permit a more complete analysis of the factors underlying the development of the Arc and exploration of the genetic disturbances associated with Arc dysfunction in hereditary hypothalamic obesity syndromes.

Abundant genetic evidence from the clinic, together with animal studies, has identified the CNS melanocortin system, including POMC and AgRP neurons and their projections to distal neurons expressing the melanocortin MC3 and MC4 receptors, as a critical component of the homeostatic neural circuitry regulating energy balance (Cone 2005). Melanocortin peptides (α-, β-, and γ-MSH in humans, only α- and γ-MSH in rodents) are endogenous agonists of the two CNS receptors, while AgRP is a competitive antagonist/inverse agonist at both receptors (Ollmann et al. 1997). The remainder of this section will therefore focus on the dyad of Arc POMC and AgRP neurons.

A study by Cowley et al. (2001) first proposed a model to explain the homeostatic basis of body weight control, whereby leptin stimulation of POMC neurons is balanced by their inhibition from nearby AgRP neurons. In this useful (albeit simplistic) model, the two subpopulations of neurons largely project to similar sites in the CNS (Bagnol et al. 1999; Wang et al. 2015b) but have opposing actions, α-MSH ultimately leading to decreased food intake and increased energy expenditure and AgRP increasing food intake and decreasing energy expenditure. The model is conceptually very similar to the earlier, but now debatable, notion of opposing mediobasal hypothalamic anorexigenic and lateral hypothalamic orexigenic zones. More recent evidence has greatly elaborated on the dyadic model without nullifying its heuristic value.

AgRP neurons also produce neuropeptide Y (NPY) (Hahn et al. 1998) and the fast inhibitory neurotransmitter GABA (Cowley et al. 2001). Although AgRP and NPY both stimulate food intake following injection into the cerebrospinal fluid or specific hypothalamic nuclei, this pharmacological action does not fully reflect the complexity of endogenous AgRP neuron function.

Researchers were puzzled by the demonstration that mutant mice engineered to lack AgRP and/or NPY did not exhibit the predicted phenotype of decreased body weight, adiposity, and food intake (Qian et al. 2002). However, ablation of AgRP neurons in the adult, but not in neonatal mouse, causes starvation and death, and this phenotype is independent of melanocortin signaling (Luquet et al. 2005; Wu et al. 2008). These paradoxical findings have at least been partially explained by the primary role of GABA signaling from AgRP neurons in their acute actions to stimulate feeding, with the neuropeptides playing accessory or modulatory roles (Tong et al. 2008; Wu et al. 2009). Stimulation of AgRP neurons by either optogenetic or chemogenetic technology leads to the rapid onset of feeding behavior, even in sated mice (Aponte et al. 2011; Krashes et al. 2011). However, further experiments have demonstrated that endogenous AgRP release does indeed stimulate feeding but on a longer time scale than either GABA or NPY release (Krashes et al. 2013). There are apparently at least two parallel neural pathways mediating these effects, one a direct projection of AgRP neurons to the lPBN (Wu et al. 2012; Betley et al. 2013) and a second polysynaptic circuit involving an inhibitory AgRP projection to MC4R-expressing glutamatergic neurons within the PVH that in turn project by a descending pathway to the lPBN (Garfield et al. 2015). It is not yet known if the latter target neurons are identical to each other for both pathways originating from the Arc.

Like AgRP neurons, subpopulations of Arc POMC neurons are characterized by diverse afferent signaling pathways, including activation by the humoral factors leptin and insulin via LepRb and InsR (Qiu et al. 2010, 2014), respectively, either direct activation or inhibition by glucose (Ibrahim et al. 2003; Parton et al. 2007), transsynaptic excitation by glutamatergic inputs (Kiss et al. 2005; Sternson and Shepherd 2005), and transsynaptic inhibition by GABAergic inputs (including those from local AgRP/NPY/GABA neurons), opioid peptides via μ-opioid receptors (Pennock and Hentges 2011), and serotonin via 5-HT2C receptors (Berglund et al. 2013). POMC neurons also synthesize cocaine- and amphetamine-regulated transcript (CART) and dynorphin peptides and are capable of the synaptic release of both GABA and glutamate (Hentges et al. 2009; Jarvie and Hentges 2012), although the physiological importance of these co-modulators and co-transmitters is still unknown. However, there is abundant and unequivocal evidence from pharmacological, genetic, and electrophysiological experiments that melanocortin peptides derived from POMC neurons play a critical physiological role in the reduction of food intake by promoting early satiation and in the reduction of energy expenditure via effects on the autonomic nervous system (Yaswen et al. 1999; Huszar et al. 1997; Butler et al. 2000; Chen et al. 2000; Xu et al. 2011). The actions of β-endorphin, an opioid peptide that is generated stoichiometrically with melanocortins during posttranslational processing of the prohormone, are less certain (Wardlaw 2011). β-Endorphin injected into the nucleus accumbens acutely stimulates feeding, particularly of highly palatable food (Majeed et al. 1986; Will et al. 2003); however, mice with a specific genetic loss of β-endorphin exhibit a mild obesity phenotype with increased food intake (Appleyard et al. 2003). The explanation for these contradictory findings has not been adequately explained.

Unlike the rapid stimulatory effects on food intake produced by the remote activation of AgRP neurons, activation of Arc POMC neurons has only produced delayed inhibitory effects on food intake after as much as 24 h (Aponte et al. 2011; Atasoy et al. 2012; Zhan et al. 2013). Similarly, only long-term inhibition of POMC neurons was capable of increasing food intake (Atasoy et al. 2012). Because the feeding inhibitory effects from optogenetic activation of POMC neurons were blocked by a melanocortin antagonist and POMC neuron activation could overcome coincident inhibition from AgRP neurons, the most parsimonious explanation for the delayed response is that melanocortin peptide release, and not the other putative peptide and amino acid transmitters produced in POMC neurons, is of principal importance to POMC neuron function in the control of energy homeostasis. However, it is worth noting that the loss of *Pomc* gene

expression selectively from the Arc has no detectable effect on body weight in mice until they are weaned at age 3 weeks (Bumaschny et al. 2012). The absence of *Pomc* expression also does not prevent the maturation of POMC neurons and the development of their widespread axonal projections throughout the brain.

The most recent advances in our understanding of the intrinsic activity of POMC and AgRP neurons and their role in energy balance come from a pair of elegant studies using in vivo Ca^{2+} imaging of the Arc with either fiber photometry or miniaturized confocal optics in freely behaving mice (Chen et al. 2015; Betley et al. 2015). These experiments revealed unexpected aspects of neuronal activity that have not been possible to assess using ex vivo slice electrophysiology. Fasted mice were shown to have tonically active AgRP neurons and tonically inhibited POMC neurons. Food presentation alone or even olfactory cues from a hidden food pellet were sufficient to immediately reverse the activity state of the two populations of Arc neurons. Furthermore, the magnitude of these responses was increased directly with the hedonic value of the presented food, and, conversely, food removal slowly restored the original activation states. Extrinsic excitation of the AgRP neurons conditioned mice to avoid a previously associated neutral flavor or preferred chamber in a place preference test. These results suggest that AgRP neuron activation has a negative valence, and, as a corollary, the state of food deprivation associated with tonically active AgRP neuron firing is intrinsically aversive. Therefore, the natural drive to eat, with consequent achievement of reward, may be motivated not only by the positive hedonic reinforcement from food but also by the reduction of negative reinforcement encoded by AgRP neuron activity. Although not explicitly tested, it is logical to propose that POMC neuron activation may have an opposing positive valence that is unrelated to its induction of satiation. Finally, these demonstrations of rapid alterations in Arc neuronal firing in anticipation of food consumption, rather than as a response to it, provide new insights concerning the role of the melanocortin system in both homeostatic and non-homeostatic control of energy balance.

4.3 Dorsomedial Nucleus

Even among the complex nuclei of the hypothalamus, the size and functional diversity of the DMH is substantial (Fontes et al. 2011; Dimicco et al. 2007). While there are many recognized subdivisions of the DMH, it is probably most useful to distinguish among the dorsal component (DMHd, which borders the dorsal hypothalamic area or DHA), the compact central zone, and the ventral region (DMHv). The DMH plays a role in the control of many autonomic functions, including thermogenesis, heart rate, and blood pressure. Like the Arc, the DMH contains a substantial number of LepRb-expressing cells (Scott et al. 2009; Patterson et al. 2011). Dorsal DMH/DHA LepRb neurons interact with the thermal control systems of the medial preoptic area and PVH and play an important role in the control of body temperature by leptin (Rezai-Zadeh et al. 2014). Consistently, deletion of LepRb in the prolactin-releasing hormone-expressing neurons of this region decreases body temperature and energy expenditure, promoting obesity in high-fat-fed animals (Dodd et al. 2014). A variety of data also suggest that the LepRb neurons in this region modulate blood pressure and contribute to the increase in blood pressure associated with the hyperleptinemia of obesity (Simonds et al. 2014).

Some brain lesion experiments also suggest a role for the DMH in the control of food intake. It is possible that the DMH contains oppositely acting sets of neurons (similar to the POMC and AgRP neurons of the Arc but more evenly balanced), which could limit the ability to detect roles in the control of food intake following traditional lesioning. It is also possible that the variable effects on feeding that result from DMH lesions may reflect differences in the subregions of the DMH targeted in various studies; certainly, DMHd/DHA LepRb neurons control autonomic output but do not modulate feeding (Rezai-Zadeh et al. 2014). Correlative evidence suggests the potential for DMH leptin action (presumably the ventral DMH) in the control of feeding, however. The deletion of LepRb from distributed populations of hypothalamic cells that express the vesicular GABA transporter

(vGat, *Slc32a1* gene) or neuronal nitric oxide synthase (nNOS, *Nos1* gene) each produces dramatic hyperphagia and obesity (Leshan et al. 2012; Vong et al. 2011). The distributions of these cells overlap mainly in the DMH, suggesting a potential role for DMH LepRb neurons in the suppression of feeding.

4.4 Paraventricular Nucleus: Hypothalamic Output

The PVH is a critical hypothalamic center that receives and integrates energy balance signals from a variety of brain regions and coordinates physiologic responses to maintain energy homeostasis predominantly through the autonomic nervous system. The PVH is a complex structure composed of a heterogeneous group of mostly glutamatergic neurons that have been classically described as parvocellular or magnocellular based on cell size and axonal projection patterns. The magnocellular neurons in the PVH, including those that express oxytocin (OXT) or vasopressin (AVP), project primarily to the posterior pituitary and release their contents directly into the general circulation to regulate peripheral tissue function. Importantly, however, dendritic release of these neuropeptides has been implicated in the overall control and coordination of PVH function.

The PVH parvocellular cells are more diverse and send projections within the central nervous system to three main areas: (1) the median eminence where secreted factors (e.g., corticotropin-releasing hormone or CRH) enter the portal hypophyseal circulation and regulate pituitary function; (2) the brain stem, including the dorsal vagal complex (composed of the NTS and DMV) and the lPBN – both of which have been implicated in feeding (Wu et al. 2009; Wan et al. 2008; Wu and Palmiter 2011; Zheng et al. 2005; Berthoud et al. 2006); and (3) the preganglionic, sympathetic output centers such as the intermediolateral cell column of the spinal cord (Sawchenko and Swanson 1982; Swanson et al. 1980; Biag et al. 2012). Parvocellular PVH neurons that respond to satiety signals, such as leptin, have been proposed to regulate feeding by modulating hindbrain responses to ascending feeding signals from the gut and periphery (Morton et al. 2005; Atasoy et al. 2012; Blevins et al. 2004, 2009). However, it is important to point out that hypothalamic factors secreted into the portal hypophyseal circulation at the median eminence undoubtedly contribute to both energy and metabolic homeostasis via regulation of pituitary function.

The overall importance of the PVH in the regulation of energy balance is underscored by the massive obesity and metabolic abnormalities associated with alterations in PVH development or function. Rodents and humans harboring deleterious mutations in the hypothalamic transcription factor *single minded-1* (Sim1) develop a hypocellular PVH and hyperphagic obesity. Moreover, lesions of the PVH also result in hyperphagic obesity and glucose dysregulation. Neither the neural architecture nor the molecular mechanisms used by the PVH to maintain energy and metabolic homeostasis are well understood. This is in large part due to the cellular heterogeneity of the PVH, the density of its projection targets, and the array of PVH afferent inputs from different brain regions (Sawchenko and Swanson 1983; Ferguson et al. 2008).

The PVH serves as an important regulatory output center for peptides and conditions known to modulate food intake, including leptin, melanocortins (from the Arc), GLP-1 (presumably from the NTS), GLP-1 agonists, and dehydration (Tung et al. 2008; Acuna-Goycolea and van den Pol 2004; Baraboi et al. 2011; Dalvi et al. 2012; Salter-Venzon et al. 2008). The melanocortin system is perhaps the best studied of these pathways, as it is essential for energy balance in rodents and humans and is directly linked to PVH function (Cone 2005; Garfield et al. 2015; Farooqi and O'Rahilly 2006; Farooqi et al. 2003). POMC and AgRP neurons in the Arc produce melanocortin agonists and antagonists, respectively, and project to PVH neurons that express melanocortin receptors (Ellacott and Cone 2004; Kishi et al. 2003; Mountjoy 2010). Endogenous and pharmacologic melanocortin agonists stimulate melanocortin receptor-bearing neurons to activate effector pathways that inhibit food intake and stimulate energy

expenditure. Melanocortin action in PVH Sim1 neurons suppresses food intake (Balthasar et al. 2005; Shah et al. 2014), and ablation of most Sim1 neurons in adult mice results in profound hyperphagic obesity with decreased energy expenditure and altered locomotor activity (Xi et al. 2012). In addition, selective deletion of MC4R from Sim1 cells leads to hyperphagic obesity (Shah et al. 2014).

Subsets of PVH neurons contain a variety of neuropeptides implicated in neuroendocrine and energy balance control, including OXT, CRH, AVP, thyrotropin-releasing hormone, and somatostatin. The anorectic effects of pharmacologic doses of OXT and CRH agonists generated a great deal of interest in PVH OXT and CRH neurons as potential regulators of energy balance. At odds with this formulation are the findings that rodents lacking OXT or OXT neurons (or CRH/CRH receptors) demonstrate minimal energy balance phenotypes; neither does the activation of PVH OXT or CRH neurons alter feeding (Sutton et al. 2014). Whether the contradiction between pharmacologic studies and genetic approaches reflects developmental compensation to the systemic inactivation of these neuropeptides is not clear, but the profound effects of Sim1 neuron (pan-PVH) manipulation suggest that yet-to-be-defined PVH neurons distinct from OXT and CRH cells represent crucial mediators of energy balance.

With the recent development of an array of genetic tools, cell-specific genetic changes in PVH cells have confirmed the critical role of the PVH in feeding regulation and have extended our understanding of the molecular components and neural circuitry of PVH function/action. MC4R action on Sim1 cells in the PVH is sufficient to normalize feeding in animals that lack MC4Rs elsewhere, and this is not attributable to direct MC4R action on OXT, CRH, or AVP neurons. Moreover, MC4R expression in Sim1 PVH neurons is required for body weight maintenance, indicating that PVH MC4R action is both necessary and sufficient for normal energy homeostasis (Balthasar et al. 2005; Shah et al. 2014). Remote activation of Sim1 PVH neurons using chemogenetic approaches suppresses feeding and increases energy utilization (Garfield et al. 2015; Sutton et al. 2014). The effects of pan-PVH activation on parameters of energy balance are not assignable to PVH OXT, CRH, or AVP neurons, since chemogenetic manipulation of these populations had minor (if any) effects on energy balance. In contrast, cell-specific activation of neuronal nitric oxidase synthase (NOS1)-expressing PVH neurons (a subset of Sim1 PVH cells) alters feeding to a similar extent as pan-PVH activation, suggesting that PVH NOS1 neurons play an important role in feeding.

The PVH sends projections to a variety of brain regions within the central nervous system. For the purposes of this discussion, we will highlight the functional roles of PVH projections to brain areas known to be important for food intake/energy expenditure, including the lPBN (feeding), NTS, and spinal cord (autonomic control). The importance of these specific PVH projections has been inferred based on published data demonstrating the importance of these target regions in energy balance. The combination of stereotaxic delivery of cell-specific viral tools into transgenic animals with technologies such as light-dependent neural activation (optogenetics) has made it possible to interrogate the physiologic function of specific PVH neuronal projections. Indeed, recent studies using these technologies have revealed a PVH → Arc orexigenic circuit and established the importance of PVH → lPBN projections for melanocortin action in the CNS (Garfield et al. 2015; Krashes et al. 2014). Similar approaches targeting other PVH projections will undoubtedly uncover additional important biological mechanisms underpinning energy balance regulation.

4.5 Ventromedial Nucleus

For several decades following the seminal studies of Hetherington and Ranson, in which the bilateral medial hypothalamic lesions (that included the VMH) produced hyperphagic obesity, the VMH was the main focus of attention regarding the neural control of energy homeostasis (Hetherington and Ranson 1940). Following

intense debate, these studies were dismissed by findings suggesting that the electrolytic lesions likely disrupted the neural connections of the medial hypothalamus, including projections from the Arc to and from the PVH (Elmquist et al. 1999; King 2006). While still not completely resolved, the role for the VMH in energy balance has been clarified by recent studies using more specific molecular and cellular methods.

The VMH contains glucose-sensing neurons that are highly responsive to changes in glucose levels, as well as those that express receptors for metabolic hormones (e.g., leptin and insulin) or for neuropeptides associated with energy balance (Scott et al. 2009; Elmquist et al. 1997; Routh 2003; Song et al. 2001; Kang et al. 2004). However, the VMH, like most hypothalamic nuclei, is not a homogeneous structure, and it is comprised of neurons with distinct neurochemical identities and characteristic projection patterns. For example, the ventrolateral subdivision (VMHvl) expresses sex steroid receptors and projects to sites related to behavioral control, whereas neurons in the dorsomedial subdivision (VMHdm) respond to metabolic cues (e.g., glucose, leptin, and insulin) and innervate areas associated with autonomic and circadian regulation (Canteras et al. 1994; Kim et al. 2011a; Elmquist et al. 1998b; Klockener et al. 2011). Among these, VMHdm projects densely to the lateral aspect of the bed nucleus of the stria terminalis and to the subparaventricular zone of the hypothalamus (Canteras et al. 1994; Elmquist et al. 1998b; Dong and Swanson 2004). The lateral bed nucleus of stria terminalis is part of the central autonomic circuitry preferentially innervating the central amygdala, periaqueductal gray matter, lPBN, and NTS (Dong and Swanson 2004). On the other hand, the subparaventricular zone receives dense innervation from the suprachiasmatic nucleus, the main circadian clock of the mammalian brain (Moore 1983; Watts et al. 1987). The neuroanatomical organization of the VMHdm suggests roles in energy balance by the control of autonomic function (e.g., thermogenesis, hepatic glucose production, glucose utilization, and secretion of insulin and glucagon) and the circadian oscillations of circulating hormones (e.g., corticosterone) in response to changes in energy stores (Kim et al. 2011a; Bernardis and Frohman 1971; Luo et al. 1999; Niijima et al. 1984; Krieger 1980; Choi et al. 1996).

To better understand the regulation and function of VMH circuits, several groups examined the temporal and anatomic distribution of gene expression in the VMH. Of the identified genes, steroidogenic factor 1 (SF1, *Nr5a1* gene) received a great deal of attention due to its VMH-specific expression within the CNS (Ikeda et al. 1995; Segal et al. 2005). The restricted expression of SF1 has allowed the development of a series of genetically modified mouse models to interrogate VMHdm function. Mice with global loss-of-function mutations in the SF1 gene show disrupted VMH development (Ikeda et al. 1995; Sadovsky et al. 1995; Luo et al. 1994; Shinoda et al. 1995), and neuron-specific deletion of SF1 results in morbid obesity – primarily due to decreased energy expenditure (Kim et al. 2011a, b; Majdic et al. 2002). Two independent groups also demonstrated that leptin signaling in VMH SF1 neurons is required for energy expenditure, glucose homeostasis, and adaptive thermogenesis and hence for the control of body weight (Dhillon et al. 2006; Bingham et al. 2008). On the other hand, selective deletion of insulin receptor from SF1 neurons induced resistance to obesogenic diet and altered glucose metabolism (Klockener et al. 2011).

The VMH also plays a prominent role in the control of glucose homeostasis (Routh 2003). VMH neuron responses to glucose are heterogenous: Glucose-excited (GE) VMH neurons increase and glucose-inhibited (GI) VMH neurons decrease their firing rate when glucose rises (Song et al. 2001). Intra-VMH 2-deoxyglucose (a non-metabolizable glucose analog that mimics low glucose) injection increases plasma glucose, glucagon, noradrenaline, and adrenaline, suggesting a role in the counter-regulatory response to hypoglycemia, presumably by activating GI neurons. Recent studies have also suggested that VMH innervation by brain stem sites also plays a role in this response (Garfield Alastair et al. 2014; Flak et al. 2014). Conversely, leptin

or melanocortin action in the VMH increases glucose uptake into tissues and/or decreases blood glucose (presumably via GE neurons). These findings support the notion that the VMH is a key component in the control of glucose homeostasis via sensing changes in glucose levels and modulation of autonomic responses (Routh 2003).

Targeted deletion of leptin- or insulin-regulated intracellular signaling pathways has unraveled some of the molecular mechanisms involved in the humoral control of the VMH function. For example, reduced activity of phosphatidylinositol 3-kinase (PI3K) in SF1 neurons decreased the adaptive autonomic response to high caloric intake without changes in glucose homeostasis (Xu et al. 2010). In addition, deletion of FOXO1 (a transcription factor downstream of PI3K signaling) resulted in improved insulin sensitivity and in a lean phenotype due to increase in energy expenditure (Kim et al. 2011b).

Non-SF1 neurons (such as those that contain brain-derived neurotrophic factor or BDNF) may also play an important role in metabolic regulation: Viral blockade of VMH BDNF induces hyperphagic obesity in mice (Unger et al. 2007). Also, deletion of estrogen receptor α (ERα) in the entire VMH results in more profound adiposity than that observed in selective ERα deletion from SF1 neurons (Xu et al. 2011; Musatov et al. 2007). Hence, VMH SF1 neurons appear to primarily control energy expenditure and glucose homeostasis, whereas non-SF1 neurons may have a more prominent role in the regulation of food intake. The specific neural pathways that lie downstream of distinct VMH neurons to control each aspect of energy homeostasis remain poorly understood, however.

4.6 Lateral Hypothalamic Area and Mesolimbic Dopaminergic System

Unlike the control of autonomic and endocrine function, foraging for and eating food require the initiation and coordination of complex behaviors. While the neural circuits that generate motor patterns represent the ultimate outputs for these behaviors, these circuits serve the brain's motivational systems (Berthoud 2007). The central control of motivation is mediated by the mesolimbic dopamine (DA) system, at the core of which lie DA neurons of the midbrain ventral tegmental area (VTA) (Berridge 2004). The VTA DA neurons project to many places, including the nucleus accumbens, where DA release modulates motivation.

Several decades-old observations also suggested a role for the LHA in motivation. Not only does lesioning the LHA promote anhedonia and abrogate the motivation to feed in experimental animals, but also animals will self-administer activating current to the LHA, suggesting that LHA activation is rewarding/motivating (Fulton et al. 2000). Since the medial forebrain bundle, which carries axons from (among others) the VTA to the nucleus accumbens, courses through the LHA, it was not initially clear whether the perturbation of the medial forebrain bundle or rather LHA neurons mediate these effects, however.

With the discovery and functional characterization of several discrete sets of LHA neurons, it became clear that LHA neurons themselves play an important role in the control of motivation, including the mesolimbic DA system. Indeed, the LHA integrates metabolic (e.g., leptin and melanocortins) and other homeostatic signals from the hypothalamus to modulate mesolimbic DA-dependent activity, attention, and motivation (Myers et al. 2009; Berthoud 2007). Like the Arc, VMH, and DMH, the LHA contains many groups of neurons, some of which function antagonistically. Important LHA neurons include orexin (aka hypocretin)-containing cells, which project to a variety of midbrain and hindbrain sites. Orexin neurons are activated by signals of energy deficit (fasting, ghrelin, etc.) to promote arousal and food seeking; conversely, leptin inhibits orexin neurons (Myers et al. 2009; Berthoud 2007). Melanin-concentrating hormone (MCH)-expressing neurons in the LHA project widely through the forebrain, including to the nucleus accumbens, and stimulate feeding (Georgescu et al. 2005). Overexpression of MCH promotes increased feeding and weight gain, while the ablation of MCH or MCH neurons decreases feeding and promotes leanness.

While both orexin and MCH neurons are glutamatergic, the LHA also contains a substantial population of GABAergic neurons, many of which contain neuropeptides, including neurotensin and galanin. While orexin neurons contain GHSR (the receptor for orexigenic ghrelin), neither orexin nor MCH cells contain LepRb (Leinninger et al. 2009). Rather, a substantial subset of LHA GABA neurons coexpresses LepRb. Like the larger population of LHA GABA neurons, many LHA LepRb neurons also contain neurotensin and/or galanin (Laque et al. 2013).

LHA LepRb neurons contribute to the control of feeding, energy expenditure, and energy balance by leptin, since intra-LHA leptin suppresses feeding in leptin-deficient animals, and deletion of LepRb in LHA neurotensin neurons decreases activity and energy expenditure, while increasing adiposity (Leinninger et al. 2011). LHA LepRb neurons project locally onto orexin (but not MCH) neurons, in addition to innervating the VTA and other midbrain sites (Louis et al. 2010). While the action of Arc-derived melanocortins apparently drives the control of MCH neurons by leptin and energy balance, leptin action via LHA LepRb neurons inhibits the activity of orexin neurons, at least in part via galanin (Opland et al. 2010; Goforth et al. 2014). LHA leptin action also promotes the expression of orexin; this somewhat counterintuitive bidirectional regulation of orexin neurons presumably reflects the need for leptin to reduce acute foraging activity, while supporting the normal function of orexin to permit alertness and attention (Louis et al. 2010).

Leptin action via LHA neurotensin neurons also modulates the mesolimbic DA function, decreasing nucleus accumbens DA transport activity (hence increasing synaptic DA transmission) (Leinninger et al. 2011). Since the chemogenetic activation of LHA neurotensin neurons increases nucleus accumbens DA concentration via the release of neurotensin in the VTA, intra-VTA neurotensin release by LHA LepRb neurons presumably represents a mechanism by which LHA LepRb neurons control mesolimbic DA function (Patterson et al. 2015). While LHA LepRb neurons represent a major mechanism by which leptin and energy status control the mesolimbic DA system, some VTA cells also contain LepRb (Leshan et al. 2010; Fulton et al. 2006; Hommel et al. 2006). VTA LepRb neurons mainly project locally and to the central nucleus of the amygdala (rather than the nucleus accumbens), and the ablation of LepRb from DA neurons fails to alter energy balance or tested parameters of mesolimbic DA function. Thus, LHA LepRb neurons represent the primary link between leptin and the control of mesolimbic DA function and motivation.

5 Conclusions

The physiological regulation of varied components of the metabolic function relies on a coordinated action of humoral and neural signals, integrated brain circuits and orchestrated motor, and behavioral and reflex responses. With the use of molecular and genetic tools and new technology, we have a much clear picture of the role of specific neuronal populations and brain pathways associated with the control of many aspects of energy homeostasis. The "dual center" hypothesis has its heuristic value, but recent evidence using more precise tools has demonstrated the complexity of the system with the action of a series of hypothalamic and brain stem nuclei. We have also gained knowledge on the relevance of selective neurotransmitters/peptides and neural pathways in several aspects of the metabolic regulation. The next challenge will be to determine how each of these components is interconnected and integrated to generate a highly coordinated physiological system.

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6 Cross-References

- Adipokines and Metabolism
- Adipose Structure (White, Brown, Beige)
- Bariatric Surgery
- Circadian Rhythms and Metabolism
- Genetics of Obesity
- Gut Hormones and Obesity
- Insulin Resistance in Obesity
- Overview of Metabolic Syndrome
- Pancreatic Islet Adaptation and Failure in Obesity and Diabetes
- Pharmacotherapy of Obesity and Metabolic Syndrome

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Adipose Structure (White, Brown, Beige)

21

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Contents

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Abstract

Our understanding of adipose tissue physiology and pathophysiology has substantially increased during the last decade. Notably, white adipose tissue (WAT) dysfunction has been proposed as a key determinant of obesity-associated metabolic complications. WAT is a complex metabolic organ composed of many cell types, including adipocytes as the main cell type involved in energy storage. Adipocytes also synthesize numerous molecules involved in the regulation of energy balance, vascular homeostasis, and insulin sensitivity. In obesity, WAT expansion is associated with intensified structural remodeling that compromises the tissue's metabolic and secretory functions. Failure to efficiently store lipids in WAT results in a "spillover" of the excess of lipids into non-adipose tissues, which further disrupts metabolic homeostasis and contributes to the development of obesity-related pathologies, known collectively as metabolic syndrome. In contrast, brown adipose tissue (BAT) is an energy-dissipating thermogenic organ that produces heat by uncoupling mitochondrial fatty acid oxidation. Activation of BAT thermogenesis can ameliorate the effects of WAT dysfunction in metabolically compromised mouse models. The recent rediscovery of BAT in humans has raised the possibility that BAT could be a therapeutic target for metabolic syndrome. In this chapter, we will discuss important structural and cellular features of the WAT and BAT and how obesity alters WAT and BAT structure and function.

Keywords

White adipocyte • Brown adipose tissue • Beige adipocyte • Angiogenesis • Extracellular matrix

1 Introduction

Fundamentally, obesity is caused by sustained positive energy balance. Adipose tissue (AT) is the major organ for energy storage in mammals, and excessive expansion of AT plays a central role in the pathology of obesity. AT is also an important endocrine organ, regulating several aspects of metabolism from appetite to nutrient partitioning and uptake by other tissues. Therefore it is important to understand the consequences of obesity on AT biology and function.

AT is a connective tissue composed predominantly of adipocytes, whose main functions are the storage of energy as triglycerides (TGs) in lipid droplets and the coordinated mobilization of these lipids to provide fuel to other organs. The AT also secretes hormones termed "adipokines" that help to coordinate these functions, as well as to inform the central nervous system of energy supplies as a permissive level of control for costly physiological processes such as a pregnancy. AT is distributed throughout the body in various depots with location-specific differences in their structure, composition, and functions. For example, white AT (WAT) can be found subcutaneously (subcutaneous WAT, scWAT) and in the intra-abdominal cavity (visceral WAT, visWAT). WAT is characterized by its ability to expand to meet the storage demands determined by nutrient excess in the context of positive energy balance. These lipids should be efficiently stored but also released when energy supply to peripheral tissues is required.

The primary function of brown adipose tissue (BAT) is heat generation (thermogenesis) to maintain body temperature. Until recently BAT was not much more than a "rodent curiosity." However the realization that human infants and adults have BAT has reinvigorated the research in this area. Brown adipocytes are uniquely adapted to thermogenesis by the expression of uncoupling protein 1 (UCP1) in their mitochondria. UCP1 uncouples substrate oxidation from ATP synthesis, so heat is produced instead, a process known as thermogenesis, which primarily serves to defend the core body temperature in the face of heat loss to the environment.

WAT structure and function are maladapted in human obesity particularly when associated with metabolic complications. We have proposed the AT expandability hypothesis that suggests that WAT dysfunction is a key determinant of obesity-associated metabolic complications. Healthy WAT maintains metabolic homeostasis

by sequestering excess nutrients and expands and retracts dynamically as energy availability fluctuates between surplus and shortfall. In contrast, in a chronic state of positive energy balance, WAT – especially visWAT – is constantly compelled to expand. WAT expansion capacity is not infinite, and beyond a genetically/epigenetically determined limit, WAT is functionally impaired both as a storage and endocrine organ. The excess of lipid species then accumulates in key metabolic organs such as skeletal muscles and the liver (referred to as ectopic lipid accumulation) which negatively affects their function (known as "lipotoxicity") and can be considered as one of the key pathogenic mechanisms associated with the development of the metabolic syndrome.

From experiments with obese rodents, it is known that BAT activation removes nutrient excess by oxidizing lipids and glucose; this can limit weight gain and mitigate the negative impact of obesity on WAT and other organs. Therefore promoting BAT thermogenesis has recently been considered as a potential therapeutic approach to treat human obesity and its associated complications. However, the success of this strategy relies on a better understanding of BAT structure and function in humans, areas that have only been rigorously investigated since 2009.

This chapter outlines the cellular and structural features and the biological functions of WAT and BAT; their anatomical distribution, plasticity, and development; as well as the roles of immune cells, the vascular network, the extracellular matrix, and the nervous system in regulating AT function. The impact of obesity on each of these aspects will also be described.

2 White and Brown Adipose Tissue: Cellular and Structural Features

2.1 Adipose Tissue Cellular and Structural Components

Adipocytes are the main cellular components of AT. In WAT, adipocytes are spherical cells that store fat in the form of TGs in a unilocular lipid droplet. Adipocyte diameter varies from 30 μm to 180 μm, depending on the anatomical location and lipid content. The lipid droplet is a dynamic structure, growing and shrinking as lipids are added or removed, a process enabled by enzymes, lipid droplet proteins, and the cytoskeleton.

In contrast, BAT adipocytes store lipid in multiple, smaller lipid droplets. Multilocularity increases lipid droplet surface area and is more suited for the quick and titrated release of stored lipids for oxidation. Brown adipocytes also have more and more specialized mitochondria, which express UCP1, the mitochondrial inner membrane protein that enables heat production by uncoupling substrate oxidation from adenosine triphosphate (ATP) production. In rodents, UCP1-expressing multilocular adipocytes can also be found dispersed in scWAT under conditions that require increased heat production (e.g., chronic cold exposure). These UCP1-positive cells are termed as "beige" or "brite" (brown-in-white) adipocytes. Whereas brown adipocytes exist as a homogenous population demarcated by connective tissue, beige adipocytes exist interspersed among white adipocytes within scWAT.

Adipocytes interact with other cellular components in AT, including the nonmyelinated nerve endings of noradrenergic sympathetic fibers, resident immune cells, and vascular cells, such as endothelial cells and pericytes. In addition, specific AT cellular components can be replenished by progenitor populations of preadipocytes and mesenchymal stem cells. Cells in AT also interact with the extracellular matrix (ECM), which is composed mainly of collagens and provides structural support and regulation of critical cellular functions such as survival and differentiation. The cellular composition of BAT and WAT are distinct and reflect their different functions. For example, there are more sympathetic nerve endings and capillaries per adipocyte in BAT compared to WAT. This is partly due to smaller adipocyte size and is adapted to the increased requirements in BAT for gas exchange and the supply of oxidative substrates. Furthermore, at least in rodents the developmental origins of BAT and WAT adipocytes are different, and even different WAT depots derive from distinct

lineages (Carobbio et al. 2013). Though this is impossible to interrogate in humans, the selective loss of particular WAT depots in different types of partial lipodystrophies suggests distinct origins for adipocytes of different WAT depots (Agarwal and Garg 2006).

2.2 Anatomical Distribution of WAT

WAT is anatomically distributed into two main depots: subcutaneous (scWAT) and visceral (visWAT) (Fig. 1a). ScWAT is found below the skin, and depending on their anatomical location, different scWAT depots have different structural and ultrastructural features (Sbarbati et al. 2010). For example, the scWAT depots localized to the abdominal area are characterized by large, tightly packed adipocytes, relatively poor vascularization, and a weak ECM. The structural scWAT is more fibrous and vascularized and is located in the limbs and hips. Finally, the fibrous scWAT is composed of smaller adipocytes and is particularly suited to tolerate mechanical stress in areas such as the heel by its enrichment with ECM components. Visceral WAT (visWAT) is composed of intraperitoneal/intra-abdominal depots, including omental, mesenteric, and gonadal depots (epididymal and paratesticular in males, periovarial and periuterine in females). Discrete visWAT depots are also found in contact with organs such as the heart (pericardial), arteries (perivascular), and kidneys (retroperitoneal). Other AT depots include mammary AT and bone marrow AT. Morphologically, adipocytes in visWAT are smaller than those in scWAT.

The amount and distribution of lipids between visWAT and scWAT depots differ depending on gender and age. For example, in females, scWAT is preferentially located in the gluteofemoral area, whereas in males it is predominantly located in the abdominal area (Tchernof et al. 2006). In males, abdominal WAT mass increases with age independently of adiposity, and in females the postmenopausal period is associated with an increase in visWAT potentially due to a relative increase in testosterone levels (Janssen et al. 2010).

2.3 Anatomical Redistribution of WAT in Obesity

Obesity is characterized by an excessive increase in fat mass that predisposes to the development of metabolic complications such as cardiovascular diseases and type 2 diabetes. To accommodate the excess of nutrients, existing adipocytes become enlarged (hypertrophy) and new adipocytes are recruited (hyperplasia). Furthermore, in obesity there is an anatomical repartitioning of WAT mass from scWAT to visWAT (Tchernof and Després 2013). Compared to scWAT, visWAT releases more pro-inflammatory cytokines and is more metabolically active, tending to liberate more free fatty acids (FFAs) into the circulation (Giorgino et al. 2005; Fain 2006). Therefore the accumulation of intra-abdominal fat may negatively affect the function of other metabolic organs by increasing systemic inflammation and elevating FFA levels in the blood.

VisWAT dysfunction is associated with ectopic lipid accumulation in important metabolic organs such as the liver, heart, pancreas, and skeletal muscle (Fig. 1b). These lipids can accumulate as intracellular lipids (e.g., within hepatocytes in the liver or within myocytes in muscle), form a new fat depot (e.g., intermuscular AT), or accumulate in preexisting visWAT depots (e.g., pericardial and perivascular depots). Ectopic lipid accumulation is associated with the so-called lipotoxic effects. For example, intracellular lipids can impair insulin sensitivity, especially in myocytes and hepatocytes (Borén et al. 2013).

2.4 Anatomical Distribution of BAT

BAT has long been known to exist in infants. Infants are at a higher risk of losing core body temperature when exposed to a cooler environment than adults, due to their larger surface-area-to-volume ratio. Though newborns are born with scWAT for insulation, they require BAT thermogenesis to counteract excessive heat loss. BAT represents about 1 % of body weight in newborns and is distributed strategically in multiple depots to

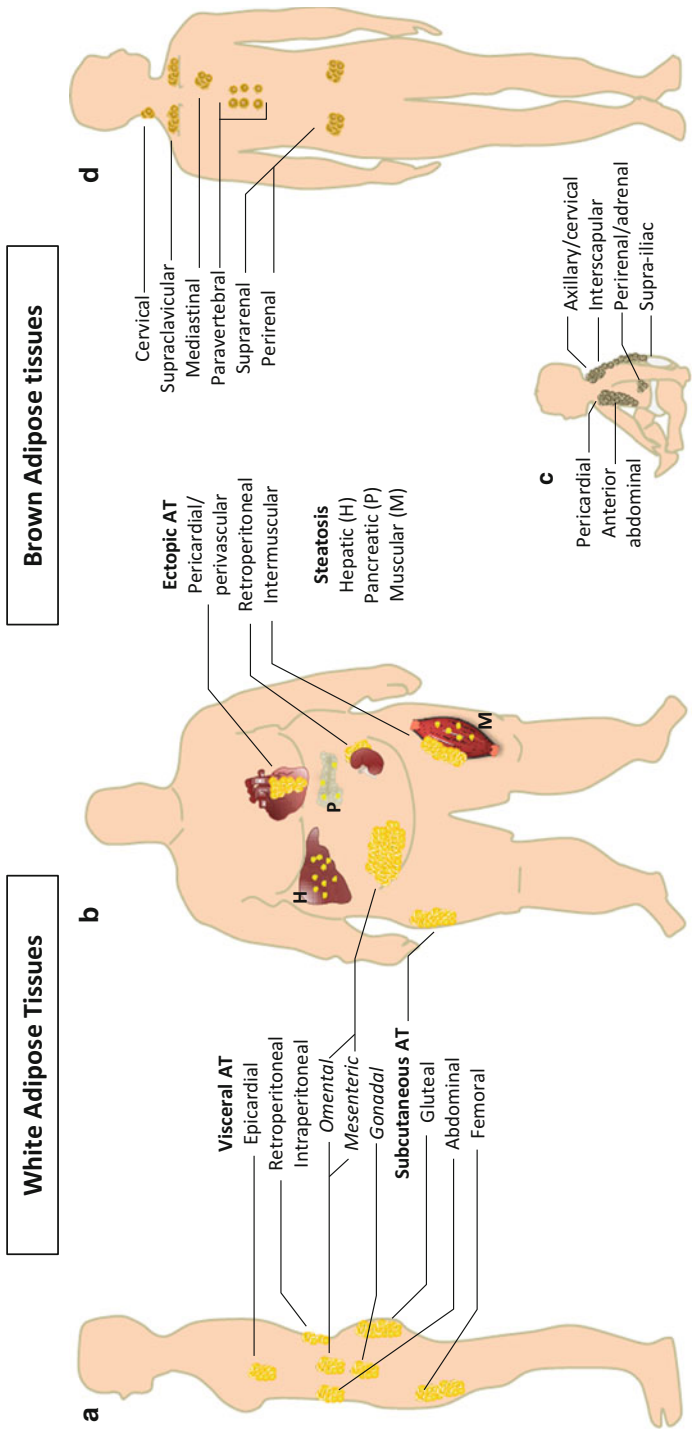

Fig. 1 Anatomical distribution of adipose tissue depots. (**a**) White adipose tissue (*AT*) depots in a lean adult (Bjørndal et al. 2011). Subcutaneous AT (*scWAT*) depots include gluteal, abdominal, and femoral depots. Visceral AT (*visWAT*) depots include epicardial, retroperitoneal, and intraperitoneal depots. Intraperitoneal depots can be further subdivided into omental, mesenteric, and gonadal depots (epididymal and paratesticular in males, periovarial and periuterine in females). (**b**) Ectopic lipid accumulation in obesity. Lipids can accumulate in preexisting or new fat depots (visceral, pericardial, perivascular, retroperitoneal, and intermuscular AT) or within cells leading to steatosis in the liver, pancreas, and muscle. (**c**) Brown adipose tissue depots in infants (Lean 1989). These depots are strategically placed to protect and warm the blood flow of key organs and areas of the body (in brackets as follows): axillary/cervical (head), perirenal/adrenal (kidneys), interscapular (spinal cord), supra-iliac (lumbar and azygos veins), pericardial (heart), anterior abdominal (liver). (**d**) Brown adipose tissue depots in adults (Nedergaard et al. 2007). Some brown adipose tissue depots persist in adults, including cervical, supraclavicular, mediastinal, paravertebral, suprarenal, and perirenal depots. References: Lean 1989; Nedergaard et al. 2007; Bjørndal et al. 2011

protect key organs and areas of the body and to warm the blood flow to these areas (Fig. 1c) (Lean 1989).

Postnatally, many infant BAT depots such as the interscapular depot lose their "brown" phenotype, including loss of UCP1 expression and increased adipocyte size (Lean 1989). However, some deeper infant BAT depots (e.g., the perirenal depot) are known to persist into adulthood (Fig. 1d). The use of metabolic image technology in the form of 2-[^{18}F]fluoro-2-deoxyglucose positron emission tomography coupled with computed tomography (FDG-PET/CT) has evidenced the presence of BAT in adult humans. FDG-PET measures the uptake and accumulation of FDG, a radioactive analogue of glucose that cannot be metabolized. FDG-accumulating tissues are visualized using PET and identified as AT using CT. Biopsies have demonstrated the presence of UCP1 in several FDG-accumulating adipose tissue depots (Fig. 1d) (Cypess et al. 2009; Lichtenbelt et al. 2009; Virtanen et al. 2009).

As a percentage of body weight, adults have much less BAT compared to infants. Also, the likelihood of BAT detection is higher in females (Ouellet et al. 2011). An exception to the gradual loss of BAT from birth through adulthood is the observed increased prevalence of BAT during puberty compared to childhood (Gilsanz et al. 2013). It is notable that BAT activity decreases with age, whereas the incidence of metabolic diseases increases with age. Indeed, decreased BAT activity is associated with surrogate parameters of metabolic dysfunction, such as increasing BMI, percent body fat, and plasma glucose levels (Ouellet et al. 2011).

Considering beige cells, data from rodents indicates that cold exposure preferentially recruits beige cells in scWAT compared to visWAT. However, it is unclear whether UCP1-expressing adipocytes can be recruited in WAT depots of healthy humans. UCP1-expressing multilocular adipocytes have been reported in WAT of patients with pheochromocytomas and paragangliomas (Frontini et al. 2013; Søndergaard et al. 2014). These catecholamine-secreting cancers may mimic the effects of chronically increased sympathetic nervous tone to WAT in response to long-term cold exposure, which is the stimulus for beige cell recruitment in rodents. However, the recruitment of UCP1-expressing adipocytes has not been demonstrated in the WAT of healthy humans under physiological conditions, and unfortunately FDG-PET/CT is not sensitive enough to distinguish clusters of thermogenic adipocytes in WAT (Muzik et al. 2013).

In addition to the question of whether beige adipocyte recruitment is a physiological phenomenon in humans, the question of whether the adipocytes in human BAT depots are more similar to rodent beige adipocytes or rodent brown adipocytes is also unresolved. For example, the UCP1-expressing adipocytes in adult human supraclavicular BAT occur in clusters interspersed among white adipocytes, a pattern reminiscent of the beige cells in rodent scWAT. In contrast, the human infant interscapular BAT depot is dominated by multilocular UCP1-expressing adipocytes and is separated from surrounding WAT by connective tissue, a structural arrangement reminiscent of the rodent interscapular BAT depot (Lidell et al. 2013).

3 Metabolic Functions of Brown and White Adipose Tissue

3.1 Metabolic Function of WAT

Classically described as an organ for energy storage, WAT is also a key metabolic endocrine organ. WAT releases circulating factors that are central to the coordinated regulation of energy metabolism. Here we will consider the mechanisms regulating WAT energy storage and mobilization, as this is most directly related to WAT structure, and we point the readers to the chapter on adipokines (▶ Chap. 22, "Adipokines and Metabolism") for further information on the endocrine function of WAT.

3.1.1 Triglyceride Storage and Mobilization of Energy Reserves

In the postprandial state, nutrients are absorbed by the intestinal tract and enter the blood stream. Most of the absorbed nutrients are stored in liver

and WAT in the form of glycogen and triglycerides, respectively. Insulin is the major anabolic hormone orchestrating in this process. To be stored in WAT, triglycerides (TGs) from blood are hydrolyzed into FFAs, taken up by the adipocyte, and re-esterified into TGs that are incorporated to the lipid droplet (Fig. 2a).

In the postabsorptive state, energy reserves are mobilized in response to catecholamines such as adrenaline, released by the adrenal medulla, and noradrenaline, released by nerve endings of the sympathetic nervous system (SNS) within WAT. In a process termed lipolysis, catecholamines bind to β-adrenergic receptors (ARs) (primarily β3 subtype in mice and β1/2 in humans), activating protein kinase A (PKA) to initiate the breakdown of intracellular TGs into FFAs and glycerol, which are released into the circulation (Fig. 2a). These are taken up by the liver and muscles (sites of FFA oxidation), and glycerol is used as a substrate for hepatic gluconeogenesis. Glucagon, which is secreted by endocrine pancreatic α-cells in response to catecholamines, plays a complementary role by promoting gluconeogenesis by the liver and in rodents lipolysis by WAT as well. Importantly, cold exposure also increases WAT lipolysis via the SNS; in this context, FFAs released by WAT are taken up by BAT and used as substrates for thermogenesis.

In the absence of a lipolytic stimulus, lipolysis is repressed by basal levels of catecholamines engaging α 2-ARs; these inhibitory receptors have a higher affinity for catecholamines compared to β-ARs. α 2-AR-mediated suppression of lipolysis is overwhelmed when the local concentration of catecholamines increases, activating pro-lipolytic β-ARs. Postprandially, lipolysis is also repressed by insulin.

Energy storage and mobilization show depot-specific differences. In particular, higher lipolytic rates are observed in visceral adipocytes compared to subcutaneous adipocytes, due to increased lipolytic responsiveness to adrenergic stimulation and reduced sensitivity to the anti-lipolytic effects of insulin and α 2-AR signaling (Giorgino et al. 2005). Because the blood supply of visWAT drains into the portal vein, in obesity hepatic metabolism may be particularly impaired by the redistribution of fat mass to the more metabolically active visWAT and the consequent increased load of FFAs into the blood.

3.1.2 Altered Metabolic Function During Obesity

Obese WAT is characterized by an altered secretion profile of adipokines, discussed in chapter (▶ Chap. 22, "Adipokines and Metabolism"), and functionally altered energy storage and mobilization. Firstly, FFA uptake and triglyceride storage are facilitated by the upregulation of FFA uptake mechanisms. For instance, LPL expression and activity are increased in obese scWAT and visWAT, and LPL expression positively correlates with BMI (Clemente-Postigo et al. 2011). Additionally, CD36 expression is induced during obesity and positively correlated with increased visWAT mass (Love-Gregory and Abumrad 2011). These processes promote WAT expansion. Secondly, the regulation of lipolysis is impaired due to reduced lipase activity and decreased responsiveness to catecholamines (Lafontan and Langin 2009).

3.2 Metabolic Function of BAT

The metabolic function of BAT has been primarily studied in rodents. Their small size, and therefore relatively increased surface-area-to-volume ratio, means that adult rodents are dependent on BAT thermogenesis to maintain their core body temperature. Heat production is an energy expensive process that has negative effects on energy balance and affects whole-body substrate utilization in rodents and likely in humans as well.

3.2.1 Thermogenesis

Brown adipocytes are uniquely optimized for thermogenic function by UCP1. UCP1 resides in and regulates the proton permeability of the inner mitochondrial membrane (IMM). In mitochondria, substrate oxidation is coupled to electron transport in order to generate a proton gradient and a potential difference across the IMM. ATP is made using the energy released when protons flow down their electrochemical gradient across the

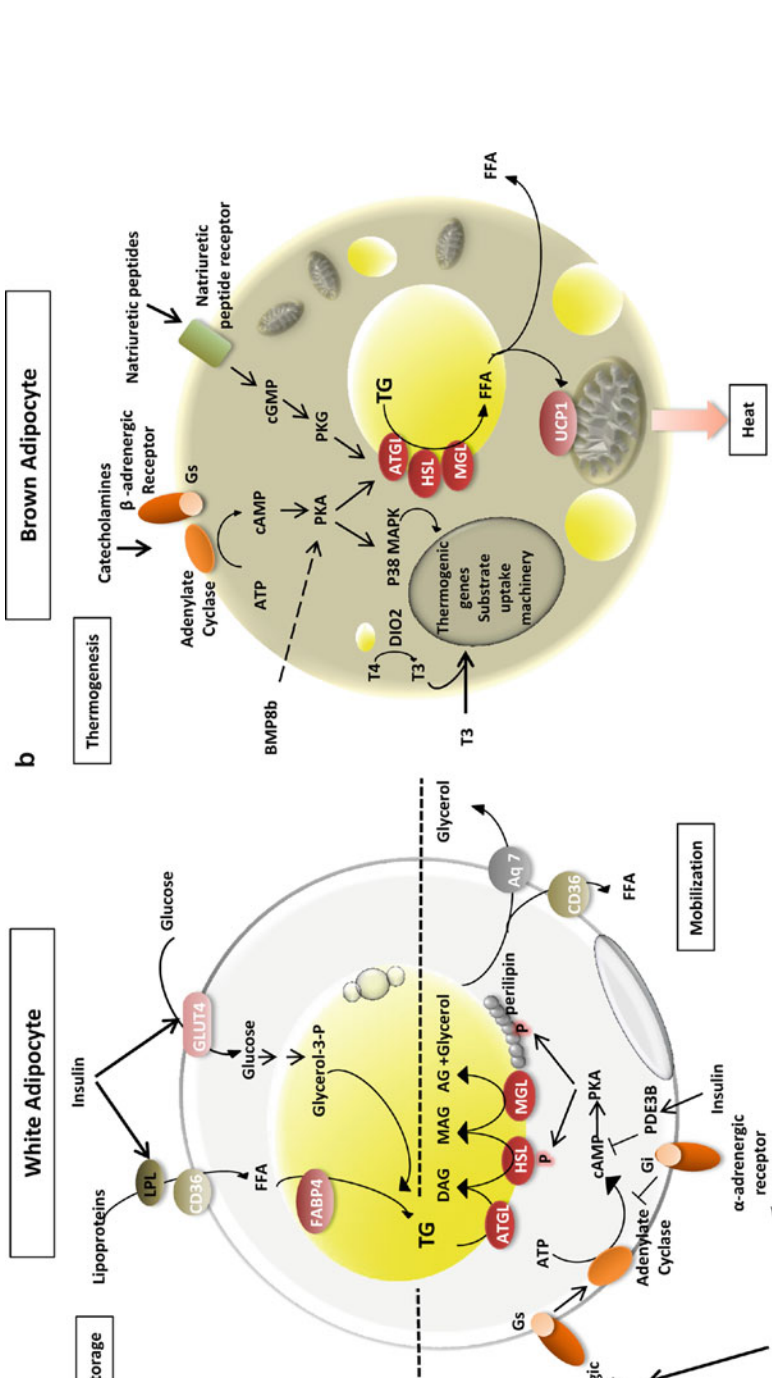

Fig. 2 Signaling pathways regulating adipocyte function. The molecular details of these pathways derive primarily from studies using rodent models. (**a**) The intracellular signaling pathways that mediate the response of white adipocytes to extracellular signals (insulin, catecholamines, and glycerol) that promote energy storage and mobilization. Insulin promotes energy storage by adipocytes. Insulin stimulates the translocation of lipoprotein lipase (*LPL*) to the vascular walls of capillaries, where it hydrolyzes triglycerides, which are carried in the blood by lipoproteins. The resulting free fatty acids (*FFAs*) are taken up by adipocytes through membrane receptors, such as fatty acid translocase (CD36), and are rapidly sequestered by lipid-binding proteins, for example, fatty acid-binding protein 4 (*FABP4*). Insulin also regulates the translocation of GLUT4 glucose transporters to the plasma membrane, allowing glucose to enter the adipocyte by facilitated diffusion. Glucose uptake is important for adipocyte lipid storage because FFAs must be reincorporated into triglyceride molecules so that they can be stored in the lipid droplet, and this process requires glycerol-3-phosphate produced by glycolysis. Catecholamines drive energy mobilization. Catecholamines bind to β-adrenergic receptors to initiate the breakdown of intracellular TGs into FFAs that are released into the circulation. β-adrenergic receptors (*ARs*) interact with the Gs subunits of heterotrimeric G proteins; Gs subunits activate adenylate cyclase, leading to increased production of cyclic AMP and subsequent protein

IMM through ATP synthases. When activated by FFAs, UCP1 increases IMM proton permeability and thereby "uncouples" substrate oxidation from ATP synthesis, so heat is produced instead.

The metabolic rate of activated BAT is so elevated that intracellular lipid stores are quickly depleted, so oxidative substrates must be replenished by the uptake of lipids and glucose from the blood. The substrate uptake machinery of brown adipocytes is similar to that of white adipocytes. Like in WAT, insulin increases substrate uptake by BAT, coordinating BAT metabolism with the fasted or fed state. However, the SNS is the primary regulator of BAT activation. In response to a thermogenic stimulus – that is, a signal indicating an increased demand for heat production such as a decrease in environmental temperature – norepinephrine is released by sympathetic nerve endings in BAT and binds to β 3-ARs on brown adipocytes. The downstream signaling pathways have been studied primarily in rodent models. Lipolysis is activated similarly as in white adipocytes except for a few key differences (Fig. 2b). Firstly, the FFAs freed from intracellular triglycerides are used for oxidation and UCP1 activation. Secondly, lipolysis in BAT is coordinated to a non-insulin-dependent upregulation of the substrate uptake machinery to increase the uptake of oxidative substrates, such as FFAs released into the blood by WAT lipolysis. Finally, sympathetic stimulation increases the transcription of key thermogenic genes such as UCP1. In addition to cold exposure, BAT is also activated in rodents in response to excess nutrient consumption, for example, due to high-fat diet (HFD) feeding, a process known as diet-induced thermogenesis (Rothwell and Stock 1983).

Independently from the SNS, brown and beige adipocytes are regulated by a number of endocrine factors in rodents (Fig. 2b). Thyroid hormone is a key endocrine regulator of BAT thermogenesis. Though triiodothyronine (T3) has central effects that can regulate sympathetic tone to BAT, T3 is also generated locally by brown adipocytes (López et al. 2013). T3 regulates the transcription of the UCP1 gene via thyroid hormone response elements in its promoter. The unliganded thyroid hormone receptor acts as a transcriptional repressor, and the binding of T3 to its receptor relieves this repression (Rabelo et al. 1996).

Other endocrine factors regulate the responsiveness of brown adipocytes to adrenergic stimulation by interacting with the cAMP/PKA pathway and its effectors. For example, BMP8b increases the maximal thermogenic response of brown adipocytes to adrenergic stimulation by potentiating PKA activity (Whittle et al. 2012). In addition, PKA shares many intracellular targets with protein kinase G (PKG). As a result, cardiac natriuretic peptides (CNPs), which act via PKG, can induce lipolysis and the expression of thermogenic genes in brown and white adipocytes, a response which is additive to that of norepinephrine (Bordicchia et al. 2012). Recently, endocrine factors that bypass the sympathetic nervous pathways altogether to regulate brown and beige adipocyte activity have also been identified (Table 1).

The relevance of endocrine activators to human BAT is under investigation. For example, in an isolated case, levothyroxine treatment for thyroid cancer also increased BAT mass and

Fig. 2 (continued) kinase A (PKA) activation. PKA phosphorylates lipid droplet membrane proteins and lipases to stimulate lipolysis, releasing FFAs and glycerol that leave the adipocyte. In absence of a lipolytic stimulus, lipolysis is repressed by basal levels of catecholamines engaging α 2-ARs, which are coupled to Gi subunits that inhibit adenylate cyclase. Postprandially, lipolysis is repressed by insulin through activation of the phosphodiesterase (PDE3B), which limits PKA activation by degrading cyclic AMP. (**b**) The intracellular signaling pathways that mediate the response of brown adipocytes to extracellular signals (catecholamines, natriuretic peptides, triiodothyronine, BMP8b) that mediate thermogenesis. Abbreviations: acylglycerol (*AG*), adenosine triphosphate (*ATP*), adipose triglyceride lipase (*ATGL*), cyclic AMP (*cAMP*), cyclic GMP (*cGMP*), diacylglycerol (*DAG*), fatty acid-binding protein 4 (*FABP4*), fatty acid translocase (*CD36*), free fatty acid (*FFA*), glucose transporter 4 (*GLUT4*), glycerol-3-phosphate (*glycerol-3-P*), lipoprotein lipase (*LPL*), monoacylglycerol (*MAG*), phosphodiesterase 3 B (*PDE3B*), protein kinase A (*PKA*), triglyceride (*TG*), triiodothyronine (*T3*), uncoupling protein 1 (*UCP1*)

Table 1 Endocrine factors that bypass the sympathetic nervous pathways to regulate brown and beige adipocyte activity

Molecules	Mechanism of action	References
FGF21	Release of FGF21 by the liver within hours of birth is an important signal promoting thermogenesis in neonatal mice. FGF21 is also released by brown adipocytes themselves, acting locally to further increase BAT thermogenesis and systemically to induce beige adipocyte recruitment in WAT	Hondares et al. 2011a, b; Fisher et al. 2012
Irisin, cardiotrophin-1	Recruit beige adipocytes in white adipose tissue by acting on white adipocytes and their precursors	Moreno-Aliaga et al. 2011; Boström et al. 2012
Lactate, nitrate, β-aminoisobutyric acid, adenosine	Activate brown adipocytes and recruit beige adipocytes	Carrière et al. 2014; Gnad et al. 2014; Roberts et al. 2014a, b
Meteorin	Induces M2 polarization of macrophages to recruit beige adipocytes in WAT	Rao et al. 2014

References: Hondares et al. 2011a, b; Moreno-Aliaga et al. 2011; Boström et al. 2012; Fisher et al. 2012; Carrière et al. 2014; Gnad et al. 2014; Rao et al. 2014; Roberts et al. 2014a, b

activity as a side effect, and upon withdrawal of levothyroxine treatment BAT activity and mass decreased (Skarulis et al. 2010). Recent evidence that circulating levels of FGF21 and irisin are increased with cold exposure in humans also suggests that these factors may be involved in cold-induced thermogenesis (Lee et al. 2014a).

3.2.2 Regulation of Whole-Body Energy Metabolism

BAT activity can promote a negative energy balance and weight loss. In rodents, BAT thermogenesis is responsible for the ~60 % increase in metabolic rate caused by decreasing housing temperature from 30 °C to 23 °C (Cannon and Nedergaard 2011). Indeed, BAT ablation or dysfunction in rodents decreases energy expenditure, causing an obese phenotype (Lowell et al. 1993; Feldmann et al. 2009). Conversely, BAT simulation by cold exposure or β 3-AR agonism increases energy expenditure, attenuates weight gain, and decreases adiposity in rodent models of obesity (Vallerand et al. 1986; Himms-Hagen et al. 1994). The full impact of BAT activation on human energy expenditure has not been fully clarified, but it is likely less than in rodents due to a reduced dependence on BAT thermogenesis and lower BAT mass as a percent of body weight. However, a direct link between increased BAT activity and adiposity is suggested by the evidence that 2-h bouts of exposure to 17 °C for 6 weeks increased BAT activity and also decreased adiposity in healthy volunteers (Yoneshiro et al. 2013).

In terms of whole-body metabolism, increased energy expenditure by BAT requires increased substrate uptake and utilization. Increased glucose and lipid disposal by activated BAT is sufficient to normalize hyperglycemia and hyperlipidemia in mouse models of diabetes and dyslipidemia (Arbeeny et al. 1995; Bartelt et al. 2011). The fact that sustained BAT activation introduces a negative energy balance may indicate that the main beneficial effects of BAT activation on diabetes and dyslipidemia are secondary to its effects in body weight. However, in some experiments activation of BAT by chronic treatment with a β 3-AR agonist did not decrease body weight but did decrease serum levels of glucose and FFAs and also increased peripheral insulin sensitivity (Liu et al. 1998). This suggests that BAT activation directly improves glucose homeostasis, so the fact that BAT activation can also protect against obesity is an added advantage. BAT endocrine activity may also regulate of whole-body energy metabolism. Some of the molecules described previously as thermogenic activators are also factors secreted by BAT itself. In particular, BAT production of certain factors known to regulate metabolism is sufficient to have a systemic impact (Table 2), suggesting that BAT may be an important node for the regulation of energy and glucose homeostasis.

Table 2 Factors with endocrine functions that are released by brown adipocytes

Molecules	Importance	References
T3	Regulates whole-body energy expenditure	Hondares et al. 2011b
FGF21, IL-6	Regulate glucose homeostasis	Li et al. 2002; Hondares et al. 2011b
Leptin, adiponectin	Regulate appetite and glucose and lipid metabolism. Expression is downregulated with increased BAT activity and therefore may be of lesser importance	Cannon and Nedergaard 2004

References: Li et al. 2002; Cannon and Nedergaard 2004; Hondares et al. 2011a

In humans, the glucose uptake rate of cold-stimulated BAT per gram of tissue exceeds that of insulin-stimulated skeletal muscle, and evidence suggests that activated BAT may regulate glycemia (Orava et al. 2011). Indeed, fasting glucose levels are lower in individuals with detectable BAT than in those without detectable BAT, though a causal link has not been established (Lee et al. 2010). In terms of an endocrine function for human BAT, FGF21 expression has been detected in neonatal BAT and in adult BAT induced by pheochromocytoma (Hondares et al. 2014). However, the secretion profile of physiological adult BAT has not been analyzed, neither in healthy conditions nor in the context of obesity and metabolic disease.

3.2.3 Effect of Obesity on Thermogenesis and Regulation of Energy Metabolism

Though increasing BAT activity in rodent models of obesity has beneficial effects on energy balance and metabolism, BAT does become dysfunctional in the context of obesity in rodents. For example, in *ob/ob* mice BAT is insulin resistant, suggesting that like other insulin-sensitive tissues, BAT is also negatively affected by hyperinsulinemia and hyperglycemia in the context of obesity (Collins et al. 1994). In line with this, a study specifically investigating BAT activation by cold and insulin stimulation in humans measured reduced responsiveness to both of these stimuli in obese patients in terms of glucose uptake and blood flow (Orava et al. 2013). These results imply that BAT activity may be impaired in human obesity.

4 Adipose Tissue Plasticity

4.1 Adipogenesis

Both BAT and WAT are established in utero. In animal models, WAT depots have been found to derive from both the mesoderm and the neural crest, so distinct developmental origins may underlie the different gene expression patterns found in different WAT depots in humans (Berry et al. 2013). Rodent studies have shown that brown adipocytes derive from the paraxial mesoderm and interestingly share a $Myf5^{+}$ lineage origin with myocytes, whereas most white adipocytes have a $Myf5^{-}$ lineage origin (Fig. 3) (Carobbio et al. 2013).

AT expansion in the adult is fundamental to the functional roles of WAT and BAT. As we have seen, to act as an effective storage organ, WAT must expand if calorie consumption is excessive and conversely contract by releasing FFAs in fasting conditions. BAT is equally plastic and can expand or contract to match its thermogenic capacity to the thermogenic needs of the organism. In both cases, AT expansion requires the production of new adipocytes. Adipocytes are nondividing cells, so new adipocytes are made from undifferentiated precursor cells with proliferative capacity that persist in adult AT: mesenchymal stem cells and preadipocytes. Adipocyte differentiaiton encompasses the production of preadipocytes – which are committed to producing adipocytes – from mesenchymal stem cells, and the terminal differentiation of preadipocytes into mature adiopcytes.

4.1.1 White Adipocyte Differentiation

The first step of white adipocyte differentiation is the generation of preadipocytes from mesenchymal precursors. In vitro, mesenchymal precursors can be maintained in an undifferentiated, proliferating state by factors such as FGF2 and activin A

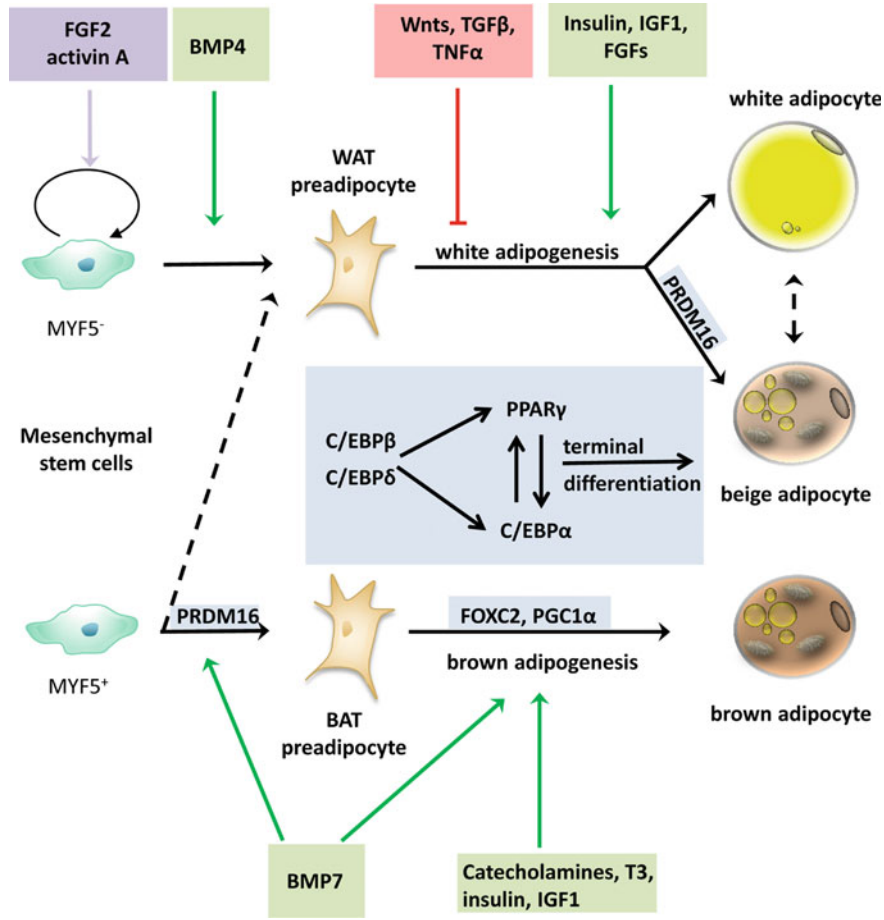

Fig. 3 Origins of adipocytes and transcriptional regulation of adipocyte differentiation. Mesenchymal stem cells and preadipocytes with proliferative and adipogenic capacity persist in adult AT. Rodent brown adipocytes derive from a MYF5^{+} lineage, unlike most white adipocytes (Carobbio et al. 2013). Beige adipocytes may derive from precursors or directly from white adipocytes (Lee et al. 2012; Rosenwald et al. 2013). C/EBPs and PPARγ transcription factors regulate adipogenesis, which is biased toward a thermogenic brown or beige phenotype by factors such as FOXC2, PGC1α, and PRDM16 (transcriptional control in *blue boxes*) (Puigserver et al. 1998; Rosen and Spiegelman 2000; Hansen and Kristiansen 2006; Lidell et al. 2011; Seale et al. 2011). Extracellular signals can maintain the undifferentiated, proliferating state of mesenchymal stem cells (*purple box*) and promote (*green boxes*) or inhibit (*red boxes*) adipocyte differentiation (Valverde 2002; Tang et al. 2004; Rosen and MacDougald 2006; Zaragosi et al. 2006, 2010; Tseng et al. 2008). References: Puigserver et al. 1998; Rosen and Spiegelman 2000; Valverde 2002; Tang et al. 2004; Hansen and Kristiansen 2006; Zaragosi et al. 2006, 2010; Rosen and MacDougald 2006; Tseng et al. 2008; Lidell et al. 2011; Seale et al. 2011; Lee et al. 2012; Carobbio et al. 2013; Rosenwald et al. 2013

and committed to the adipocyte cell lineage by BMP4 (Tang et al. 2004; Zaragosi et al. 2006, 2010). Adipogenesis is the production of adipocytes from preadipocytes, and extensive studies of this process in vitro have highlighted a cascade of transcription factors that regulates adipocyte differentiation (Fig. 3) (Rosen and Spiegelman 2000). C/EBPβ and C/EBPδ are induced first during mitotic clonal expansion of preadipocytes and subsequently induce C/EBPα (alpha) and PPARγ 2, which maintain the terminal differentiation of the adipocyte. This is characterized by cell cycle arrest and the induction of mature white adipocyte machinery, such as the lipogenic program, which is regulated by the transcription factor SREBP1c.

In vitro, the white adipogenic transcriptional cascade can be initiated or suppressed by extracellular signals (Fig. 3) (Rosen and MacDougald 2006). For example, insulin, insulin-like growth factor 1 (IGF-1), and glucocorticoids induce adipogenesis. Although FGF2 stimulates mesenchymal stem cell proliferation, this factor and other FGF family members (FGF1, FGF10) have also been shown to promote adipogenesis. In contrast, Wnt family members (such as WNT10b), TGF-β, and inflammatory cytokines (such as TNFα inhibit adipogenesis).

The identification of adipocyte precursors in the vasculature of murine and human scWAT (and rodent BAT) suggests that angiogenesis (the generation of new capillaries, discussed later) and adipogenesis are spatially and temporally coupled, linking the production of new adipocytes to the expansion of important ancillary components such as capillary networks (Tang et al. 2008; Tran et al. 2012).

4.1.2 Brown and Beige Adipocyte Differentiation

Like in WAT, mesenchymal stem cells and preadipocytes with proliferative and adipogenic capacity persist in adult BAT. Because, at least in rodents, brown adipocytes share a $Myf5^{+}$ lineage origin with myocytes, a unique component of brown adipocyte differentiation is the repression of myogenic genes, a role ascribed to co-activator PRDM16 (Seale et al. 2008). The source of beige adipocytes in rodent WAT is debated. It is possible that these cells arise by transdifferentiation of white adipocyte or by adipogenesis from beige-specific precursors (Lee et al. 2012; Rosenwald et al. 2013).

In vitro studies using rodent cells suggest that the transcriptional cascade that controls terminal differentiation into mature brown, and presumably beige, adipocytes shares many similarities to that of white adipocytes, including transcriptional control by C/EBPs and PPARγ 2 (Hansen and Kristiansen 2006). However, certain transcription factors direct this process toward a brown versus white adipocyte cell fate. For example, FOXC2 modulates the expression and activity of adrenergic signaling molecules, PGC1α regulates both mitochondrial and thermogenic gene expressions, and PRDM16 represses white adipocyte genes during beige adipocyte recruitment (Fig. 3) (Puigserver et al. 1998; Lidell et al. 2011; Seale et al. 2011).

Similar to brown adipocyte activation, brown adipogenesis is also regulated by the SNS and endocrine mechanisms. For example, brown preadipocyte proliferation can be stimulated by insulin, IGF-1, and catecholamines (via the β 1-AR) (Valverde 2002). Adrenergic signaling via the β 3-AR induces differentiation by promoting the transcription of thermogenic genes via transcriptional machinery such as PGC1α, CREB, and ATFII. Relief of thyroid hormone receptor repression of UCP1 transcription by T3 is important for terminal brown adipocyte differentiation, as is insulin's induction of lipogenic genes during adipogenesis (Valverde 2002). Interestingly, BMP7 alone can stimulate the differentiation of brown preadipocytes and commit mesenchymal precursors to a brown adipocyte cell fate (Tseng et al. 2008).

4.2 Adipose Tissue Expansion

WAT expansion can be achieved by increasing adipocyte number (hyperplasia) and increasing the size of the preexisting adipocytes (hypertrophy). At early stages of obesity, adipocyte size can increase up to 20-fold. More adipocytes are also made to increase the storage capacity of AT. In order to maintain proper WAT function in spite of an increased caloric burden, hyperplasia rather than hypertrophy is the preferable adaptation because hypertrophy negatively affects adipocyte function as suggested by the positive correlation between adipocyte size, insulin resistance, and increased risk of type 2 diabetes (Lundgren et al. 2007). Adipocyte hypertrophy is also associated with inflammatory gene expression and an altered secretory profile (Skurk et al. 2007). Unfortunately, hypertrophic AT displays a decreased adipogenic capacity, which aggravates hypertrophy by limiting the production of new adipocytes that could increase the tissue's storage capacity (Isakson et al. 2009). The overall failure of WAT as a storage organ of

lipids occurs when its maximum storage capacity is reached, leading to lipotoxicity in non-adipose tissues.

The body's demand for heat production by BAT also regulates BAT expansion. The amount of heat BAT is able to generate depends on the number of brown adipocytes. In rodents, when BAT thermogenesis is insufficient to maintain core body temperature, for example, in response to an acute reduction in environmental temperature, thermogenesis by muscle shivering makes up the difference. Over the course of 4 weeks at the cooler temperature, BAT thermogenesis is "adapted" to fully meet the thermogenic requirement of the organism. This is achieved by increasing BAT mass ("recruitment") and its thermogenic capacity. BAT recruitment is stimulated by a sustained increase in sympathetic tone to BAT. Incidentally, chronic sympathetic stimulation of WAT also recruits beige cells. The term "acclimation" refers to the physiological regulation of BAT mass so that BAT thermogenesis balances heat loss to the environment at a new environmental temperature. BAT can expand or atrophy depending on the changing thermogenic demands of the organism.

Three recent studies have demonstrated that chronic cold exposure is able to activate and recruit BAT in humans (van der Lans et al. 2013; Yoneshiro et al. 2013; Lee et al. 2014b). This is promising evidence that human BAT is an active, highly plastic "trainable" tissue responsive to physiological stimuli and that lessons learned from BAT recruitment in rodents have translational value. The effect of obesity on the ability to recruit BAT in humans has not been explored directly. However, as we have seen, insulin plays a key role in brown preadipocyte proliferation and differentiation. In the context of obesity, BAT is insulin resistant, and the likelihood of BAT detection decreases as BMI and adiposity increase (Ouellet et al. 2011). Though it is impossible to assign cause or consequence, given the evidence from rodent models, it is reasonable to hypothesize that insulin resistance in BAT may contribute to its reduced mass in obesity. The effect of obesity on beige adipocyte recruitment is even less well understood.

5 Immunity in WAT and BAT

5.1 Macrophages

Macrophages are found in WAT even in lean individuals; indeed, in rodents resident macrophages may contribute to the maintenance of WAT metabolic homeostasis (Cancello et al. 2006; Odegaard et al. 2007). These macrophages have a so-called anti-inflammatory "M2" phenotype (Lumeng et al. 2007a). Obesity is characterized by increased local inflammation in WAT, especially visWAT, in association with a general increase in systemic inflammation levels (Cancello et al. 2006; Kim et al. 2006). Local inflammation is promoted by adipocyte hypertrophy and hypoxia, which causes increased expression by adipocytes of inflammatory cytokines (e.g., TNFα, IL-6, and IL-1β) and chemokines (e.g., CCL2, CCL5, CXCL1, CXCL2, CXCL8).

Chemokines are chemoattractant cytokines that recruit and activate a variety of immune cells, most importantly macrophages. Macrophages bind to and migrate through the endothelium (the single layer of endothelial cells of a capillary) by binding to adhesion molecules that are expressed by endothelial cells and induced by inflammatory cytokines (Fig. 4) (Springer 1990). In human obesity, macrophage infiltration is more pronounced in visWAT compared to scWAT (Cancello et al. 2006). Inflammatory cytokines and FFAs released by adipocytes contribute to polarizing infiltrating macrophages (and potentially resident M2 macrophages) to a "M1" phenotype, which is characterized by production of inflammatory cytokines (Saganami et al. 2005; Lumeng et al. 2008). Macrophages that secrete high levels of inflammatory cytokines in spite of expressing M2 markers such as CD206 have also been found in obese visWAT and scWAT (Zeyda et al. 2007). Within obese WAT, macrophages accumulate around the dead adipocytes forming the so-called crown-like structures, taking up cellular debris, and accumulating lipids (Cinti et al. 2005). Overall, this leads to a positive feedback loop that reinforces local inflammation and WAT

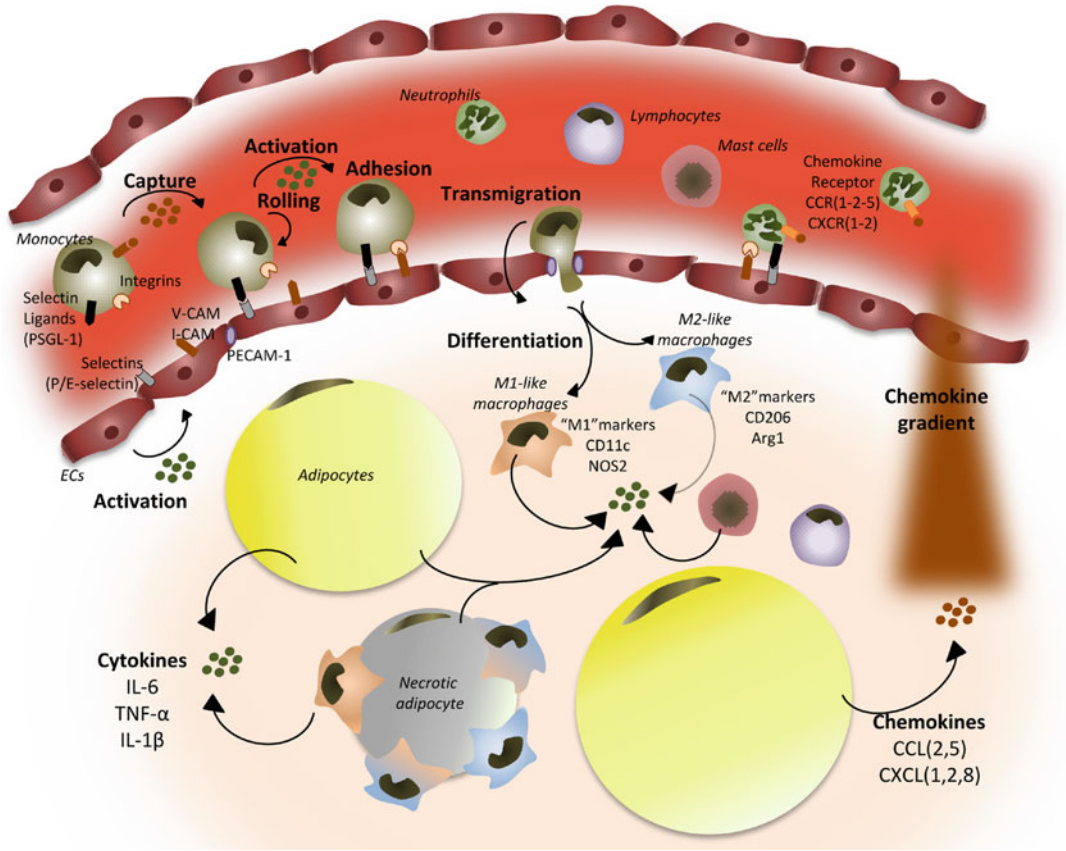

Fig. 4 Immune cell infiltration into obese adipose tissue and macrophage polarization. In obese WAT, hypertrophic and necrotic adipocytes secrete cytokines and chemokines that result in the accumulation of immune cells and tissue inflammation. Cytokines (TNFα, IL-6, and IL-1β) activate endothelial cells (*ECs*) to express various cellular adhesion molecules, including selectins, I-CAM, V-CAM, and PECAM-1 (intracellular, vascular, and platelet-endothelial cell adhesion molecule, respectively) (Springer 1990). Immune cells (monocytes, mast cells, neutrophils, and lymphocytes) are recruited to the endothelium by chemokines (CCL2, CCL5, CXCL1, CXCL2, CXCL8) binding to chemokine receptors. In a process termed diapedesis, the immune cells bind to the endothelium, become activated by cytokines, roll along the endothelium, and finally adhere, enabling their transmigration through the endothelium. Except neutrophils, which remain adherent to endothelium, most of immune cells infiltrate AT either through para- or transcellular mechanisms (Springer 1990). Monocytes differentiate within WAT into M1 (CD11c and NOS2 expressing) or M2 (CD206 and Arg1 expressing) macrophages according to their initial circulating phenotype and/or in response to the local microenvironment. Macrophages expressing M1 and/or M2 markers are organized in crown-like structures around dead adipocytes and participate, along with hypertrophic adipocytes and other infiltrating immune cells, to the maintenance of AT inflammation. References: (Springer 1990)

dysfunction (Fig. 4): inflammatory cytokines released by macrophages and adipocytes alike further promote adipocyte inflammation, insulin resistance, altered production of adipokines, impaired adipogenesis, and vascular remodeling (Saganami et al. 2005; Permana et al. 2006; Lumeng et al. 2007b; Bourlier et al. 2008).

5.2 Other Immune Cells in Obese WAT

Immune cell infiltration into obese WAT is not limited to macrophages. In fact in HFD-induced obese mice, the accumulation of T lymphocytes precedes macrophage infiltration into visWAT (Kintscher et al. 2008). In the same model,

early infiltration of B lymphocytes was also described in visWAT before any changes in body weight and insulin sensitivity (Duffaut et al. 2009). Furthermore, neutrophil accumulation in the lumen of the vasculature of scWAT and visWAT positively correlates with BMI (Nijhuis et al. 2009). The accumulation of activated neutrophils in AT vessels may promote endothelial cell senescence and chemokine production, which could increase the infiltration of immune cells and further aggravate AT inflammation (Rouault et al. 2013). Finally, though the absolute number of mast cells remains unchanged, mast cell degranulation activity is increased in the AT of obese patients, further contributing to inflammatory cytokine release (Divoux et al. 2012). Taken together, these alterations highlight how profoundly obesity induces inflammation in WAT.

5.3 The Lymphatic System in WAT

There is a greater density of lymphoid structures in visWAT compared to scWAT, which may be significant in the context of inflammation in obesity (Pond 2005). Apart from its roles in lipid absorption and immunity, the lymphatic system may also be a conduit for adipokines, which have been found in higher concentrations in lymph compared to the blood in humans (Miller et al. 2011). Adipocyte-derived pro-inflammatory cytokines including IL-6 and TNFα were also found in lymph in lean subjects (Miller et al. 2011). Therefore it is possible that local inflammation in visWAT in obesity may contribute to increased systemic inflammation due to the close association between visWAT and the lymphatic system.

5.4 Role of Macrophages in BAT

Macrophages seem to have an important physiological role controlling BAT activation in rodents. As well as regulating sympathetic tone to BAT, cold exposure also affects the phenotype of resident macrophages in rodent BAT, polarizing them to an M2 phenotype. These M2 macrophages then release norepinephrine, contributing to adrenergic activation of brown adipocytes (Nguyen et al. 2011). If and how this mechanism is altered in rodent models of obesity has not yet been investigated. Furthermore, M2 polarization of WAT macrophages also has been shown in rodents to contribute to beige cell recruitment via norepinephrine secretion (Qiu et al. 2014). Though brown adipocytes, like white adipocytes, become hypertrophic in rodent models of obesity, an inflammatory phenotype in BAT of obese mice has not been demonstrated as a mediator of BAT dysfunction in obesity.

6 Vascularization of Adipose Tissue

6.1 Mechanisms of Angiogenesis in WAT

Blood is supplied to adipose tissues via arterioles that branch into capillary beds. Arterioles are composed of a layer of smooth muscle cells surrounding a layer of endothelial cells (the endothelium). Capillaries are smaller in diameter and lack a smooth muscle cell layer. The vasculature is a key structure contributing to WAT function, transporting lipids intended for storage in WAT and adipokines and FFAs released by WAT. AT perfusion can be regulated by vasodilatation or vasoconstriction mediated by factors secreted by endothelial cells and by the SNS via ARs expressed on smooth muscle cells.

The vascular network must be remodeled during AT expansion. Angiogenesis is the development of a vascular network from a preexisting one and requires the proliferation and migration of endothelial cells to form a new capillary (Fig. 5). Upon maturation, the new vessel is stabilized by the production of ECM components, which form the basement membrane, and the recruitment of pericytes, which are mural cells of blood vessels. Microvascular pericytes stabilize new vessels by producing factors such as angiopoietins that promote endothelial survival and also represent a pool of adipocyte progenitors (Imhof and

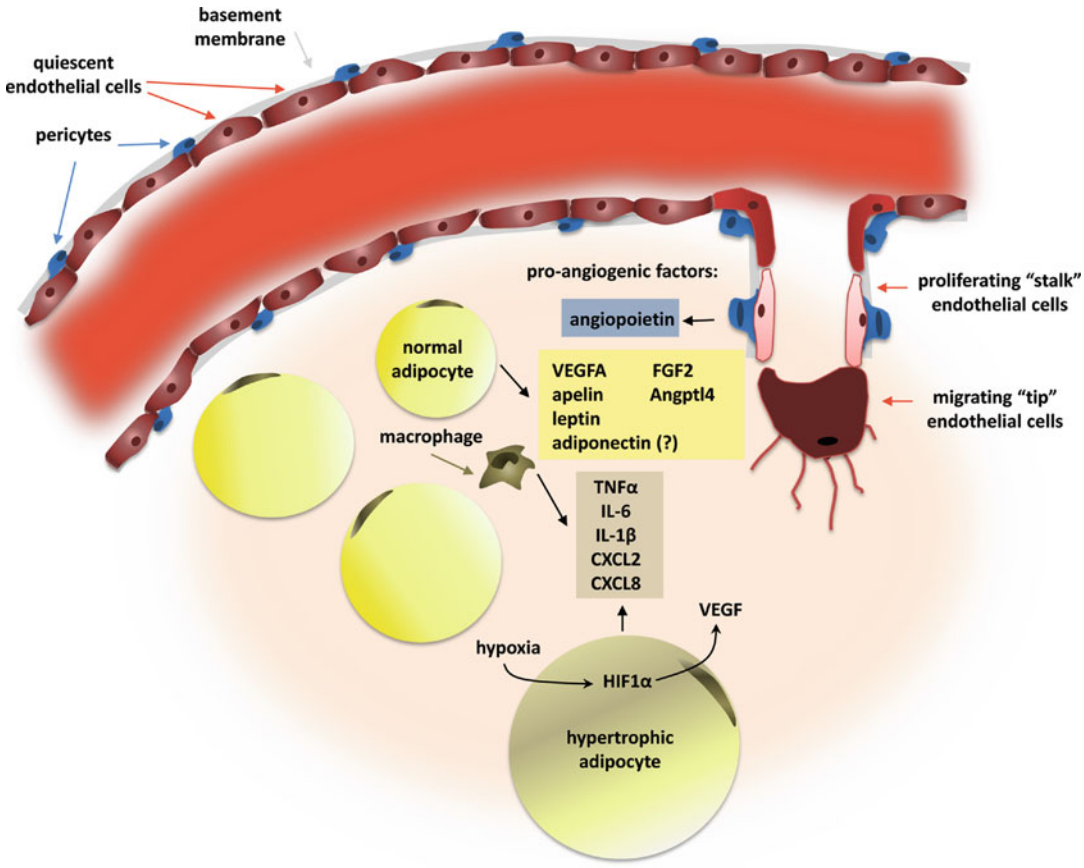

Fig. 5 Mechanisms of angiogenesis in obese adipose tissue. The main structural cells of blood vessels are endothelial cells and pericytes. Angiogenesis is driven by pro-angiogenic factors released by pericytes (angiopoietins) and adipocytes (VEGF-A, FGF2, apelin, Angptl4, leptin, potentially adiponectin) (Cao et al. 2001; Sundberg et al. 2002; Bråkenhielm et al. 2004; Ouchi et al. 2004; Kunduzova et al. 2008; Gealekman et al. 2011). Macrophages and hypertrophic adipocytes in obese WAT secrete inflammatory factors with angiogenic properties, including cytokines (TNFα, IL-6, IL-1β) and some chemokines (CXCL2, CXCL8) (Coppack 2001). Hypoxia also drives VEGF expression (Elias et al. 2013). The formation of a new vessel is initiated by the migration of endothelial "tip cells" at the tip of the new capillary and proliferating endothelial "stalk" cells that drive elongation. Endothelial cells produce ECM components to generate a new basement membrane, and pericytes stabilize the new vessel (Sundberg et al. 2002). References: Cao et al. 2001; Coppack 2001; Sundberg et al. 2002; Bråkenhielm et al. 2004; Ouchi et al. 2004; Kunduzova et al. 2008; Gealekman et al. 2011; Elias et al. 2013

Aurrand-Lions 2006; Traktuev et al. 2008). Angiogenesis is regulated by angiogenic factors produced by adipocytes, adipocyte precursors, vascular cells, and even macrophages (Fig. 5).

6.2 Vascular Dysfunction in Obese WAT

Obese WAT is characterized by increased angiogenic activity due to inflammation and hypoxia. For example, many inflammatory factors that are increased in obese WAT also have angiogenic properties, including cytokines (TNFα, IL-6, IL-1β) and some chemokines (CXCL2, CXCL8) (Coppack 2001). Additionally, the expression of hypoxia-responsive angiogenic factors, such as VEGF, is upregulated in obese WAT and more so in visWAT compared to scWAT (Villaret et al. 2010). However, angiogenesis is insufficient to prevent the development of hypoxia, particularly in visWAT (Villaret et al. 2010).

This may be caused by an impairment in vascular function, especially due to dysfunctional endothelial cells.

As well as playing a key role in angiogenesis, endothelial cells are important regulators of vascular integrity. Firstly, they control the passage of materials from the tissue to the blood and vice versa. On top of acting as a semipermeable barrier, endothelial cells also respond to various stimuli by releasing factors that regulate vasodilation and vasoconstriction, such as such as nitric oxide (NO) and endothelin-1 (ET-1), respectively. Importantly, insulin is one such stimulus, so it is not surprising that endothelial cell dysfunction is linked to insulin resistance. Insulin resistance decreases NO production and also increases endothelial cell expression of immune cell adhesion molecules, which facilitates monocyte infiltration (Potenza et al. 2009). Furthermore, inflammatory factors such as IL-6 and TNFα inhibit insulin-induced NO production and vasodilatation while increasing the secretion of the vasoconstrictor ET-1 (Rask-Madsen et al. 2003; Andreozzi et al. 2007). Overall, endothelial cell insulin resistance favors inflammation and vasoconstriction. Furthermore, endothelial cells from the visWAT of obese patients show increased expression of inflammatory markers, which may contribute to premature endothelial cell senescence, thereby further impairing vascular integrity (Villaret et al. 2010).

Endothelial cell senescence could also be promoted by the angiogenic environment of obese WAT, given that adipocyte-derived VEGF-A causes endothelial cell senescence in vitro (Villaret et al. 2010). Indeed, the altered secretion profile of hypertrophic adipocytes may directly contribute to endothelial cell dysfunction. For example, adiponectin and leptin positively regulate endothelial cell function: both promote NO production, and adiponectin has anti-inflammatory and antiapoptotic effects (Chen et al. 2003; Kobayashi et al. 2004; Kobashi et al. 2005). Thus, leptin resistance and reduced expression of adiponectin in obesity may limit their beneficial actions of these adipokines on endothelial cells. Finally, in vitro experiments suggest that endothelial cell dysfunction has a direct negative impact on adipocyte function. Cocultures of visWAT endothelial cells and adipocytes from obese subjects showed reduced lipolytic and insulin responses and increased inflammatory secretion profiles compared to cocultures of cells from lean subjects (Pellegrinelli et al. 2014b). Treatment with angiopoietin-1, a pericyte-derived factor, reduced the inflammatory profile endothelial cells from obese visWAT, and coculture of these treated cells with adipocytes from obese visWAT reduced cytokine secretion by the adipocytes (Pellegrinelli et al. 2014b).

In summary, the combination of inflammation, altered adipokine secretion, and endothelial cell dysfunction undermines vascular integrity in obese WAT. Therefore in spite of an adaptive increase in angiogenic activity in obese WAT, hypoxic areas still develop.

6.3 Angiogenesis in BAT

BAT is more vascularized than WAT. The vasculature plays a fundamental role in BAT thermogenesis as it is required to conduct BAT-generated heat throughout the body. In line with this, BAT activation is coupled to SNS-mediated vasodilatation and increased blood flow, which also ensures adequate gas exchange (Orava et al. 2013). Furthermore, angiogenesis accompanies BAT expansion in rodents in response to chronic cold exposure, ensuring the vascularization of newly formed brown adipocytes, which can derive from precursors residing in the vasculature (Tran et al. 2012). Mature brown adipocytes themselves stimulate vascular remodeling by secreting angiogenic factors including VEGF, FGF2, and NO. This response is not triggered by hypoxia; rather, it may be a direct effect of adrenergic stimulation of brown adipocytes (Xue et al. 2009). A reduction in capillary density accompanied by hypoxia is found in the BAT of diet-induced obese mice, in association with "whitening" of brown adipocytes (accumulation of lipid, loss of mitochondria, and reduced adrenergic signaling) (Shimizu et al. 2014). Interestingly, in this model BAT functionality was rescued by delivery to VEGF-A to

BAT, highlighting the dependence of thermogenesis on adequate vascularization.

Finally, beige cell recruitment in WAT is coupled to increased vascular density as well, and experimentally increasing vascularization in adipose tissue by overexpression of VEGF is sufficient to recruit beige cells in WAT (Xue et al. 2009).

7 Adipose Tissue Extracellular Matrix

7.1 Structure, Composition, and Physiological Role of the Extracellular Matrix in WAT

The extracellular matrix (ECM) is a complex network of macromolecules that is produced by and surrounds the component cells of AT (Fig. 6a1). Collagen and elastin fibers are the major structural proteins of the ECM, and they are bound by other components, such as fibronectin, laminins, and proteoglycans. The ECM provides structural support for the cells in AT and can also directly regulate AT function. For example, proteoglycans can regulate the release of secreted factors such as chemokines and growth factors. Additionally, the ECM communicates bidirectionally with cells via the binding of cellular integrins to ECM components such as fibronectin. Integrins are plasma membrane transmembrane proteins that are involved in both "outside-in" (ECM binding activates downstream signaling in cells) and "inside-out" signals (intracellular regulation of integrin/ECM binding activity) (Hu and Luo 2013). An important example of "outside-in" signaling is the interaction of ECM components with adipocyte cytoskeletal structures at focal adhesion complexes via integrins, thereby regulating cell shape (Fig. 6a2). This is relevant for adipogenesis, a process that requires drastic changes in cellular morphology as spindle-shaped preadipocytes grow larger and rounder as they differentiate into mature adipocytes (Rodríguez Fernández and Ben-Ze'ev 1989).

The ECM of adipocytes, known as the basement membrane (BM), is particularly enriched with collagen types IV and XVIII, laminin, and the glycoprotein entactin (Mariman and Wang 2010). In contrast, the ECM of preadipocytes is composed primarily of collagen types I and II and fibronectin (Mariman and Wang 2010). Therefore during adipogenesis the preadipocyte ECM must be degraded and the mature adipocyte BM synthesized (Fig. 6a3). ECM turnover is mediated by enzymes that degrade existing ECM structures, such as fibrinolytic plasmin and matrix metalloproteinases (MMPs), and by enzymes involved in the modification and cross-linking of newly synthesized components, such as ADAM proteases and lysyl oxidase (LOX), respectively (Mariman and Wang 2010). These processes are especially relevant to WAT expansion, when existing ECM components must be degraded to create room for new and larger adipocytes, and the ECM must be restructured around the expanded tissue. Interestingly, ECM composition and evolution during adipogenesis differ between WAT depots. For example, collagen IV and fibronectin expressions are higher in visWAT, whereas collagen I expression is higher in scWAT (Mori et al. 2014).

7.2 WAT Fibrosis in Obesity

Fibrosis, the excessive deposition of ECM proteins, is induced in obese scWAT and visWAT around adipocytes and blood vessels (Divoux et al. 2010). Transcriptomic analyses of scWAT from obese subjects show an induction of ECM components such as integrins, collagens, proteoglycans, laminins, proteases, and LOX (Henegar et al. 2008). This upregulation positively correlates with BMI and the expression of inflammatory markers (Henegar et al. 2008). Indeed, it is likely that chronic low-grade inflammation in obese WAT contributes to the development of fibrosis. In a time-course microarray study of the WAT of diet-induced obese mice, inflammatory-related genes were induced in visWAT prior to genes involved in fibrosis (Kwon et al. 2012). Furthermore, macrophage accumulation into visWAT preceded the appearance of fibrosis in the same model (Strissel et al. 2007). Immune cells may promote fibrosis by promoting TGF-β signaling, either by secreting TGF-β and its family member activin A or by

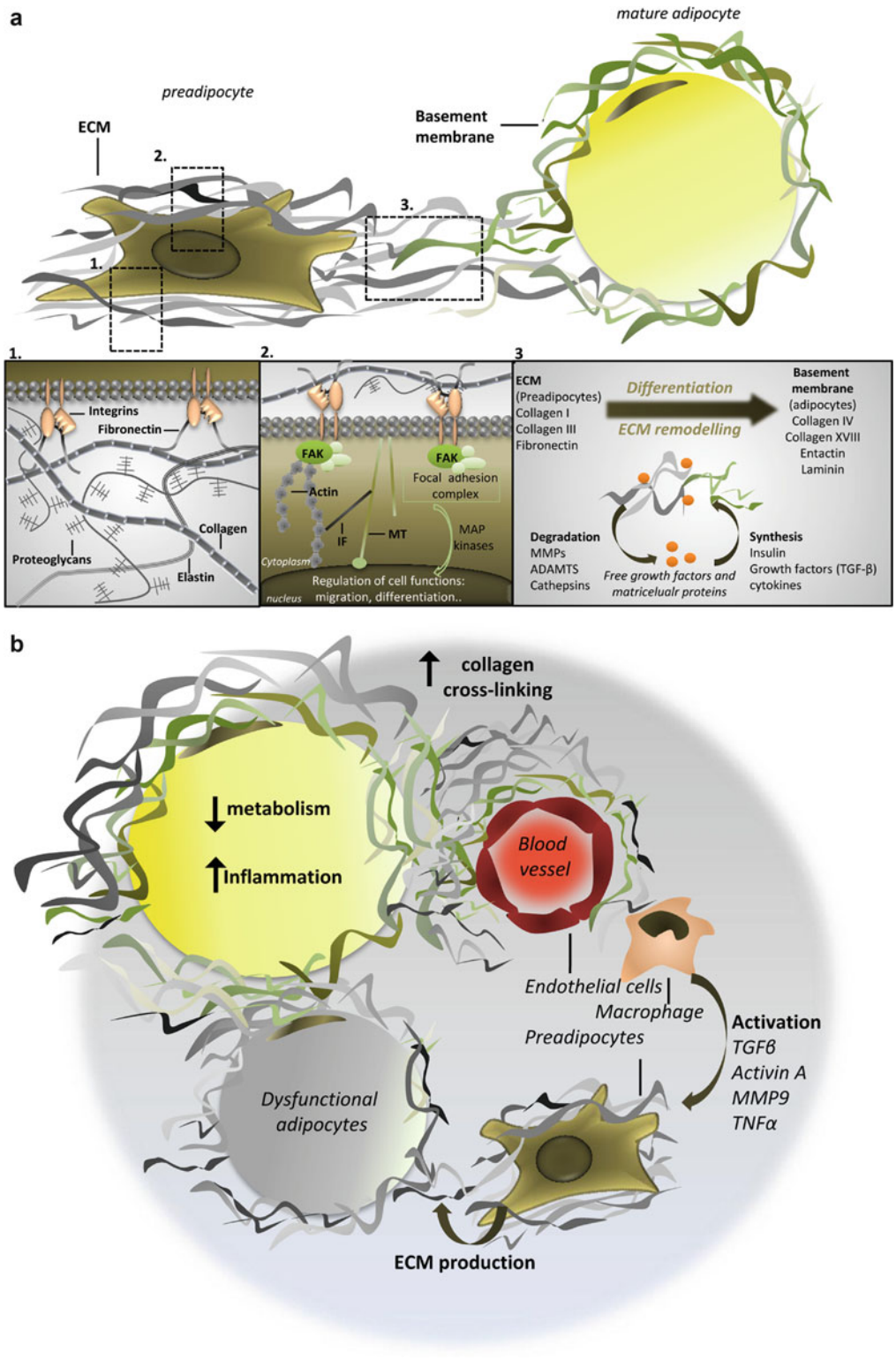

Fig. 6 (continued)

releasing MMP9, a protease that can activate TGF-β (Yu and Stamenkovic 2000; Dreier et al. 2004; Tracy 2012). Activin A and TGF-β (beta) induce preadipocytes, endothelial cells, and mature adipocytes to synthesize ECM components; in particular, preadipocytes from obese scWAT adopt a fibroblast-like phenotype (Fig. 6b) (Keophiphath et al. 2009; Divoux et al. 2010; Hocking et al. 2010). The resulting fibrosis can impose mechanical constraints that may negatively impact adipocyte function and limit adipose tissue expansion, exacerbating metabolic dysfunction.

7.3 Structure, Composition, and Physiological Role of the Extracellular Matrix in BAT

Although the ECM is a well-described WAT, few studies focus on the BAT ECM and its remodeling in pathophysiological conditions. The BM of rodent brown adipocytes is known to contain collagen IV, laminin, and fibronectin and may be more enriched with heparin sulfate proteoglycan compared to the white adipocyte BM (Haraida et al. 1996). It would be expected that brown adipocytes in BAT might interact with their ECM in a similar way to white adipocytes in WAT.

A few recent studies have specifically highlighted how the BAT ECM may regulate BAT function. For example, MAGP-1 (microfibril-associated glycoprotein 1) stabilizes microfibril networks to confer tissue elasticity and also regulates cellular signaling by interacting with cell-surface receptors and modulating the bioavailability of growth factors such as TGF-β. MAGP-1-deficient mice displayed increased TGF-β activity in BAT and reduced thermogenesis and UCP1 gene expression, a phenotype which was rescued by TGF-β neutralization (Craft et al. 2014). Fibrosis in BAT may also impair thermogenesis. In one study, BAT inflammation and fibrosis were genetically induced in rodents by overexpression of endotrophin (a C-terminal cleavage product of the COL6α 3 chain), and this was accompanied by reduced energy expenditure (Sun et al. 2014). Fibrosis was induced in another rodent model by VEGF neutralization; this led to capillary dropout in BAT, local hypoxia, immune cell infiltration, fibrosis, and ultimately brown adipocyte apoptosis (Bagchi et al. 2013). It remains to be seen whether obesity is associated with BAT fibrosis and whether fibrosis negatively affects BAT activity in humans.

Fig. 6 The extracellular matrix of adipose tissue. (**a**) ECM composition, signaling, and remodeling in adipocytes. (*1*) The ECM is a network of macromolecules composed of structural proteins (collagens and elastin), adhesion proteins (fibronectin), and proteoglycans. (*2*) The ECM regulates cell functions such as migration and differentiation through interactions with extracellular receptors such as integrins (Hu and Luo 2013). This can occur via the activation of FAK (focal adhesion kinase) in focal adhesion complexes and downstream MAP kinase/actin-dependent signaling or directly though mechanical cues transmitted into cells via cytoskeleton of microtubules (*MT*) and intermediary filaments. (*3*) ECM remodeling is a key component of adipogenesis. The preadipocyte ECM is composed primarily of collagen I, collagen III, and fibronectin (Mariman and Wang 2010). The basement membrane (*BM*) is a specialized ECM surrounding mature adipocytes composed of collagen IV, collagen XVIII, entactin, and laminin (LeBleu et al. 2007). During differentiation, the preadipocyte ECM is degraded by proteases (MMPs, ADAMT, and cathepsins) (Mariman and Wang 2010). This liberates growth factors and matricellular proteins that are important for the synthesis of the new mature adipocyte BM, which is stimulated by insulin, TGF-β, and cytokine signaling (Mariman and Wang 2010). The ECM is also involved in the changes to cellular morphology associated with adipogenesis (Rodríguez Fernández and Ben-Ze'ev 1989). (**b**) Cellular and physiological contributors to fibrosis in WAT. Preadipocytes, immune cells, endothelial cells, and mature adipocytes all contribute to WAT fibrosis. Inflammation likely precedes fibrosis, as macrophages accumulate in obese WAT prior to fibrosis, where they promote inflammation (TNFα) as well as ECM synthesis via TGF-β and activin A signaling (Yu and Stamenkovic 2000; Dreier et al. 2004; Kwon et al. 2012; Tracy 2012; Dani 2013). Preadipocytes are proposed as the major effectors of AT fibrosis. Fibrosis negatively impacts adipocyte metabolism by decreasing metabolic functions such as lipolysis and adipokine secretion and by inducing an inflammatory response (Pellegrinelli et al. 2014a). References: Rodríguez Fernández and Ben-Ze'ev 1989; Yu and Stamenkovic 2000; Dreier et al. 2004; LeBleu et al. 2007; Mariman and Wang 2010; Kwon et al. 2012; Tracy 2012; Dani 2013; Hu and Luo 2013; Pellegrinelli et al. 2014a

8 Innervation of Adipose Tissue

8.1 Nervous Networks in Adipose Tissue

Efferent sensory and afferent sympathetic nerves have been identified in rodent WAT and BAT (Giordano et al. 1996; De Matteis et al. 1998). In rodents, sympathetic innervation is greater in BAT compared to WAT and greater in scWAT compared to visWAT (Murano et al. 2009). Nerve endings are in contact with adipocytes and blood vessels. As we have seen, the norepinephrine released from sympathetic nerves regulates AT perfusion and several components of AT function, from WAT lipolysis to BAT thermogenesis. In rodents, sympathetic stimulation of WAT also suppresses the release of leptin and adiponectin from WAT and can induce the secretion of autocrine and endocrine factors including BMP8b, FGF21, and T3 (Fernandez et al. 1987; Hondares et al. 2011a; Whittle et al. 2012).

Sympathetic activity is regulated by the hypothalamus, which receives information related to energy availability to regulate lipolysis and environmental and core body temperature to regulate thermogenesis. When a sympathetic response is required, this information is transmitted to sympathetic premotor neurons located in the rostral raphe pallidus and parapyramidal areas of the hindbrain, as determined by neuronal viral tracer studies in rodents (Tupone et al. 2014). These premotor neurons synapse with preganglionic neurons whose cell bodies reside in the spinal intermediolateral nucleus. Finally, these preganglionic neurons regulate the activity of the norepinephrine-releasing postganglionic neurons with nerve endings in AT (Tupone et al. 2014). Distinct regulation of sympathetic tone to different WAT and BAT depots has been observed in animal models because different depots are innervated by distinct populations of postganglionic neurons (Brito et al. 2008). Along with norepinephrine, sympathetic nerves in rodent WAT and BAT also release neuropeptide Y (NPY), which has been shown to inhibit lipolysis and promote leptin release by human white adipocytes in vitro (Giordano et al. 1996; Serradeil-Le Gal et al. 2000). Interestingly, feedback loops between the sympathetic and sensory nervous systems in both WAT and BAT have been identified (Niijima 1999; Ryu et al. 2015). Finally, the presence and significance of parasympathetic innervation of rodent WAT are under debate (Kreier and Buijs 2007).

8.2 Nervous Remodeling in AT

In rodents, cold exposure increases the density of sympathetic innervation in BAT and WAT depots (Vitali et al. 2012). Indeed, during BAT recruitment in rodents, the nervous network is remodeled to innervate new brown adipocytes (Vitali et al. 2012). The expression of several neurotrophins that regulate neuron survival and plasticity has been detected human or rodent WAT and BAT and may underlie these observations. For example, nerve growth factor (NGF) is required for sympathetic neuron survival and is secreted by white and brown adipocytes (Néchad et al. 1994; Peeraully et al. 2004). Neurotrophins with chemoattractant (neuregulin 4) and chemorepellent (semaphorins) properties have also been detected (Giordano et al. 2001; Mejhert et al. 2013; Wang et al. 2014).

Obesity is associated with reduced adrenergic responsiveness of BAT and WAT, a phenomenon that has been attributed to adipocyte dysfunction. Additionally, changes at a central level, such as hypothalamic insulin resistance and neuroinflammation, have downstream effects on the nervous regulation of AT (Purkayastha and Cai 2013). However, impairment of or damage to the nervous network within AT as a result of obesity has not been highlighted to date.

9 Conclusions

In conclusion, proper AT function depends on the coordinated interaction of adipocytes, precursor cells, immune cells, blood vessels, nerves, and the ECM. Obesity is characterized by an absolute increase in and an anatomical redistribution of WAT mass, which leads to insulin resistance and

other metabolic complications. Obesity also alters the ultrastructure and cellular composition of WAT, negatively affecting WAT function and ultimately impairing its ability to buffer excess nutrients. This can lead to ectopic lipid accumulation in non-adipose tissues that further exacerbates metabolic dysfunction.

The rediscovery of BAT, a type of AT uniquely specialized for calorie burning, in adult humans has created the opportunity for novel therapeutic strategies to treat obesity and metabolic syndrome. Although WAT far outstrips BAT in terms of percent of body mass, in rodents the high activity of BAT is an important contributor to nutrient partitioning and utilization and body weight regulation. Conceptually, therapeutically increasing BAT activity could eliminate excess nutrients, improving WAT function with knock-on effects on whole-body metabolism. The success of this approach will depend on a better understanding of BAT structure and function in healthy adult humans and whether potential BAT-based therapeutic strategies can overcome any limitations caused by the negative impact of obesity on BAT function.

10 Cross-References

- Adipokines and Metabolism
- Brain Regulation of Feeding and Energy Homeostasis
- Carbohydrate, Fat, and Protein Metabolism in Obesity
- Dyslipidemia in Obesity
- Insulin Resistance in Obesity
- Linking Inflammation, Obesity, and Diabetes
- Principles of Energy Homeostasis

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Adipokines and Metabolism

22

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Abstract

Adipose tissue is the main site of energy storage in the form of triglycerides. Mature adipocytes also produce enzymes, growth factors, cytokines, chemokines, and hormones (adipokines) implicated in the modulation of feeding, energy homeostasis, lipid and glucose metabolism, inflammation, coagulation, and cardiovascular system. Obesity alters the expression, circulating levels, and signaling mechanisms of adipose-secreted factors, and these changes have been linked to the development of insulin resistance, type 2 diabetes, dyslipidemia, atherosclerosis, cancer, and other diseases.

Keywords

Adipose tissue • Adipokine • Leptin • Adiponectin • Resistin • Insulin • Obesity

1 Introduction

White adipose tissue (WAT), the main type of adipose tissue in mammals, is composed of specialized cells for lipid storage (adipocytes) embedded in a highly vascularized and innervated loose connective tissue. Mature white adipocytes contain a single large fat droplet occupying >90 % of the cell volume, and the nucleus and cytoplasm are squeezed into the remaining cell volume, creating a signet ring appearance. In addition to adipocytes, WAT contains adipocyte progenitor cells, macrophages, leukocytes, fibroblasts, and endothelial cells. The highest amounts of WAT are found in the subcutaneous regions and surrounding abdominal and thoracic organs.

Triglycerides stored in white adipocytes represent the major energy reserves of the body and are in a constant state of flux in relation to feeding and fasting. Insulin is increased in response to meals, binds to the insulin receptor, and suppresses lipolysis via activation of phosphodiesterase 3B which hydrolyzes cAMP and inactivates protein kinase A (PKA). Insulin also suppresses lipolysis through a cAMP-independent pathway mediated by stimulation of protein phosphatase-1 which inactivates hormone-sensitive lipase (HSL). Epinephrine and norepinephrine levels increase during fasting and bind to their cognate receptors on adipocytes triggering activation of adenylate cyclase, increasing cAMP which activates PKA leading to phosphorylation and activation of HSL. In addition to HSL, adipocytes express other triglyceride hydrolases including desnutrin/ATGL, triacylglycerol hydrolase, and adiponutrin. Other proteins implicated in triglyceride metabolism in adipose tissue include perilipins, adipose fatty acid-binding protein (aP2), caveolin-1, aquaporin 7, and lipotransin. Perilipin-1 coats lipid droplets and prevents access of triglyceride lipases, thus limiting basal lipolysis. aP2 transports fatty acids to the plasma membrane to be released into plasma. Glycerol released from triglyceride hydrolysis is exported via aquaporin 7. Lipotransin may be involved in shuttling HSL from the cytosol to the lipid droplet during adipocyte stimulation.

In addition to enzymes and transporters involved in fuel homeostasis, adipose tissue produces and secretes several proteins including adhesion molecules, growth factors, adipokines, cytokines, chemokines, and complement and coagulation factors (Table 1). This review will focus on the biology of leptin, adiponectin, and resistin.

2 Leptin

Leptin is a 167-amino-acid peptide which is mainly produced and secreted by WAT and to a lesser extent by placenta, mammary gland, ovary, skeletal muscle, stomach, pituitary gland, and lymphoid tissue (Margetic et al. 2002). Plasma leptin concentrations are proportional to the amount of body fat. In addition, leptin levels increase in response to overfeeding and during starvation (Considine et al. 1996; Chan et al. 2003). Leptin is secreted in a pulsatile manner and displays a circadian rhythm with a nadir at midafternoon and peak levels at midnight. The pulsatile leptin secretion is similar in obese and lean people, but the pulse amplitude is higher in obesity (Licinio et al. 1997). Leptin levels exhibit

Table 1 Proteins produced by adipose tissue

Enzymes and transporters	Receptors	Secreted proteins
Lipid metabolism	*Peptide and glycoprotein*	*Adipokines*
LPL	Insulin	Leptin
HSL	Glucagon	Adiponectin
ATGL	FSH	Resistin (rodents)
Triacylglycerol hydrolase	GH	Angiotensinogen
Adiponutrin	Ang-II	Fasting-induced adipose factor (angiopoietin-like protein-4)
CETP	CCK-B/gastrin	Apelin
aP2	Adiponectin	Omentin
CD36	*Nuclear*	Retinol-binding protein (RBP4)
ApoE	PPARγ	Visfatin
Perilipins		Vaspin
Caveolin-1	Glucocorticoid	*Cytokines*
Aquaporin 7	Estrogen	TNF-α
Lipotransin	Progesterone	MIF
Glucose metabolism	Androgen	IL-1β, IL-4, IL-6, IL-8, IL-10, IL-18
IRS-1, IRS-2	Thyroid	*Chemokines*
PI3K	Vitamin D	Chemerin
Akt	NF-κB	MCP-1
Protein kinase λ/ζ		MIP-1α
GSK-3α		*Complement factors*
GLUT4		Adipsin
Steroid metabolism		Acylation-stimulating protein
Aromatase		*Acute phase proteins*
11β-HSD-1		CRP
17β-HSD		Serum amyloid A3 (SAA3)
Estrogen sulfotransferase		Haptoglobin
		Growth/angiogenic/coagulation factors
		FGF-1, FGF-2, FGF-7, FGF-9, FGF-10, FGF-18
		IGF-1
		HGF
		NGF
		VEGF
		TGF-β
		Angiopoietin-1 and angiopoietin-2
		Tissue factor
		PAI-1
		Extracellular matrix
		α2-Macroglobulin
		VCAM-1
		ICAM-1
		Collagen I, III, IV, VI
		Fibronectin
		MMP1, MMP7, MMP9, MMP10, MMP11, MMP14, MMP15
		Lysyl oxidase

a sexual dimorphism, being higher in premenopausal women than men and declining in postmenopausal women (Rosenbaum and Leibel 1999). Subcutaneous fat produces more leptin than visceral fat, and this may in part contribute to higher leptin levels in women compared to men (Montague et al. 1997). Besides sex steroids, leptin is increased by insulin and glucocorticoids and reduced by catecholamines and inflammatory cytokines (Ahima and Osei 2004).

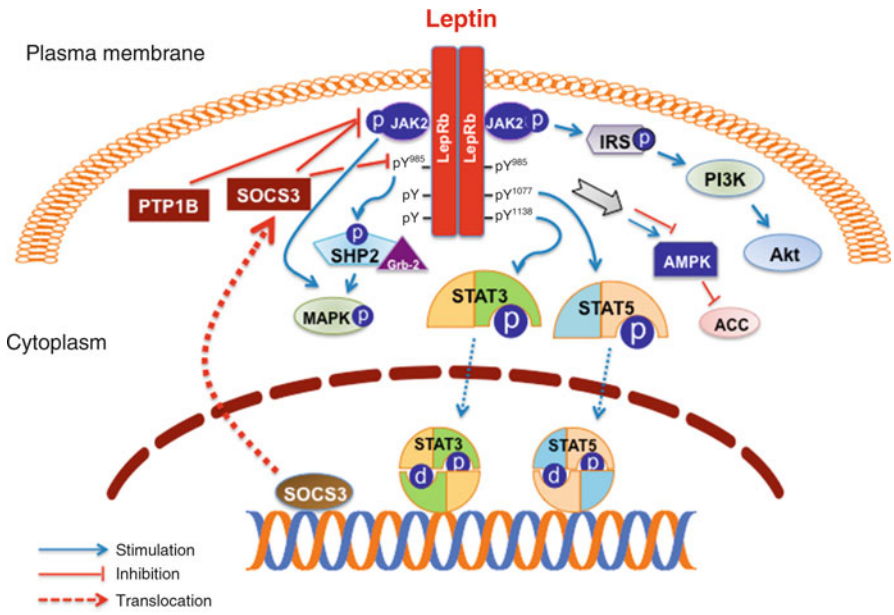

Fig. 1 Leptin signaling. Leptin binds to LepRb resulting in its dimerization and formation of LepRb/JAK2 complex. Activated JAK2 autophosphorylates and also phosphorylates Tyr^{985}, Tyr^{1077}, and Tyr^{1138} in LepRb. STAT3 and STAT5 bind to phospho-Tyr^{1138} and phospho-Tyr^{1077} in LepRb and are subsequently phosphorylated. The active STAT3 and STAT5 dimers translocate to the nucleus and activate the transcription of neuropeptides and other target genes. SOCS3, a target gene of STAT3, inhibits JAK2/STAT3 by interacting with phospho-Tyr^{985} or JAK2 and acting as a feedback inhibitor of leptin signaling. PTP1B inhibits leptin signaling through dephosphorylation of JAK2. After JAK2 activation, SH2-containing protein tyrosine phosphatase 2 (SHP2) binds to phospho-Tyr^{985} in LepRb and recruits the adaptor protein growth factor receptor-bound protein 2 (Grb2), leading to activation of the mitogen-activated protein kinase (MAPK) signaling pathway. Leptin activates MAPK independently of SHP2 and also regulates PI3K signaling through IRS phosphorylation. Forkhead box O1 (FoxO1), mammalian target of rapamycin (mTOR), and phosphodiesterase 3B (PDE3B) are important downstream targets of PI3K in the leptin signaling pathway. Leptin also regulates feeding and metabolism through 5′ adenosine monophosphate-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) in the brain and peripheral organs (From Park HK, Ahima RS. F1000Prime Rep. 2014 Sep 4;6:73. doi: 10.12703/P6-73. eCollection 2014. Used with permission under the Creative Commons License)

2.1 Leptin Signaling

Leptin exerts its effects via leptin receptors (LepRs) located throughout the central nervous system (CNS). Four alternatively spliced isoforms of LepR have been identified in humans. The long isoform of leptin receptor (LepRb) is abundantly expressed in the hypothalamus and other brain regions, where it regulates energy homeostasis and neuroendocrine function, and considered as the main leptin receptor (Kelesidis et al. 2010). LepRb is mainly responsible for inhibition of food intake and stimulation of energy expenditure, while the short isoforms of LepR are thought to mediate the transport of leptin across the blood–brain barrier (Bjorbaek et al. 1998). Evidence suggests that leptin transport into the hypothalamus is mediated by tanycytes through LepR (Balland et al. 2014).

Leptin binds to LepRb leading to activation of Janus kinase 2 (JAK2)–signal transducer and activator of transcription 3 (STAT3) (Fig. 1). Leptin signaling also interacts with insulin receptor substrate (IRS)–phosphatidylinositol 3-kinase (PI3K), SH2-containing protein tyrosine phosphatase 2 (SHP2)–mitogen-activated protein kinase (MAPK), 5′ adenosine monophosphate-activated protein kinase (AMPK)/acetyl-CoA carboxylase (ACC), and other signaling pathways. Activation of JAK2–STAT3 signaling plays a crucial role in leptin's ability to regulate energy homeostasis (Bates et al. 2003; Dardeno et al. 2010). Leptin

signaling is terminated by suppressor of cytokine signaling 3 (SOCS3) which inhibits JAK2–STAT3. Induction of protein tyrosine phosphatase 1B (PTP1B) also inhibits leptin signaling (Dalamaga et al. 2013; Moon et al. 2013; Morris and Rui 2009).

Leptin acts directly on anorexigenic neurons that synthesize pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) and orexigenic neurons that synthesize Agouti-related peptide (AgRP) and neuropeptide Y (NPY). During fasting, plasma leptin levels decline rapidly leading to stimulation of AgRP and NPY and suppression of POMC and CART, thereby increasing food intake and decreasing energy expenditure (Ahima et al. 1999; Cowley et al. 2001). The lateral hypothalamus contains neurons that express melanin-concentrating hormone (MCH) and orexins. These neuropeptides are decreased by leptin resulting in suppression of feeding (Robertson et al. 2008; Dalamaga et al. 2013; Abizaid et al. 2006). Other leptin targets in the lateral hypothalamus innervate the ventral tegmental area (VTA), linking leptin to the hedonic control of feeding mediated by the mesolimbic dopaminergic system (Leinninger et al. 2009). Leptin also acts on ventromedial hypothalamic neurons that express the transcription factor steroidogenic factor 1 (SF-1) (Kim et al. 2011a). Mice with SF-1 deletion in the Ventromedial Hypothalamus are susceptible to obesity associated with impaired thermogenesis (Kim et al. 2011b). Brain-derived neurotrophic factor in the Ventromedial Hypothalamus has been linked to leptin's effects on feeding and energy balance (Liao et al. 2012). Subpopulations of neurons in the nucleus tractus solitarius (NTS) express LepRb, glucagon-like peptide 1 (GLP-1), and cholecystokinin (CCK), and leptin acts synergistically with GLP-1 and CCK in the NTS to increase satiety (Garfield et al. 2012).

In addition to regulating food intake, leptin stimulates sympathetic nervous activity and brown adipose tissue (BAT) thermogenesis (Haynes et al. 1997; Scarpace et al. 1997). The thermogenic effect of leptin is mediated partly via suppression of MCH and Forkhead box O1 (FoxO1) (Segal-Lieberman et al. 2003; Kim et al. 2012). Mice lacking leptin and MCH are less obese than leptin-deficient *ob/ob* mice and display greater energy expenditure and locomotor activity compared to *ob/ob* mice (Leinninger 2011). Leptin has neurotrophic effects on hypothalamic neurons implicated in feeding and energy homeostasis. Neural projections from the arcuate to paraventricular nucleus (PVN) are reduced in *ob/ob* mice and restored by leptin treatment in neonatal mice (Bouret et al. 2004). Leptin administration in *ob/ob* mice rapidly normalizes synaptic inputs to POMC and AgRP neurons to levels seen in wild-type mice (Pinto et al. 2004). Leptin's actions in neurodevelopment have been demonstrated as well in murine cerebral cortex and hippocampus (Bouret 2010). Brain imaging studies have also revealed structural and functional deficits reversible by leptin treatment in congenital leptin deficiency (Matochik et al. 2005; London et al. 2011).

The role of leptin in energy homeostasis is most evident in leptin deficiency. *ob/ob* mice develop hyperphagia, low metabolic rate, and early onset obesity, associated with high expression of NPY and MCH and low expression of POMC in the hypothalamus (Ahima and Osei 2004; Pelleymounter et al. 1995). Congenital leptin deficiency in humans also leads to hyperphagia and morbid obesity reversible by leptin treatment (Farooqi et al. 1999, 2002). In contrast, most obese people have high levels of leptin expression in adipose tissue and plasma leptin levels, and they respond poorly to leptin treatment (Fig. 2). This suggests "leptin resistance" in common forms of obesity arising from overnutrition and sedentary lifestyle (Hukshorn et al. 2002; Moon et al. 2011b; Mittendorfer et al. 2011). Specific mechanisms underlying leptin resistance in "common obesity" are unknown and may include impaired leptin transport across blood–brain barrier and disruption of leptin signaling via hypothalamic inflammation, endoplasmic reticulum stress, and unknown factors (Myers et al. 2012; Jung and Kim 2013).

2.2 Effects of Leptin on Neuroendocrine System

Reduced leptin levels during fasting trigger various hormonal responses (Ahima and Osei 2004; Boden et al. 1996), including hypogonadotropic

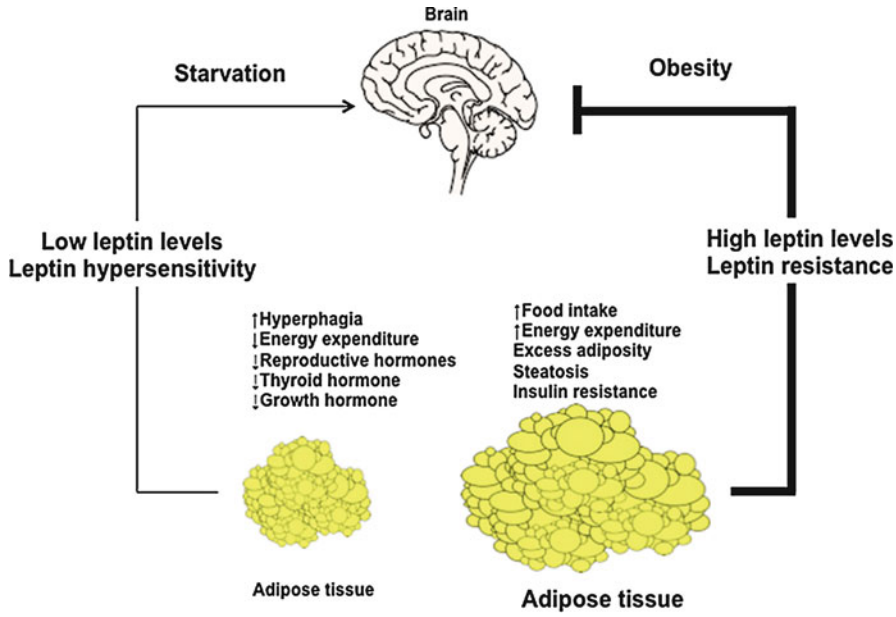

Fig. 2 Physiology of leptin in starvation and obesity. Leptin levels fall during starvation and stimulate food intake by increasing expression of orexigenic neuropeptides and decreasing expression of anorexigenic neuropeptides. In addition, the decline of leptin level modulates mesolimbic dopamine system and hindbrain circuits to increase food intake and also has effects on sympathetic nervous system to decrease energy expenditure. Low leptin levels trigger neuroendocrine adaptations resulting in suppression of thyroid hormone, reproductive hormone, and growth hormone. Leptin levels are increased in obesity, but the feedback response in the brain is blunted due to leptin resistance (From Park HK, Ahima RS. Metabolism. 2015 Jan;64(1):24–34. doi: 10.1016/j.metabol.2014.08.004. Epub 2014 Aug 15. License number 3674271217804, Elsevier Publishers)

hypogonadism, suppression of thyroid and growth hormone (GH) levels, and activation of the hypothalamic–pituitary–adrenal axis in mice, which are prevented by leptin treatment (Ahima et al. 1996; Chan et al. 2003, 2008) (Fig. 2). Leptin replacement restores thyroid hormone, testosterone, and luteinizing hormone (LH) levels in fasted mice (Ahima et al. 1996) and LH pulsatility and testosterone levels in starved human volunteers (Ahima et al. 1996; Chan et al. 2003, 2006). Leptin replacement facilitates pubertal development in *ob/ob* mice and leptin-deficient humans, establishing a crucial role of leptin in reproduction (Chehab et al. 1996; Farooqi et al. 2002; Licinio et al. 2004). Leptin also prevents the pubertal delay associated with starvation and exerts a permissive effect on puberty in normal mice (Gruaz et al. 1998; Cheung et al. 2001; Elias and Purohit 2013). Low leptin levels are also linked to impaired leptin pulsatility and hypogonadism in hypothalamic amenorrhea and lipoatrophy (Miller et al. 1998; Chan and Mantzoros 2005). Leptin treatment increases LH levels, LH pulse frequency, and estradiol levels and corrects abnormal thyroid and cortisol levels in hypothalamic amenorrhea (Welt et al. 2004; Chou et al. 2011). Similarly, leptin replacement normalizes LH and sex steroid levels in individuals with generalized lipoatrophy (Musso et al. 2005).

These findings suggest that leptin is an important signal linking energy stores to the neuroendocrine axis. However, the underlying mechanisms are still unclear. Gonadotropin-releasing hormone (GnRH) neurons lack LepR; thus, it is likely that leptin acts indirectly to regulate the reproductive axis (Quennell et al. 2009; Hausman et al. 2012). Although kisspeptin may mediate the effects of leptin, mice with selective deletion of LepR from hypothalamic Kiss1 neurons show normal pubertal development and fertility, indicating that leptin action in Kiss1 neurons is not essential for puberty and reproduction

(Donato et al. 2011). Kiss1 neurons in the arcuate nucleus express LepR (Louis et al. 2011; Sanchez-Garrido and Tena-Sempere 2013), but leptin signaling in these neurons occurs after completion of sexual maturation and is not crucial for leptin action during puberty (Cravo et al. 2013; Elias 2014).

Leptin regulates thyroid hormone by stimulating thyrotropin-releasing hormone (TRH) via upregulation of proTRH gene expression and increasing the processing of proTRH (Legradi et al. 1997; Sanchez et al. 2004). Healthy humans have circadian and pulsatile levels of leptin and TSH, while congenital leptin deficiency results in a highly disorganized secretion of TSH (Mantzoros et al. 2001). After leptin replacement, leptin-deficient individuals exhibit an increase in thyroid hormone levels but no change in TSH (Farooqi et al. 2002). Leptin administration prevents the fasting-induced suppression of TSH pulses but does not reverse the fall in tri-iodothyronine (T3) levels (Chan et al. 2003). In women with hypothalamic amenorrhea, leptin administration increases free T3 and T4 levels (Welt et al. 2004). Leptin treatment also reverses the declines in T3 and T4 levels during weight loss (Rosenbaum et al. 2005; Kissileff et al. 2012).

2.3 Metabolic Effects of Leptin

Leptin treatment decreases glucose, insulin, and lipids before weight loss is achieved in *ob/ob* mice (Pelleymounter et al. 1995; Schwartz et al. 1996). In individuals with congenital leptin deficiency, leptin replacement rapidly decreases insulin resistance, steatosis, and plasma lipids and glucose (Farooqi et al. 2002; Licinio et al. 2004). Similarly, leptin treatment decreases insulin resistance, steatosis, and glucose in generalized lipoatrophy (Shimomura et al. 1999; Gavrilova et al. 2000; Asilmaz et al. 2004; Musso et al. 2005; Oral et al. 2002; Mulligan et al. 2009; Petersen et al. 2002). Leptin decreases visceral fat in normal rats (Barzilai et al. 1997) and in patients with lipoatrophy (Lee et al. 2006; Mulligan et al. 2009). CNS leptin administration inhibits de novo lipogenesis and enhances lipolysis in the adipose and liver (Gallardo et al. 2007; Buettner et al. 2008). Leptin also stimulates fatty acid oxidation by activating AMPK in skeletal muscle and preventing the accumulation of lipid metabolites associated with lipotoxicity (Minokoshi et al. 2002).

Studies in diabetic mice suggest that leptin administration normalizes glucose levels by suppressing glucagon and hepatic intermediary metabolites (Wang et al. 2010). CNS leptin treatment decreases glucose and glucagon through insulin-independent mechanisms (Fujikawa et al. 2010). Leptin suppresses hepatic glucose production by ameliorating hyperglucagonemia and increasing peripheral glucose uptake, partly by targeting POMC- and AgRP-expressing neurons in the arcuate nucleus (Coppari et al. 2005; Huo et al. 2009; German et al. 2011; Berglund et al. 2012). Restoration of LepR expression in the arcuate nucleus decreases insulin and glucose in LepR-null mice. Moreover, a selective expression of LepRb in hypothalamic POMC neurons prevents diabetes in LepR-deficient *db/db* mice, independently of changes in feeding and weight (Coppari et al. 2005; Huo et al. 2009; Berglund et al. 2012). Deletion of leptin targets, SOCS3 or PTP1B, in POMC neurons also improves glucose metabolism (Kievit et al. 2006; Banno et al. 2010). Furthermore, genetically mediated alteration of PI3K activity in POMC neurons affects hepatic insulin sensitivity (Hill et al. 2009). A selective re-expression of LepRb in AgRP neurons mediates antidiabetic actions of leptin in *db/db* mice by suppressing glucagon (Goncalves et al. 2014). Leptin inhibits insulin gene expression and glucose-stimulated insulin secretion, and insulin stimulates both leptin synthesis and secretion, thus establishing an adipose tissue–islet axis (Seufert 2004). Leptin also protects pancreatic β-cells from lipotoxicity (Seufert 2004; Lee et al. 2011b).

Leptin has been linked to bone metabolism. In rodents, leptin alters cortical bone formation via β-adrenergic stimulation or GH/insulin-like growth factor (IGF)-1 effects on trabecular bone remodeling. Leptin may influence cortical bone metabolism through hypothalamic neuropeptides, e.g., NPY, which inhibits cortical bone formation

(Baldock et al. 2006; Hamrick and Ferrari 2008). Leptin acts directly on marrow stromal cells to increase osteoblast differentiation and inhibit adipocyte differentiation. Leptin stimulates osteoblast proliferation and mineralization (Thomas et al. 1999; Gordeladze et al. 2002). Leptin's effect on bone biology is evident in leptin-deficient states in humans. Leptin treatment stimulates bone formation, bone mineral density, and content in the lumbar spine of patients with hypothalamic amenorrhea (Welt et al. 2004; Chou et al. 2011; Sienkiewicz et al. 2011). Potential actions of leptin on bone may involve increased IGF-1 and estrogen and reduction of cortisol. Furthermore, leptin may inhibit bone formation via sympathetic nervous activation (Takeda et al. 2002) (Elefteriou et al. 2005; Takeda and Karsenty 2008).

2.4 Effects of Leptin on Immunity

Leptin has important roles in modulating innate and adaptive immunity (Carbone et al. 2012). Leptin stimulates neutrophil chemotaxis and macrophage phagocytosis, and production of pro-inflammatory cytokines, e.g., IL-6, IL-12, and TNF-α (Lord et al. 1998; Loffreda et al. 1998). Leptin inhibits the proliferation of regulatory T cells, stimulates T helper 1 cells (Carbone et al. 2012; De Rosa et al. 2007), and may contribute to protection from infections and the development of autoimmunity (Carbone et al. 2012; Moon et al. 2013). Leptin treatment in *ob/ob* mice and short-term fasted wild-type mice reverses immune dysfunction associated with hypoleptinemia (Howard et al. 1999). Congenital leptin deficiency is associated with a higher incidence of infection, likely due to a reduction of circulating CD4+ T cells and impaired T cell proliferation and cytokine release (Farooqi et al. 2002). In women with hypothalamic amenorrhea and chronic leptin deficiency, leptin replacement increases soluble TNF-α receptor and restores CD4+ T cell counts and proliferative responses, suggesting that leptin promotes immune reconstitution in chronic hypoleptinemia (Chan et al. 2005, 2006; Matarese et al. 2013). Leptin treatment exacerbates experimental autoimmune encephalomyelitis, while leptin deficiency in *ob/ob* mice is protective against encephalomyelitis (Matarese et al. 2001; Sanna et al. 2003). Patients with multiple sclerosis have increased leptin levels in blood and cerebrospinal fluid and reduced peripheral regulatory T cells (Matarese et al. 2005). These findings suggest potential roles of leptin in the pathogenesis of autoimmune diseases.

2.5 Clinical Uses of Leptin

Leptin has potent effects in states of leptin deficiency (Vatier et al. 2012). Leptin replacement reduces body weight and fat and reverses neuroendocrine and metabolic abnormalities in congenital leptin deficiency (Farooqi et al. 2002; Licinio et al. 2004). Leptin treatment restores menstrual cycles, normalizes the gonadal, thyroid, and adrenal axes, and improves bone mineral density and bone formation in women with hypothalamic amenorrhea and hypoleptinemia (Chou et al. 2011; Sienkiewicz et al. 2011). Leptin treatment also improves insulin sensitivity, dyslipidemia, and hepatic steatosis in patients with lipoatrophy (Oral et al. 2002; Mulligan et al. 2009; Chan et al. 2011).

In contrast to leptin deficiency, most forms of obesity are associated with leptin resistance (Moon et al. 2011b; Mittendorfer et al. 2011). Amylin acts synergistically with leptin to reduce adiposity in obese rodents, while preventing the compensatory reduction in energy expenditure associated with weight loss (Trevaskis et al. 2008; Roth et al. 2008). Clinical studies have shown that a combination of leptin and an amylin analog, pramlintide, induces greater weight loss compared to leptin or pramlintide alone (Roth et al. 2008; Ravussin et al. 2009). Unlike rodents, leptin and pramlintide have additive effects on body weight (Moon et al. 2011a). Metformin, exendin-4, and fibroblast growth factor (FGF)-21 have all been shown to increase leptin sensitivity in rodents (Kim et al. 2006; Muller et al. 2012). Exercise also increases leptin sensitivity in human skeletal muscle (Guerra et al. 2011).

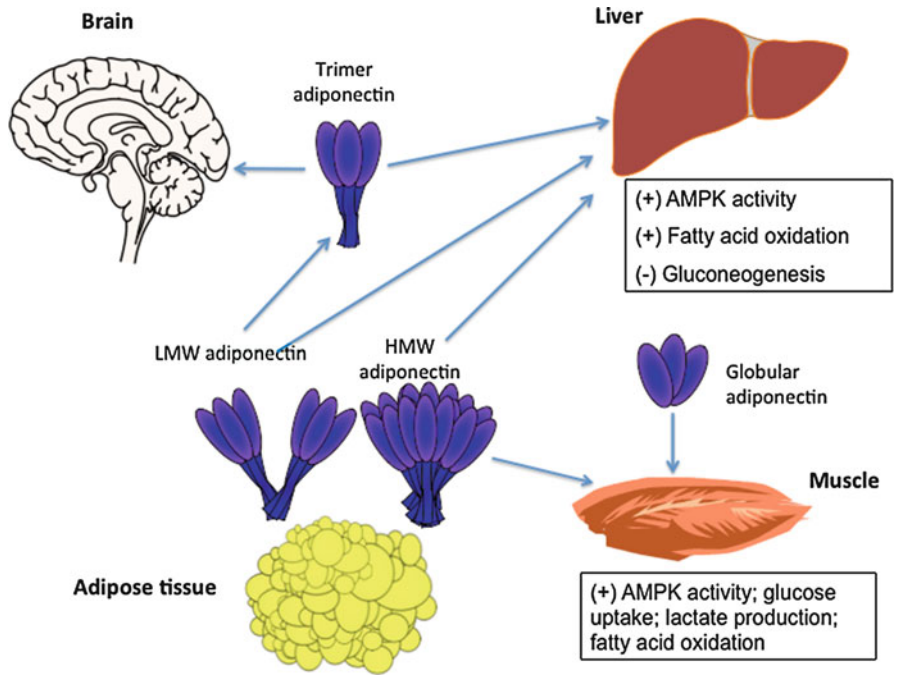

Fig. 3 Adiponectin proteins and target organs. The globular form of adiponectin, expressed in *E. coli*, stimulates fatty acid oxidation when it is administered in mice. The globular form of adiponectin is not detectable in mammalian tissues and unlikely to have a physiological function

Leptin replacement overcomes hunger, reduced energy expenditure, and neuroendocrine adaptation which drives weight regain in response to weight loss. In clinical studies, leptin replacement therapy restored thyroid hormone levels, sympathetic nervous activity, and energy expenditure and reversed declines in satiation in weight-reduced individuals (Rosenbaum et al. 2005; Kissileff et al. 2012). Brain imaging studies have shown that leptin prevents alterations in neuronal activity associated with weight loss-induced homeostatic, emotional, and cognitive control of food intake (Rosenbaum et al. 2008). These findings raise the possibility that leptin treatment can promote weight loss maintenance (Mantzoros et al. 2011).

Another potential clinical use of leptin is in the area of neurodegenerative disorders such as Alzheimer disease. Some studies indicate that leptin promotes neurogenesis, axonal growth, synaptogenesis, and neuroprotection (Bouret 2010; Paz-Filho et al. 2010). Prospective studies have shown that low leptin levels are associated with higher risk of dementia and Alzheimer disease (Holden et al. 2009; Lieb et al. 2009; Davis et al. 2014).

3 Adiponectin

Adiponectin is expressed mainly in adipose tissue and circulates in different multimeric forms (Schraw et al. 2008; Wang and Scherer 2008) (Fig. 3). The trimeric adiponectin is the main form in human cerebrospinal fluid (Kusminski et al. 2007). The high molecular weight (HMW, 18–36) multimer of adiponectin is abundant in plasma in females, and the trimeric and hexameric forms are abundant in plasma in males (Pajvani et al. 2003; Peake et al. 2005; Hamilton et al. 2011). Unlike leptin, plasma adiponectin levels are reduced in obesity, increased following fasting, and decreased by refeeding (Arita et al. 1999). The levels of HMW adiponectin are highly predictive of insulin sensitivity (Pajvani et al. 2004). Insulin-sensitizing thiazolidinediones

increase the levels of HMW adiponectin in human and mice (Nawrocki et al. 2006). Mice lacking adiponectin do not respond to thiazolidinedione treatment confirming that adiponectin plays an essential role in mediating the antidiabetic effect of thiazolidinediones (Nawrocki et al. 2006).

The adiponectin promoter contains binding elements for C/EBPα, PPARγ, Sterol Regulatory Element-Binding Proteins, and LRH-1 (liver receptor homolog-1) (Liu and Liu 2010). FoxO1-C/EBPα complex activates adiponectin gene transcription, and this process is facilitated by SIRT1 (Qiao and Shao 2006). In contrast, FoxO1 binds to PPARγ and blocks its target genes (Fan et al. 2009). Although the transcriptional regulation of adiponectin is important, studies indicate that the levels of adiponectin are mainly regulated through post-translational modification, involving folding and processing in the endoplasmic reticulum and trafficking through the Golgi apparatus. Endoplasmic reticulum chaperones, ERp44 and Ero1α, are required for the formation of adiponectin complexes (Wang et al. 2007; Xie et al. 2006).

3.1 Adiponectin Signaling

Adiponectin signals through two seven-transmembrane domain-containing proteins, AdipoR1 and AdipoR2, which are widely expressed and induce AMPK phosphorylation and activity (Amin et al. 2010). AdipoR1 mRNA is abundant in the skeletal muscle, spleen, lung, heart, kidney, and liver. AdipoR1 stimulates AMPK activation and inhibits gluconeogenesis and lipogenesis (Miller et al. 2011). AdipoR2 is expressed in the liver, induces PPARα, increases glucose uptake and fatty acid oxidation, and reduces oxidative injury and inflammation (Yamauchi et al. 2007). In addition to AMPK and PPARα, adiponectin signaling involves other downstream effectors such as APPL1 (Xin et al. 2011), Ca^{2+}, and SIRT1 (Iwabu et al. 2010; Yamauchi and Kadowaki 2013). Adiponectin decreases ceramide levels in various tissues, and this effect may explain the insulin-sensitizing, anti-inflammatory, and antiapoptotic actions of adiponectin. Adiponectin also binds to T-cadherin, which lacks transmembrane and intracellular signaling domains but could serve as a receptor for high-order adiponectin multimers (Hug et al. 2004). Plasma adiponectin levels are increased in T-cadherin-deficient mice suggesting a role of this protein as a transporter of adiponectin (Denzel et al. 2010).

3.2 Metabolic Effects of Adiponectin

Adiponectin deficiency has been linked to obesity, insulin resistance, and metabolic syndrome. AdipoR1 and AdipoR2 levels are reduced in livers of obese mice, and this has been related to attenuation of AMPK activity and insulin resistance (Yamauchi et al. 2007). Adenovirus-mediated expression of AdipoR1 and AdipoR2 reverses these defects. AdipoR1 and AdipoR2 may have different roles since ablation of AdipoR1 in the liver prevents the ability of adiponectin to activate AMPK while ablation of AdipoR2 decreases PPARα signaling (Yamauchi et al. 2007; Liu et al. 2007). Deficiency of both AdipoR1 and AdipoR2 prevents adiponectin binding and induces steatosis, inflammation, oxidative stress, and insulin resistance. AdipoR1 deficiency decreases energy expenditure, increases body fat, and induces insulin resistance, while AdipoR2 deficiency increases energy expenditure, decreases body weight and fat, and improves glucose metabolism (Liu et al. 2007; Bjursell et al. 2007).

AdipoR1 and AdipoR2 are widely distributed in the brain, and some studies indicate that adiponectin affects energy and glucose metabolism by targeting the brain (Spranger et al. 2006; Pan et al. 2006; Qi et al. 2004). Trimeric and LMW forms of adiponectin are present in cerebrospinal fluid (Kusminski et al. 2007; Ebinuma et al. 2007; Kubota et al. 2007), and the concentration of adiponectin in cerebrospinal fluid increases after intravenous injection, consistent with blood-to-brain transport (Qi et al. 2004; Kubota et al. 2007). Intracerebroventricular administration of adiponectin increases energy expenditure and

fatty acid oxidation, and these effects may be mediated through Corticotropin Releasing Hormone and melanocortin signaling (Qi et al. 2004). Other studies suggest an opposite effect of adiponectin on energy balance (Combs et al. 2004; Kim et al. 2007). Overexpression of adiponectin in wild-type and *Lep*$^{ob/ob}$ mice resulted in obesity; however, insulin resistance and inflammation were reduced in these obese mice (Kim et al. 2007). Systemic administration of adiponectin increased AMPK activity in the arcuate nucleus through AdipoR1 signaling, resulting in hyperphagia and weight gain (Kubota et al. 2007). In contrast, adiponectin-deficient mice displayed reduced AMPK activation in the hypothalamus, associated with reduced food intake, increased energy expenditure, and resistance to obesity. Adiponectin levels in cerebrospinal fluid are increased in response to fasting and decreased after refeeding, suggesting that adiponectin may act as a starvation signal (Kubota et al. 2007).

AdipoR1 and AdipoR2 are expressed in pancreatic β-cells (Kharroubi et al. 2003), and adiponectin enhances glucose-stimulated insulin secretion and prevents apoptosis of β-cells. PPARγ (Rao et al. 2012), MEK–ERK, and PI3K–Akt signaling mediate the effects of adiponectin on insulin secretion (Wijesekara et al. 2010), while activation of ERK and Akt mediates the antiapoptotic effects of adiponectin (Brown et al. 2010). Adiponectin decreases blood glucose by inhibiting hepatic glucose production (Berg et al. 2001; Combs et al. 2001). Studies have shown that adiponectin inhibits hepatic lipogenesis in mice (Yamauchi et al. 2001; Kim et al. 2007; Asterholm and Scherer 2010) by suppressing the expression of SREBP1c via AdipoR1–LKB1–AMPK signaling (Awazawa et al. 2009). Adiponectin may also modulate hepatic insulin signaling via IRS2–IL6–STAT3 signaling (Awazawa et al. 2011).

Adiponectin stimulates differentiation, glucose uptake, and triglyceride accumulation in 3T3-L1 adipocytes (Fu et al. 2005). Leptin-deficient *ob/ob* mice overexpressing adiponectin developed excessive fat storage in subcutaneous depots, but they were protected from visceral adiposity, steatosis, and inflammation, indicative of metabolically healthy phenotype (Kim et al. 2007). High plasma adiponectin levels are also associated with metabolically healthy obesity in humans (Karelis et al. 2005), a condition characterized by increased subcutaneous fat, preservation of insulin sensitivity, reduced oxidative stress and inflammation, and lower cardiovascular risk.

Earlier studies demonstrated potent effects of the globular (head) form of adiponectin on fatty acid oxidation in skeletal muscle (Fruebis et al. 2001) (Fig. 3). Adiponectin stimulates AMPK phosphorylation and activity, inhibits acetyl-CoA carboxylase (Yamauchi et al. 2002; Tomas et al. 2002), increases expression of acetyl-CoA oxidase, Uncoupling Protein-2, and Uncoupling Protein-3 (Yamauchi et al. 2003), and activates p38 MAPK and PPARα (Yoon et al. 2006). Adiponectin also signals through calcium-mediated pathway via AMPK to affect mitochondrial function in myocytes (Iwabu et al. 2010). Adiponectin acting through AdipoR1 in skeletal muscle triggers extracellular Ca^{2+} influx, leading to activation of Ca^{2+}/calmodulin-dependent protein kinase kinase β (CaMKKβ), AMPK, SIRT1, and PGC-1α, which enhances mitochondrial function and fatty acid oxidation (Iwabu et al. 2010).

3.3 Effects of Adiponectin on Inflammation and Cardiovascular Risk

Adiponectin exerts major cardioprotective effects by modulating LDL, HDL, and total cholesterol and glucose levels and inflammation (Pischon et al. 2004; Rothenbacher et al. 2005; Schulze et al. 2005; Otsuka et al. 2006). Adiponectin knockout mice are more vulnerable to vascular and myocardial injury, while adenovirus overexpression of adiponectin protects adiponectin knockout and wild-type mice from myocardial ischemia (Shibata et al. 2005). These effects may be mediated through AdipoR1 and AdipoR2 acting via ceramidase activity (Holland et al. 2011). T-cadherin binds adiponectin in cardiomyocytes and may be involved in cardioprotection, as evident by the increased

susceptibility of T-cadherin knockout mice to myocardial injury (Denzel et al. 2010).

Adiponectin reduces oxidative stress and improves endothelial function through activation of AMPK–eNOS and PKA signaling (Ouedraogo et al. 2007; Wong et al. 2011; Lee et al. 2011a). Calreticulin/CD91-PI3K-Akt-COX2 signaling also serves as a downstream mediator of adiponectin in blood vessels (Ohashi et al. 2009). Population studies have demonstrated associations of adiponectin and proteinuria in patients with chronic kidney disease (Zoccali et al. 2003; Lo et al. 2011; Zoccali and Mallamaci 2011). In mice, adiponectin decreases oxidative injury and albumin permeability in podocytes and ameliorates renal interstitial fibrosis (Rutkowski et al. 2013). Adiponectin has direct anti-inflammatory effects on macrophages in adipose tissue, promoting a switch from pro-inflammatory M1 to anti-inflammatory M2 macrophages (Ohashi et al. 2010). Adiponectin stimulates transcription of IL-6, and this has been linked to elevated plasma IL-6 levels and IRS-2 expression and hepatic insulin signaling (Awazawa et al. 2011).

3.4 Role of Adiponectin in Cancer

Epidemiological studies have established a strong association of adiponectin and cancer (Dalamaga et al. 2012), particularly endometrium (Petridou et al. 2003), breast (Mantzoros et al. 2004), colon (Wei et al. 2005), and kidney (Spyridopoulos et al. 2007). Adiponectin levels are also associated with leukemia (Petridou et al. 2006), lymphoma (Petridou et al. 2009), myeloma (Dalamaga et al. 2009), and chronic lymphocytic leukemia (Dalamaga et al. 2010). The underlying mechanisms are unclear and may involve effects of adiponectin on other tumorigenic factors or direct AdipoR-mediated cellular signaling regulating insulin sensitivity, tumor growth, and angiogenesis. Some in vitro studies have shown potent pro-angiogenic and tumorigenic effects of adiponectin mediated partly by local changes in sphingosine levels and ceramidase activity (Landskroner-Eiger et al. 2009; Hefetz-Sela and Scherer 2013).

4 Resistin

Resistin is a cysteine-rich protein that was discovered during a search for genes downregulated by thiazolidinedione drugs (Steppan et al. 2001). Murine resistin is mainly expressed in mature white adipocytes and suppressed by thiazolidinediones (Shojima et al. 2002; Hartman et al. 2002) and insulin treatment (Shojima et al. 2002; Haugen et al. 2001) and upregulated by glucose (Shojima et al. 2002; Rajala et al. 2002). Resistin expression in mouse adipocytes is also inhibited by inflammatory cytokines, e.g., TNF-α (Shojima et al. 2002; Fasshauer et al. 2001). Resistin is decreased in the adipose tissue during fasting and increased in response to refeeding in mice (Steppan et al. 2001; Rajala et al. 2002, 2004). Obese mice have high plasma resistin levels; however, resistin mRNA expression is suppressed in adipose tissue in these mice (Rajala et al. 2004; Barnes and Miner 2009). Unlike murine resistin, human resistin is expressed in monocytes and macrophages and is induced by TNF-α (Kaser et al. 2003; Lehrke et al. 2004). The lack of resistin expression in human adipocytes may be due to loss of a genomic binding site for PPARγ which controls resistin gene (*retn*) expression in mouse adipocytes (Tomaru et al. 2009).

Murine resistin circulates mainly as a disulfide-linked hexamer, but a smaller trimeric protein is also detected. The trimeric form of resistin is more potent in decreasing hepatic insulin sensitivity in mice (Patel et al. 2004). However, oligomerization is necessary for the inhibitory action of resistin on glucose uptake in cardiomyocytes (Graveleau et al. 2005). Human resistin also circulates as trimeric and oligomeric forms, and the latter is thought to be more potent in stimulating the production of inflammatory cytokines (Gerber et al. 2005; Aruna et al. 2008; Filkova et al. 2009).

4.1 Resistin Signaling

The resistin receptor has not yet been clarified; however, studies indicate that decorin and tyrosine kinase-like orphan receptor 1 resistin receptors

may mediate effects of resistin on WAT expansion or modulate glucose homeostasis (Daquinag et al. 2011; Sanchez-Solana et al. 2012). Murine resistin decreases the phosphorylation of AMPK in the liver, skeletal muscle, and WAT (Muse et al. 2004; Banerjee et al. 2004; Satoh et al. 2004). Resistin inhibits the phosphorylation of insulin receptor substrates and activation of phosphatidylinositol-3-kinase (PI3K) and protein kinase B/Akt in the liver, muscle, and WAT (Muse et al. 2004; Satoh et al. 2004; Steppan et al. 2005). Resistin induces SOCS3, a known inhibitor of insulin signaling, in the liver, muscle, and WAT (Barnes and Miner 2009; Qi et al. 2006; Steppan et al. 2005; Muse et al. 2007; Lazar 2007).

Adenylyl cyclase-associated protein 1 (CAP1) has been identified as a functional resistin receptor (Lee et al. 2014). Human resistin binds directly to CAP1 in monocytes and increases cAMP, PKA activity, and NF-κB-mediated transcription of inflammatory cytokines (Lee et al. 2014). CAP1 overexpression in monocytes enhances the effects of resistin treatment. In contrast, a reduction of CAP1 expression reduced the effects of resistin on inflammatory activity in monocytes as well as in transgenic mice expressing human resistin (Lee et al. 2014).

4.2 Metabolic Effects of Resistin in Rodents

Earlier studies demonstrated potent effects of resistin on glucose homeostasis in mice. Neutralization of resistin with anti-resistin antibody enhanced insulin sensitivity in obese mice (Steppan et al. 2001). CNS or systemic resistin treatment or transgenic overexpression of resistin induced hepatic insulin resistance in mice (Steppan et al. 2001; Rajala et al. 2003; Muse et al. 2004; Li et al. 2009). In contrast, the deletion or knockdown of resistin increased hepatic insulin sensitivity in obese mice (Banerjee et al. 2004; Qi et al. 2006). Resistin knockout mice developed hypoglycemia during fasting, associated with suppression of gluconeogenic enzymes in the liver (Banerjee et al. 2004). Resistin treatment of 3T3-L1 adipocytes, murine cardiomyocytes, and skeletal muscle cells decreased insulin-stimulated glucose uptake (Steppan et al. 2001; Graveleau et al. 2005; Palanivel et al. 2006; Fan et al. 2007), indicating that resistin plays an important role in glucose homeostasis in rodents. Resistin also promotes fatty liver and cirrhosis in mouse models (Singhal et al. 2008; Roth et al. 2012; Dong et al. 2013).

4.3 Biological Effects of Human Resistin

The expression of human resistin is increased in peripheral mononuclear cells as they differentiate into macrophages (Patel et al. 2003; Lehrke et al. 2004; Savage et al. 2001). Thiazolidinedione drugs suppress the expression of human resistin in macrophages (Lehrke et al. 2004; Samaha et al. 2006). Resistin is also detectable in the stromal vascular fraction in the WAT, cirrhotic liver, and atherosclerotic lesions, consistent with the view that macrophages are the main source of human resistin (Savage et al. 2001; Fain et al. 2003; Bertolani et al. 2006; Burnett et al. 2005; Jung et al. 2006; Pagano et al. 2005). Given the potent metabolic effects of murine resistin, there are questions concerning the biological actions of human resistin.

Epidemiological studies have revealed conflicting associations of resistin and obesity in humans (Azuma et al. 2003; Moschen et al. 2009; de Luis et al. 2011; McTernan et al. 2003; Lee et al. 2003; Reilly et al. 2005; Jain et al. 2009). However, some studies have suggested positive associations of resistin and inflammation, insulin resistance, and cardiovascular diseases. Several single-nucleotide polymorphisms (SNPs) are associated with resistin levels (Menzaghi et al. 2006). The -638 G $>$ A, -420 C $>$ G, and -358 G $>$ A polymorphisms in the promoter region of human resistin gene (*RETN*) were associated with resistin levels in Japanese obese individuals (Azuma et al. 2004). The G/G genotype at SNP -420 in *RETN* was associated with susceptibility to type 2 diabetes and also was correlated with monocyte resistin expression and plasma resistin levels (Osawa et al. 2004, 2005). A

cross-sectional study in Japanese subjects showed that plasma resistin was associated with SNP −420 and also correlated with insulin resistance (Osawa et al. 2007). The −420G and −537A alleles were associated with increased resistin levels but not with T2DM in a Korean cohort (Cho et al. 2004). Among Chinese, both −420G and +62A alleles were strongly predictive of glucose levels (Xu et al. 2007). A study in Italy showed that the presence of −420 C/G SNP in *RETN* was associated with obesity and metabolic syndrome (Norata et al. 2007). In the Framingham Offspring Study, SNPs in the 3′ region of *RETN* were associated with resistin levels (Hivert et al. 2009). El-Shal et al. (El-Shal et al. 2013) found that both −420 C > G and +299 G > A SNP were significantly associated with resistin, obesity, and insulin resistance in obese people in Egypt.

Tang et al. (Tang et al. 2008) have reported that −420 C/G SNP in *RETN* is associated with coronary artery disease, but studies of the −420 variant in Europeans and Caucasians found no correlation with atherosclerosis (Norata et al. 2007; Qasim et al. 2009). How may resistin affect the development of atherosclerosis? Human resistin increases the proliferation and migration of human endothelial and vascular smooth muscle cells, mediated through PI3K or p38 mitogen-activated protein kinase signaling pathways (Mu et al. 2006; Calabro et al. 2004; Shen et al. 2006). Resistin attenuates insulin signaling, inhibits endothelial nitric oxide synthase, and increases oxidative stress in endothelial cells (Shen et al. 2006; Chen et al. 2010). In addition, resistin increases intercellular adhesion molecule-1, vascular cell adhesion molecule-1, P-selectin, fractalkine, Monocyte Chemoattractant Protein-1, PAI-1, endothelin-1, matrix metalloproteinases, and vascular endothelial growth factor receptors, which increase monocyte adhesion in vascular endothelial cells (Barnes and Miner 2009; Jung et al. 2006; Verma et al. 2003; Mu et al. 2006; Hsu et al. 2011; Manduteanu et al. 2010). Resistin promotes foam cell transformation (Burnett et al. 2005; Jung et al. 2006; Xu et al. 2006; Rae et al. 2007) and induces thrombosis via tissue factor expression in human coronary artery endothelial cells (Calabro et al. 2011; Jamaluddin et al. 2012).

Plasma resistin levels correlate with inflammatory and fibrinolytic markers such as C-reactive protein (CRP), TNF-α, IL-6, or plasminogen activator inhibitor (PAI)-1 in type 2 diabetes, coronary artery disease, chronic kidney disease, and sepsis (Lehrke et al. 2004; McTernan et al. 2003; Reilly et al. 2005; Shetty et al. 2004; Axelsson et al. 2006; Senolt et al. 2007; Sunden-Cullberg et al. 2007) as well as the general population (Reilly et al. 2005; Osawa et al. 2007; Bo et al. 2005; Kunnari et al. 2006; Qi et al. 2008; Fargnoli et al. 2010; Konrad et al. 2007). Hyperresistinemia has been observed in patients with rheumatoid arthritis and inflammatory bowel disease and tracks well with disease activity (Filkova et al. 2009; Senolt et al. 2007; Konrad et al. 2007). Elevated resistin levels are related to disease severity of sepsis and acute pancreatitis and predictive of mortality in critically ill patients (Sunden-Cullberg et al. 2007; Schaffler et al. 2010; Koch et al. 2009).

To understand the molecular pathways mediating the biology of human resistin, Qatanani et al. (Qatanani et al. 2009) produced a transgenic mouse expressing human resistin via a macrophage promoter and bred them with resistin knockout mice. The "humanized" resistin mice developed inflammation and insulin resistance consistent with epidemiological studies (Chen et al. 2009; Schwartz and Lazar 2011). To further elucidate the biology of human resistin, Park et al. (Park et al. 2011) generated mice lacking murine resistin but transgenic for a bacterial artificial chromosome containing human resistin (BAC-Retn). Lipopolysaccharide treatment increased resistin levels in this model and resulted in mild hypoglycemia. The BAC-Retn mice developed hepatic insulin resistance under chronic endotoxemia, accompanied by inflammation in the liver and skeletal muscle (Park et al. 2011). These results are in agreement with a study showing that resistin competes with lipopolysaccharide (LPS) for binding to Toll-like receptor 4 (TLR4) to mediate the pro-inflammatory action of resistin (Tarkowski et al. 2010).

5 Conclusion

This review highlights the roles of adipose tissue in energy homeostasis and the biology of adipokines and other secreted proteins that mediate a variety of local and systemic functions. A better understanding of the production and signaling pathways of adipokines will benefit the diagnosis and treatment of diabetes, lipid disorders, cardiovascular diseases, cancer, and other diseases associated with obesity. Future research requires systematic approaches in human and animal models to elucidate how adipokines specifically affect energy homeostasis and other physiological processes via hormonal, paracrine, or autocrine mechanisms and how these affect the pathogenesis of various diseases.

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6 Cross-References

- ▶ Adipose Structure (White, Brown, Beige)
- ▶ Brain Regulation of Feeding and Energy Homeostasis
- ▶ Insulin Resistance in Obesity
- ▶ Linking Inflammation, Obesity, and Diabetes
- ▶ Overview of Metabolic Syndrome

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Gut Hormones and Obesity

23

Elizabeth G. Mietlicki-Baase and Matthew R. Hayes

Contents

Abstract

Feeding is ultimately controlled by the central nervous system but is strongly influenced by numerous physiological signals arising from the periphery that either promote or limit energy intake. Broadly speaking, these gut hormones act via neuroendocrine mechanisms to communicate information on changing energy status from the periphery to the brain. Some of these peptides are produced by the gastrointestinal tract itself. Most of these gastrointestinal-derived signals, including cholecystokinin, glucagon-like peptide-1, and peptide YY, promote meal termination; in contrast, the hunger hormone ghrelin promotes the ingestion of food when readily available energy is low. Additionally, supporting organs like the pancreas release feeding-relevant neuroendocrine signals that regulate the internal milieu during nutrient influx. Together, these gut peptides control energy balance through a complicated interplay of physiological, behavioral, and neuroendocrine events. Individual signals are well investigated for their role in the maintenance of normal energy balance, but their roles in obesity – whether relating to the development or consequences of elevated body weight – are often understudied. This represents a critical area of ongoing research. Here, we review several of the major gastrointestinal- and pancreatic-derived gut hormones that contribute to the control of food intake. We discuss their impact on the control of energy balance in

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lean (i.e., nonobese) individuals and summarize some of the major findings regarding the role of each peptide in the obese state.

Keywords
Ghrelin • Cholecystokinin • Glucagon-like peptide-1 • Peptide YY • Insulin • Amylin

1 Introduction

While energy balance is ultimately regulated by the central nervous system (CNS), the organs of the alimentary canal and supporting organs of the peritoneal cavity supply numerous neuroendocrine signals that are necessary for the physiological and behavioral processes that affect energy balance. This chapter will provide a brief overview of some of these "gut hormones" and their contribution to energy balance regulation. We focus our attention on the gastrointestinal- and pancreatic-derived peptides that have been extensively studied both in the context of normal physiology and in the pathophysiological state of obesity. Accordingly, the hormonal systems reviewed here are, in our opinion, those systems that represent the greatest opportunity for future pharmacological targets to treat obesity. Importantly, some of the gut peptides discussed below are also synthesized centrally within the brain and are more accurately referred to as neuropeptides. Thus, an important consideration for all of the peptides described is a discussion about the mechanisms (behavioral, endocrine, and autonomic) and neuroanatomical sites of action within the brain and periphery for each of these hormonal systems.

All gut peptides regulate feeding behavior by either negatively or positively influencing food intake during a meal and/or between meals, influencing the intermeal interval and the frequency of meal taking (Ritter 2004; Grill and Hayes 2012; Moran 2006). This involves a constant stream of gut-to-brain communication through humoral mechanisms, as well as neuronal signaling via the vagus nerve. Once a meal has begun and food enters the oral cavity, cranial nerves VII, IX, and X relay various properties of the ingesta (e.g., taste and texture of the food) to the brainstem that promote further feeding if the food is perceived as palatable (Norgren 1983). As food is swallowed and enters into the gastrointestinal (GI) tract, information about the volume of the ingested food through the mechanical distension of the stomach is relayed to the nucleus tractus solitarius (NTS) by the vagus nerve. These gastric-inhibitory signals subsequently begin to counteract the positive meal-promoting signals from the oral cavity. Additionally, the various chemical and nutritive properties of the food result in the release of a number of gut peptides and neurotransmitters from the GI tract and supporting organs of the alimentary canal (e.g., pancreas) that also communicate to the brain via humoral (i.e., endocrine) and neuronal pathways about the ongoing status of the meal. The majority of these signals are referred to as *satiation signals*, or within-meal food intake-inhibitory signals (Ritter 2004). The accumulation of these satiation signals eventually leads to *satiety* or meal termination. Satiety then persists from the end of one meal to the start of the next meal.

Gut peptide-mediated activation of vagal afferents is thought to occur largely through a paracrine-like mechanism of action on specific receptors expressed on the dendritic terminals of vagal afferent neurons whose cell bodies are found in the *nodose ganglia* [see (Ritter 2004; Grill and Hayes 2012) for review]. These dendritic vagal afferent terminals innervate all organs in the peritoneal cavity, and the receptors for gut peptides are expressed in close cellular proximity to the specialized endocrine cells that are responsible for the synthesis and secretion of the particular hormone. Support for vagal afferent mediation of many GI-derived satiation signals comes from basic science studies showing that chemical or surgical ablation of the vagal afferents attenuates the intake-inhibitory response to the peripherally administered satiation signal [see (Ritter 2004; Grill and Hayes 2012) for review]. Where possible, for each of the hormones reviewed within this chapter, we will discuss the requirement of vagal afferent mediation for any energy balance effects produced by that signal.

Given the remarkable number of redundant gut peptide, neuropeptide, and neurotransmitter systems that exist in the body to regulate energy balance, it seems initially paradoxical that obesity rates continue to rise worldwide (Ng et al. 2014), a fact which suggests an absence of homeostatic equilibrium when it comes to energy balance. Many theories have been proposed, discussed, heavily reviewed, and cited on this topic (McAllister et al. 2009; Thomas et al. 2012). We and others (Rosenbaum et al. 2010) view the evolutionary development of energy balance regulation as one designed not to maintain leanness or normal energy equilibrium, but rather to defend adiposity and the surplus of energy storage. From this perspective it is worth noting that the brain initiates autonomic, behavioral, and endocrine responses not just in response to the accumulation of a given neuropeptide signal and receptor activation but also in response to the *reduction* of a given signal. In this chapter, while we discuss the impact obesity has on each of the gut peptide systems in comparison to physiological effects mediated by each hormone in a nonobese state, we also note, where appropriate, opportunities for future pharmacological targets to treat obesity. A brief summary of the major facts presented in this chapter is provided in Table 1.

2 Gastrointestinal Hunger Signaling

Meal initiation occurs in response to both internal hunger signals that communicate energy need, as well as external environmental cues and appetite signals that include entrainment, social, memory, and cognitive and sensory aspects of feeding behavior. Importantly though, the subjective feeling of hunger is generated by both the reduction of GI-derived satiation signals as the previous meal has been digested and absorbed, as well as an accumulation of central and peripheral orexigenic signals that promote feeding. Here we discuss the sole gut peptide that is classified as a hunger (orexigenic) hormone.

2.1 Ghrelin

The hormone ghrelin was initially recognized for its ability to promote growth hormone secretion (Kojima et al. 1999; Date et al. 2000b), but a role for this peptide in the control of energy balance was identified shortly after its discovery (Nakazato et al. 2001; Wren et al. 2001a; Tschop et al. 2000). The function of ghrelin in energy homeostasis is unique, in that it is the only currently known gut hormone that increases feeding and body weight gain. Ghrelin is thus commonly referred to as the "hunger hormone."

Ghrelin is produced primarily in the X/A-like cells of the stomach (Date et al. 2000a), although it may also be synthesized within the brain (Cowley et al. 2003). Ghrelin exists in two major forms in the body, des-acyl ghrelin and acylated ghrelin (Hosoda et al. 2000). Acylation is accomplished by the actions of an enzyme called ghrelin O-acyltransferase (GOAT) (Yang et al. 2008). Circulating levels of acylated ghrelin are lower than des-acyl ghrelin (Murakami et al. 2002; Hosoda et al. 2000); however, the orexigenic effects of ghrelin are attributed predominantly to its acylated form (Asakawa et al. 2005). The effects of des-acyl ghrelin on energy balance are less clear and somewhat controversial (Inhoff et al. 2009). At least one study indicates a hyperphagic effect of des-acyl ghrelin (Toshinai et al. 2006), but more recent studies suggest that it reduces feeding and body weight (Heppner et al. 2014; Zhang et al. 2008) and may in fact antagonize some of the effects of the acylated form (Delhanty et al. 2012; Stevanovic et al. 2014). Thus, throughout this section, "ghrelin" refers to the acylated form of the peptide unless otherwise specified.

Circulating levels of ghrelin increase with fasting (Tschop et al. 2001a). Ghrelin secretion during periods of hunger is stimulated by a number of physiological factors, including reduced blood glucose levels (Lauritzen et al. 2015), changes in levels of feeding- and glycemic-relevant hormones such as insulin (Flanagan et al. 2003), as well as alterations in intracellular signaling molecules such as mTOR (Xu et al. 2009). In addition, individuals who

Table 1 Summary of gut hormones reviewed in this chapter. Complete references for information included in this table may be found in the relevant chapter section. Abbreviations: ARC, arcuate nucleus of the hypothalamus; CNS, central nervous system; CT, calcitonin receptor; DMH, dorsomedial hypothalamus; GHS-R, growth hormone secretagogue receptor; GLP-1R, glucagon-like peptide-1 receptor; GOAT, ghrelin O-acyltransferase; ICV, intracerebroventricular; IR, insulin receptor; LH, lateral hypothalamus; NTS, nucleus tractus solitarius; PBN, parabrachial nucleus; PVN, paraventricular nucleus of the hypothalamus; RAMP, receptor activity modifying protein; R_q, respiratory quotient; VMH, ventromedial hypothalamus; VTA, ventral tegmental area.

Gut peptide	Energy balance effects	Primary site (s) of production	Primary receptor mediating energy balance effects	Site(s) of action – non-inclusive	Effects of obesity	Strategies for obesity treatment
Ghrelin (acylated)	Stimulate feeding, reduce energy expenditure (increase R_q, decrease body temperature)	Stomach (X/A cells), hypothalamus	GHS-R	CNS: hypothalamus (ARC, PVN, LH), dorsal vagal complex, hippocampus, amygdala, VTA	Decreased plasma ghrelin levels	Reduce ghrelin bioactivity (immunoglobulins, Spiegelmers, block GOAT enzyme required for acylation)
Cholecystokinin (CCK)	Reduce feeding, promote satiation	Intestine (I cells), CNS	CCK-1	Vagal afferents; CNS: hypothalamus, NTS, PBN	Reduced sensitivity	Combine with other satiation/ adiposity signals (i.e. leptin, gastric distension)
Glucagon-like peptide-1 (GLP-1)	Reduce feeding	Intestine (L cells), NTS	GLP-1R	Vagal afferents; CNS: hypothalamus (PVN, DMH, VMH, LH), hippocampus, VTA, PBN, nucleus accumbens		GLP-1R agonism Liraglutide – FDA-approved for obesity treatment Exendin-4 – FDA-approved for diabetes, also reduces body weight
Peptide YY [PYY(l-36) and PYY(3–36)]	Peripheral: reduce feeding; Central: increase/decrease feeding, depending on site-of-action	Intestine (L cells)	Y2 (anorexigenic) Y1, Y5 (orexigenic)	Anorexigenic: vagal afferents; ARC Orexigenic: ICV administration	Low plasma PYY (3–36) levels	Restore PYY(3–36) levels, perhaps via increased aerobic exercise
Insulin	Reduce feeding	Pancreas (beta cells)	IR	CNS	Increased circulating insulin levels; reduced sensitivity	
Amylin	Reduce feeding, increase energy expenditure (decrease R_q, increase body temperature)	Pancreas (beta cells)	CT/RAMP heterodimer	CNS: area postrema, VTA, VMH	Increased circulating amylin levels, but remains effective to reduce feeding	Amylin receptor agonism Pramlintide – FDA-approved for diabetes, also reduces body weight

take meals on a regular schedule from day to day will eventually exhibit an entrainment of ghrelin levels to their meal times (Cummings et al. 2001). This temporal link between peak ghrelin levels and the onset of feeding has led to the notion that ghrelin may serve as a meal initiation signal (Cummings et al. 2001). Once food is ingested, circulating ghrelin declines (Tschop et al. 2001a). This reduction is influenced by a number of postingestive factors (Williams et al. 2003) including overall energy intake (Callahan et al. 2004) and increased tonicity in the gastrointestinal tract (Overduin et al. 2014). Interestingly, the postprandial suppression of ghrelin is related to the macronutrient content of the meal. Research indicates that intake of carbohydrates is more effective to reduce ghrelin than intake of fats or proteins (Overduin et al. 2005; Erdmann et al. 2004).

Ghrelin stimulates feeding by binding and activating its receptor, the growth hormone secretagogue receptor (GHS-R) (Shuto et al. 2002; Asakawa et al. 2003). This is a G protein-coupled receptor that is coupled predominantly to the G_q pathway and possibly the G_s pathway (Falls et al. 2006; Cuellar and Isokawa 2011). The GHS-R is widely distributed throughout the body, including in the brain (Dass et al. 2003; Gnanapavan et al. 2002; Shuto et al. 2001; Guan et al. 1997). As ghrelin can cross the blood-brain barrier (Banks et al. 2002, 2008), the circulating peptide can potentially activate both central and peripheral receptor populations. Although some of the energy balance effects of ghrelin may be vagally mediated (le Roux et al. 2005; Page et al. 2007), most of the research on ghrelin's hyperphagic effects has focused on its actions within the brain. In particular, the ability of ghrelin to regulate feeding via effects in the arcuate nucleus of the hypothalamus (ARC) is well established (Cowley et al. 2003; Currie et al. 2005; Traebert et al. 2002). The GHS-R is expressed on neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons in the ARC (Willesen et al. 1999). When ghrelin binds to its receptor on these neurons, it increases expression of NPY and AgRP (Kamegai et al. 2001; Shintani et al. 2001), neuropeptides with orexigenic effects. In addition, GHS-R activation of NPY/AgRP neurons stimulates the release of GABA onto proopiomelanocortin (POMC) neurons within the ARC (Cowley et al. 2003), reducing the activity of this hypophagia-producing neuronal population. These complementary effects of increasing NPY/AgRP activity, while concomitantly suppressing POMC activity, contribute to the overall stimulation of feeding by ghrelin.

In addition to its effects within the hypothalamus, ghrelin acts at a number of other structures within the brain to promote positive energy balance. These include hindbrain sites such as the dorsal vagal complex (Faulconbridge et al. 2003) as well as a number of forebrain nuclei including the paraventricular nucleus of the hypothalamus (Currie et al. 2005; Olszewski et al. 2003a), the lateral hypothalamus (Olszewski et al. 2003b), the hippocampus (Kanoski et al. 2013), and the amygdala (Alvarez-Crespo et al. 2012). Several recent studies have focused on the ability of ghrelin to modulate activity of the mesolimbic dopamine pathway, including the ventral tegmental area (VTA) (Skibicka et al. 2011; Naleid et al. 2005; Egecioglu et al. 2010; King et al. 2011; Cone et al. 2014). This is an intriguing direction of research, as the mesolimbic system is known to be involved in food reward and motivated behavior (Narayanan et al. 2010; Vucetic and Reyes 2010). Studies show that ghrelin can act directly in mesolimbic nuclei such as the VTA to increase food intake and the motivation to obtain a palatable food (Skibicka et al. 2011; Egecioglu et al. 2010; King et al. 2011). Furthermore, ghrelin influences dopaminergic neurotransmission in the mesolimbic pathway. A recent study from Roitman's group shows that intracerebroventricular administration of ghrelin enhances phasic dopamine responses in the nucleus accumbens evoked by a food-related cue, but has no effect on responses to a neutral (non-food) cue (Cone et al. 2014). Collectively, these studies suggest that ghrelin may have interesting effects on reward and motivational processes for feeding.

The control of energy balance involves not only regulation of energy intake but also energy

expenditure. In addition to its orexigenic actions, ghrelin also promotes positive energy balance by reducing energy expenditure (Yasuda et al. 2003; Asakawa et al. 2001). Rodent studies demonstrate that ghrelin reduces body temperature and increases respiratory quotient (R_q) (Yasuda et al. 2003; Currie et al. 2005; De Smet et al. 2006). This shift in fuel utilization reflected by the change in R_q is thought to contribute to the ability of ghrelin to increase adiposity (Tschop et al. 2000; Wren et al. 2001b).

Obese individuals typically have lower plasma levels of ghrelin than do lean individuals. This is observed in fasting levels of ghrelin, but additionally, the postprandial suppression of ghrelin is not as large in obese individuals compared to lean (English et al. 2002; Tschop et al. 2001a, b; Shiiya et al. 2002). Weight loss results in an increase in plasma ghrelin (Hansen et al. 2002; Cummings et al. 2002), which may contribute to the increased hunger experienced during and after dieting-induced weight loss. Because ghrelin stimulates hunger and increases feeding, reducing the bioactivity of ghrelin may promote weight loss. In animal models, reduction of ghrelin levels has been accomplished through the use of technologies such as anti-ghrelin immunoglobulins (Takagi et al. 2013) and Spiegelmers (Shearman et al. 2006; Teubner and Bartness 2013); indeed, these strategies reduce feeding and body weight. However, a number of issues, including bioavailability concerns and side effects, have limited the translatability of these types of approaches to humans (Schellekens et al. 2010). Another idea has been to reduce active ghrelin by blocking the GOAT enzyme, thus blocking acylation (Gualillo et al. 2008). This possibility has not yet been widely examined.

3 Gastrointestinal Satiation Signals

The abundant vagal afferent innervation (Wang and Powley 2000) and proximal location of the stomach within the GI tract provide an early monitoring system for the status of meal ingestion. Specifically, the food intake-inhibitory signals produced by the stomach arise from the mechanical distension of the stomach (rather than the chemical/nutritive properties of the ingested food) (Powley and Phillips 2004; Phillips and Powley 1996; Mathis et al. 1998). Unlike the satiation signals that arise from the intestine, the intake-inhibitory signals arising from the stomach are not mediated by gut peptides. Rather, a portion of the dendritic vagal sensory endings innervating the stomach are specialized to be responsive to stretch and/or tension and are referred to as intraganglionic laminar endings and intramuscular arrays [see (Ritter 2004) for review]. The vagal dendritic detection of tension and stretch within the gastric wall results in glutamatergic neuronal transmission from vagal axon projections to NTS neurons in the caudal brainstem [see (Grill and Hayes 2012) for review]. In addition, as the gastric wall is distended, the neurotransmitter serotonin (5-HT) is secreted from gastric enterochromaffin (EC) cells and is thought to provide the principal stomach-derived intake-inhibitory signal. This 5-HT-mediated hypophagic response engaged by gastric distension occurs principally by the activation of ionotropic 5-HT type-3 receptors (5-HT3R) expressed on the dendritic terminals of vagal afferents innervating the stomach in a paracrine-like mediated fashion (Hayes et al. 2004a, 2006; Hayes and Covasa 2006; Mazda et al. 2004; Glatzle et al. 2002). Below, where appropriate, we discuss how gastric distension and GI-derived satiation signaling interact with gut peptides to control energy balance.

3.1 Cholecystokinin (CCK)

The neuropeptide CCK, released peripherally from intestinal "I" cells in response to ingestion of nutrients, is arguably one of the most biologically potent satiation signals [see (Ritter 2004; Moran 2006) for review]. Indeed, over four decades ago, Gibbs, Young, and Smith first reported that exogenous systemic administration of CCK produces a dose-dependent decrease in meal size (Gibbs et al. 1973). This initial finding was the first to demonstrate that a GI-derived

peptide was negatively influencing food intake, providing the seminal discovery for future scientific fields looking at the gut-to-brain communication involved in the control of energy balance.

Systemic CCK acts via CCK-1 receptors which are densely distributed in the periphery on the afferent terminals of the vagus nerve and in select regions of the CNS. Importantly though, the primary site of action for either endogenous or exogenous systemic CCK is not the CNS, but rather the vagal afferents (Smith et al. 1985). Support for the physiological requirement of endogenous CCK-1 receptor signaling in controlling meal size, and energy balance more broadly, comes from the findings that blockade of CCK-1 receptors using selective antagonists results in a short-term increase in food intake (Moran et al. 1992; Hayes and Covasa 2005; Hayes et al. 2004b; Reidelberger and O'Rourke 1989; Reidelberger et al. 1991), as well as data showing that rats with genetic deletion of the CCK-1 receptor are chronically hyperphagic and obese (De Jonghe et al. 2005; Moran et al. 1998; Takiguchi et al. 1997).

CCK-induced suppression of intake is enhanced when combined with other GI-derived satiation signals. For example, data from Schwartz and Moran (1996; Schwartz et al. 1993) show that when CCK and gastric distension are applied in combination, there is a dose- and volume-dependent increase in firing rate and total spike number of electrophysiological recordings made on single vagal afferent fibers. Thus, the vagus is postulated to integrate these GI-derived satiation signals, leading to an enhanced behavioral suppression of food intake when CCK and gastric distension are combined (Schwartz and Moran 1996; Moran et al. 2001; Ritter 2004). Interestingly, these two GI-derived satiation signals also mechanistically interact within a meal to suppress the ongoing meal. Specifically, CCK-1 receptor activation reduces gastric emptying and thereby enhances gastric distension as the animal continues to feed (Bozkurt et al. 1999; Moran and McHugh 1982; Schwartz et al. 1991a). Further, the vagal interactions between CCK and gastric distension involve participation of other GI-derived satiating signals, such as 5-HT, which is both released in response to gastric distension (Mazda et al. 2004) and interacts with CCK to reduce food intake (Hayes and Covasa 2005). Indeed, blockade of 5-HT3R attenuates the suppression of food intake by CCK (Daughters et al. 2001; Hayes et al. 2004a).

Recent evidence also suggests that in addition to the traditional role of CCK as a within-meal intake-inhibitory signal, CCK interacts with hormonal systems like insulin or leptin (Matson et al. 1997, 2000; Emond et al. 1999; Riedy et al. 1995) that serve as a readout of long-term energy stores to control energy balance [see (Begg and Woods 2012; Grill and Hayes 2012) for review]. In the case of leptin, it is thought that leptin potentiates the anorectic effects of CCK and other GI-derived satiation signals [see (Grill and Hayes 2012) for review]. This interaction between leptin and CCK is not confined to one nucleus within the brain, but rather involves distributed sites of action throughout the body that include but are not limited to vagal afferents (Peters et al. 2004, 2006), the NTS (Hayes et al. 2010b), parabrachial nucleus (Flak et al. 2014), and hypothalamic nuclei (Barrachina et al. 1997; Emond et al. 1999).

Despite the abundant literature that exists examining the role of the CCK system in control of feeding and evidence indicating its requirement for normal energy balance regulation (Moran et al. 1992; Hayes and Covasa 2005; Hayes et al. 2004b; Reidelberger and O'Rourke 1989; Reidelberger et al. 1991), there have been a number of road blocks that have precluded the development of safe and efficacious pharmacological tools targeting CCK as a means for weight loss in obese humans. One major hurdle that will need to be overcome is the reduced sensitivity to the intake-inhibitory effects of exogenous CCK when animals are maintained on a high-fat diet (Covasa and Ritter 1998; Savastano and Covasa 2005). This response is independent of obesity, yet the diminished sensitivity seems to be exacerbated by obesity (Duca et al. 2013). Similarly, detrimental to future CCK-based pharmacotherapies for obesity is the pronounced tachyphylaxis that develops with repetitive CCK administrations (Crawley and Beinfeld 1983). Finally and perhaps

most important for CCK-1 receptor agonists will be a need for analogs that remain efficacious without producing pancreatitis, a well-known response to chronic CCK-like treatments in mammals (Lampel and Kern 1977; Makovec et al. 1986). To this end, at least one compound, GI181771X (GlaxoSmithKline), appears to have little effect on pancreatic endpoints in overweight/obese humans (Myer et al. 2014); unfortunately, chronic treatment with this therapeutic did not reduce food intake and body weight in overweight and obese humans (Jordan et al. 2008), possibly for the physiological reasons described above.

3.2 Glucagon-Like Peptide-1 (GLP-1)

The biological processes regulated by the GLP-1 system are abundant and include insulin secretion, blood glucose regulation, suppression of gastric emptying, visceral stress, cardiovascular and thermogenic effects, modulation of reward- and goal-directed behaviors, and, importantly, a critical role in the control of food intake and energy balance [see (Holst 2007; Hayes et al. 2014) for review]. Here, we focus our attention on summarizing aspects of the GLP-1 system in the regulation of energy intake. We also discuss the utility of GLP-1-based drugs as realistic pharmacotherapies for the treatment of obesity.

GLP-1 promotes negative energy balance by reducing food intake and body weight [see (Hayes et al. 2010a) for review]. Within the periphery, GLP-1 is principally secreted by enteroendocrine "L" cells of the distal small intestine and large intestine in response to the ingestion of food. GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4) to inactive metabolites and therefore has a short circulating half-life of less than 10 min (Holst 2007), rendering native GLP-1 inappropriate for therapeutic use. GLP-1 acts on the GLP-1 receptor (GLP-1R), a G protein-coupled receptor, which has a varied tissue distribution in mammals (pancreas, intestine, brain, heart, etc.) (Goke et al. 1995; Merchenthaler et al. 1999; Wei and Mojsov 1995). Under normal physiological circumstances, intestinally derived GLP-1 activates GLP-1R expressed on the dendritic terminals of the vagal afferents innervating the GI tract in a paracrine-like mode of action [see (Hayes et al. 2014) for review]. However, the relevant GLP-1R populations mediating the food intake-suppressive effects of GLP-1R pharmacological agonists (e.g., liraglutide, exendin-4) or inhibitors of DPP-4 (e.g., sitagliptin) are more diverse. For example, when the long-lasting GLP-1R agonists liraglutide or exendin-4 are administered systemically, each can sufficiently penetrate the blood-brain barrier and gain access to the brain in amounts sufficient to drive physiological and behavioral responses (Kanoski et al. 2011, 2012). Indeed, activation of GLP-1R expressed in the CNS will recapitulate many of the same behavioral and physiological responses that are observed following peripheral GLP-1R ligand administration (Hayes et al. 2008; Kinzig et al. 2002; Knauf et al. 2005; Schick et al. 2003), making it difficult to disentangle the effects originating in the periphery from those effects mediated by direct CNS activation. Therefore, one of the current challenges of the obesity field is to characterize the energy balance responses mediated by individual GLP-1R-expressing nuclei and the physiological mechanisms mediating these responses.

To date, studies have shown a physiological and/or pharmacological role for food intake control by GLP-1R activation in a variety of CNS nuclei, including the NTS, paraventricular, dorsomedial, ventromedial, and lateral hypothalamus, as well as the ventral hippocampus, VTA, parabrachial nucleus, and nucleus accumbens shell and core [see (Hayes et al. 2014) for review]. While research pursuant to the exploration of GLP-1-mediated effects in all of these nuclei is certainly warranted, of particular interest is research aimed at identifying GLP-1-modulation of food reward processes. Indeed, with the growing appreciation that the excessive food intake that contributes to human obesity is not driven by metabolic need, a number of laboratories have made major advances in our understanding of the role that GLP-1 signaling in the nuclei of the mesolimbic reward system has on

energy balance control (Alhadeff et al. 2012; Dickson et al. 2012; Dossat et al. 2011). Perhaps most attractive from an obesity treatment perspective is the finding that GLP-1R activation in the VTA and nucleus accumbens core selectively reduces intake of highly palatable, energy dense foods and does not suppress intake of standard bland diet (Alhadeff et al. 2012; Mietlicki-Baase et al. 2013a, 2014). Further, at least in the case of the VTA, systemic administration of GLP-1R agonists is able to directly activate VTA-expressing GLP-1R to suppress food intake and body weight gain in rats (Mietlicki-Baase et al. 2013a). With the recent approval of the GLP-1R agonist liraglutide for the treatment of obesity (Mordes et al. 2015), we now need further basic science investigations that aim to identify adjunct behavioral and pharmacological therapies that can be combined with GLP-1R ligands to enhance the food intake- and body weight-suppressive effects of these pharmacotherapies.

3.3 Peptide YY (PYY)

Peptide YY (PYY), a member of a peptide family that also includes neuropeptide Y (NPY) and pancreatic polypeptide (PP), is named for the presence of two tyrosine (Y) residues that flank the ends of the peptide sequence. It is co-released with GLP-1 from the L cells of the small and large intestine after the ingestion of food (Eissele et al. 1992; Lundberg et al. 1982; Adrian et al. 1987). PYY is initially secreted in a longer form [PYY(1-36)] that has no effect on food intake (Sloth et al. 2007) but is rapidly cleaved by dipeptidyl peptidase-IV (DPP-IV) to form PYY(3-36) (Medeiros and Turner 1994). Although first identified in the early 1980s (Tatemoto 1982), the effects of PYY(3-36) on energy balance remained controversial for many years (Batterham and Bloom 2003; Batterham et al. 2002; Tschop et al. 2004; Boggiano et al. 2005). Contributing in part to this controversy is the fact that the two endogenous circulating isoforms of PYY [PYY(1-36) and PYY (3-36)] bind to Y1, Y2, and Y5 receptors (Blomqvist and Herzog 1997; Silva et al. 2002) with different affinities; while PYY(1-36) binds to all of these receptors, PYY(3-36) is thought to have the highest affinity for the Y2 receptor (Keire et al. 2002). Further, while it is now accepted that peripheral administration of PYY (3-36) suppresses feeding and body weight in humans and in animal models (Batterham and Bloom 2003; Batterham et al. 2002; Scott et al. 2005), in contrast, central [lateral, third, and fourth intracerebroventricular (ICV)] administration of either PYY(1-36) or PYY(3-36) potently *stimulates* food intake (Morley et al. 1985; Corp et al. 1990, 2001; Raposinho et al. 2001; Clark et al. 1987). Thus, while there is growing attention being devoted to the PYY system as a potential future target for obesity treatment, it is clear that an abundance of work is still needed to discern the physiological effects mediated by PYY Y-receptor signaling. Here, we provide a brief overview of PYY-mediated effects on energy balance with attention devoted to site and mechanism of action for the PYY isoforms.

During fasting, plasma levels of both PYY (1-36) and PYY(3-36) are low, but during meal taking and in a postprandial state, plasma PYY levels rise rapidly (Adrian et al. 1985). The amount of the peptide that is released is proportional to caloric intake (Degen et al. 2005), but it is worth noting that the macronutrient content of the meal can influence PYY secretion (Gibbons et al. 2013; El Khoury et al. 2010; Seimon et al. 2009). Peripherally released PYY is hypothesized to act as a satiation signal in concert with other GI-derived neuroendocrine signals like GLP-1, ultimately providing an ever-accumulating negative feedback satiation signal that eventually leads to meal termination (Moran et al. 2005). This hypothesis is consistent with rodent data demonstrating that acute peripheral administration of PYY(3-36) reduces meal size (Stadlbauer et al. 2013). One possible mechanism mediating the meal size-suppressive effects of systemic PYY(3-36) could involve the ability of systemic PYY to reduce gastric emptying (Allen et al. 1984; Chen et al. 1996), thus simultaneously providing less gastric capacity for further meal taking, as well as increasing vagally mediated

satiation signaling from the volumetric distension of the stomach.

From the perspective of creating pharmacotherapies to treat obesity, it is worth noting that chronic systemic administration of PYY(3-36) also reduces food intake (Vrang et al. 2006; Reidelberger et al. 2008; Moriya et al. 2009). This peptide can cross the blood-brain barrier (Nonaka et al. 2003) and is thought to primarily act within the CNS to exert its hypophagic effects, although vagal mediation also likely contributes to the intake inhibition (Koda et al. 2005). Like ghrelin, particular attention has been paid to the actions of PYY on the neuropeptide Y (NPY) system (Ballantyne 2006; Ueno et al. 2008). However, PYY differs from ghrelin in that it can directly activate the Y receptors (Aicher et al. 1991; Chen et al. 1997). Indeed, PYY (3-36) is thought to exert its anorectic effects via agonism of the Y2 receptor (Abbott et al. 2005), specifically Y2 receptors expressed on ARC NPY/AgRP neurons (Abbott et al. 2005; Teubner and Bartness 2013). Support for this hypothesis is provided by data showing that pharmacological antagonism of Y2 receptors in the ARC attenuates the ability of peripherally administered PYY (3-36) to suppress feeding (Abbott et al. 2005). However, as discussed above, the suppression of intake by PYY activation of ARC Y2 receptors appears to be in contrast to PYY's actions on other nuclei distributed throughout the brain, where PYY(3-36) results in an increase in food intake (Morley et al. 1985; Corp et al. 1990, 2001; Raposinho et al. 2001; Clark et al. 1987). Thus, further research is needed to determine all of the CNS sites of action for systemically delivered PYY-like agonists in the hope for treatment of obesity in humans.

Mice with diet-induced obesity exhibits low plasma levels of PYY(3-36) (Rahardjo et al. 2007). As experimental suppression of PYY(3-36) signaling induces obesity in mice (Boey et al. 2006), there may be a causal link between PYY(3-36) and the development of obesity. Supporting this notion, a study in mice tracking the development of diet-induced obesity showed that PYY(3-36) levels declined as body weight increased (Chandarana et al. 2011). Studies in humans are largely consistent with the rodent literature, showing that obese individuals have low fasting levels of PYY(3-36) as well as reduced postprandial PYY(3-36) release (Meyer-Gerspach et al. 2014; Gatta-Cherifi et al. 2012; Zwirska-Korczala et al. 2007; Batterham et al. 2003). In fact, even after weight loss, levels of PYY(3-36) remain persistently low (Lien et al. 2009), which may make maintenance of reduced body weight difficult (Chandarana et al. 2011). The fact that PYY (3-36) is decreased in obesity has led to interest in the idea that restoring PYY(3-36) levels may reduce food intake and body weight and thus may be an effective treatment for obesity (Zac-Varghese et al. 2011; Troke et al. 2014; De Silva and Bloom 2012). Indeed, acute administration of PYY(3-36) reduces energy intake not only in lean but also in obese humans (Batterham et al. 2003). To date, the potential utility of PYY (3-36) as an antiobesity pharmacotherapy has been limited due to side effects and low efficacy (Gantz et al. 2007; Troke et al. 2014). However, an alternative strategy is to increase PYY by engaging in more frequent exercise; several reports describe a positive association between plasma levels of PYY(3-36) and aerobic exercise (Ueda et al. 2009; Broom et al. 2009; Jones et al. 2009).

4 Pancreatic Beta-Cell-Derived Hormones

The influx of nutrients that occurs during a meal presents a challenge to many aspects of homeostasis, including glycemia. Proper processing of the ingested food is required to maintain glucose homeostasis. Blood glucose levels are regulated largely by insulin, which is released from pancreatic beta cells. Communication between the GI tract, pancreas, and brain is therefore required for glycemic control. However, the hormonal signals produced by the pancreas also have potent effects on feeding and body weight. Here, we consider the roles of insulin and another pancreatic peptide, amylin, in the control of energy balance.

4.1 Insulin

Insulin has arguably been the most well studied of the pancreatic-derived hormones for its effects on glycemic control (see Boucher et al. 2014; Schwartz et al. 2013 for review). In addition to its ability to regulate glucose levels, insulin receptor signaling can also affect food intake, although the reliability of insulin-mediated energy balance effects is sometimes questioned [see (Begg and Woods 2012; Woods and Langhans 2012) for review]. While insulin obviously promotes the lowering of plasma blood glucose, an effect which may impact subsequent food intake, the energy balance effects of insulin receptor signaling are independent from its effects on glycemia (Woods et al. 1984). Thus, while some of the energy balance effects of insulin may be mediated by peripheral organs such as the liver (Surina-Baumgartner et al. 1995), the majority of the intake-suppressive effects of peripheral insulin are thought to be centrally mediated (Woods et al. 2003; Banks 2004). Circulating insulin enters the CNS via facilitated transport (Baura et al. 1993). Additionally, while insulin may be produced centrally (Gerozissis 2004; Clarke et al. 1986), the predominant source of CNS insulin is thought to be from beta cells (Banks 2004; Banks et al. 1997).

Within the CNS, insulin receptor signaling has been shown to reduce food intake and body weight in several species (e.g., baboons, rats, sheep, mice, etc.) (Woods et al. 1979, 1984; Brief and Davis 1984; Brown et al. 2006; Foster et al. 1991). Many studies have examined the ability of insulin to regulate feeding via its actions in the hypothalamus and in particular the ARC. Insulin receptors are tyrosine kinase receptors that are expressed on NPY-containing as well as POMC-expressing ARC neurons, and insulin is known to modulate the activity of both of these neuronal populations (Qiu et al. 2014; Williams et al. 2010; Sato et al. 2005; Malabu et al. 1992; Kim et al. 1999; Wang and Leibowitz 1997; Schwartz et al. 1991b, 1992; Sipols et al. 1995). In particular, intracerebroventricular administration of insulin reduces NPY expression in the ARC (Schwartz et al. 1991b; Wang and Leibowitz 1997) as well as the paraventricular nucleus (Schwartz et al. 1992), possibly via recruitment of GABAergic circuits (Sato et al. 2005). Insulin also increases POMC expression (Kim et al. 1999), consistent with an overall reduction in food intake.

Activation of the insulin receptor results in rapid phosphorylation of insulin receptor substrate (IRS). In particular, IRS-2 appears to be important for the control of energy balance by insulin, as whole body (Burks et al. 2000; Lin et al. 2004) or hypothalamic knockdown (Kubota et al. 2004) of IRS-2 promotes obesity. A number of intracellular pathways downstream of IRS have been documented as required signaling events to mediate the intake-suppressive effects of insulin receptor activation. Principal among these is the PI3K signaling pathway (Niswender et al. 2003). Intracerebroventricular administration of insulin activates hypothalamic PI3K, as well as its downstream target Akt (Niswender et al. 2003). Pharmacological inhibition of PI3K attenuates the ability of centrally delivered insulin to suppress food intake (Niswender et al. 2003), indicating the requirement of PI3K activation for the anorectic effects of insulin. Engagement of the PI3K pathway is also important for insulin-mediated control of energy balance in extra-hypothalamic sites such as the amygdala (Castro et al. 2013).

Intriguingly, converging evidence suggests that insulin activation of the IRS-2/PI3K pathway in the VTA may have a role in reward processing. Insulin receptors (Figlewicz et al. 2003) and IRS-2 (Pardini et al. 2006) are expressed in the VTA, and direct intra-VTA administration of insulin increases PIP3, a product of PI3K activation (Figlewicz et al. 2007). Furthermore, VTA PI3K blockade may antagonize the ability of intra-VTA insulin to reduce dopamine release in the mesolimbic reward system (Mebel et al. 2012). Insulin-mediated activation of the IRS-2/PI3K/Akt pathway has been associated with changes in reward in various experimental paradigms, but the direction of effect appears to depend on the paradigm and/or type of reinforcing stimulus. IRS-2/PI3K/Akt activation by insulin decreases reward in an intracranial self-stimulation paradigm (Bruijnzeel et al. 2011), but activation of this intracellular signaling pathway *increases* conditioned place preference for drugs of abuse such as cocaine (Iniguez et al. 2008) and morphine

(Russo et al. 2007). Despite the finding that direct VTA injection of insulin reduces intake of palatable food (Mebel et al. 2012), the effects of insulin and the IRS-2/PI3K/Akt pathway in the VTA on food reward have not been well investigated. This is particularly surprising given earlier data showing that intracerebroventricular administration of insulin reduces sucrose self-administration (Figlewicz et al. 2006) and conditioned place preference for palatable food (Figlewicz et al. 2004), lending support to the notion that central insulin signaling mediates aspects of food reward. However, the particular role of the VTA and IRS-2/PI3K signaling in insulin-mediated food reward remains unknown; this represents an important, yet currently under-investigated area of research.

In the context of obesity, insulin is often referred to as a lipostatic signal (Benoit et al. 2004; Woods et al. 1985), in that circulating concentrations of insulin reflect levels of adiposity which communicate to the CNS to appropriately regulate energy balance (Ahren 1999). This concept fails to some extent; despite an accumulating magnitude of insulin signaling as adiposity increases, insulin resistance develops, and the obese individual does not subsequently reduce energy intake and increase energy expenditure to reduce adiposity levels. Thus, despite their higher plasma insulin, obese individuals are resistant to the intake- and body weight-suppressive effects of the peptide (De Souza et al. 2005; Posey et al. 2009; Catalano et al. 2005; Istfan et al. 1992; Tremblay 1995). These effects are not entirely due to an insufficiency in insulin penetrance into the CNS (Kaiyala et al. 2000), as direct central administration of insulin is less effective at reducing food intake in obese animals maintained on high-fat diet (Chavez et al. 1996; Elchebly et al. 1999).

4.2 Amylin (Islet Amyloid Polypeptide)

The peptide hormone amylin is co-secreted with insulin from pancreatic beta cells at a 1:100 ratio after food is consumed (Ogawa et al. 1990; Lutz 2010a). As one might expect given its association with insulin release, amylin has complementary beneficial effects to insulin on glycemic control (Schmitz et al. 2004), mainly mediated through delayed gastric emptying (Clementi et al. 1996), inhibition of glucagon release (Fehmann et al. 1990), and potent anorectic effects (Lutz et al. 1994, 1995b; Lutz 2010b). Specifically, amylin is well documented as a satiation signal for its robust ability to reduce food intake via suppression of meal size (Lutz et al. 1994, 1995b; Lutz 2010b).

As surgical vagotomy does not block amylin-induced hypophagia (Lutz et al. 1995a), the effects of the peptide on feeding are thought to be mediated by direct activation of amylin receptors in the brain (Lutz 2005). Amylin receptors are fairly unique in that they contain one of two splice variants of the calcitonin receptor (CTa/CTb; a G protein-coupled receptor) that heterodimerizes with one of the receptor activity modifying proteins (RAMP1, RAMP2 or RAMP3) (Hay et al. 2004). Despite the widespread expression of amylin receptors throughout the central neuraxis (Beaumont et al. 1993; Sexton et al. 1994; Skofitsch et al. 1995; Becskei et al. 2004; Hilton et al. 1995), investigations of CNS nuclei and neuronal mechanisms mediating the anorectic effects of amylin have, until recently, focused on classic homeostatic circuitry. Indeed, while the ability of amylin to regulate food intake and body weight has been studied for over 20 years, we are only beginning to understand the distributed network of CNS sites mediating its energy balance effects.

The majority of reports describing the hypophagic effect of amylin have focused on its ability to regulate food intake via actions at the area postrema (AP) of the hindbrain (Lutz et al. 1998, 2001; Mollet et al. 2004; Riediger et al. 2001). Lesions of this nucleus attenuate the ability of peripherally administered amylin to produce hypophagia (Lutz et al. 1998, 2001) and direct microinjection of amylin into the AP reduces feeding (Mollet et al. 2004). However, amylin binding is distributed widely throughout the brain (Christopoulos et al. 1995; Hilton et al. 1995; Paxinos et al. 2004; Sexton et al. 1994), and amylin

can cross the blood-brain barrier (Banks and Kastin 1998; Banks et al. 1995), collectively suggesting that amylin's access to the CNS is not limited to circumventricular structures such as the AP. To this end, recent research has shown that amylin can act directly in the VTA to control food intake (Mietlicki-Baase et al. 2013b, 2015). VTA amylin receptor activation appears to have especially potent suppressive effects on palatable food intake, as well as the motivation to obtain a palatable food (Mietlicki-Baase et al. 2013b, 2015), an interesting finding given the role of the VTA and the mesolimbic system in regulating the intake of palatable and rewarding ingesta (Meye and Adan 2014; Narayanan et al. 2010). Additionally, a few studies have investigated the actions of amylin in the ventromedial nucleus of the hypothalamus (VMH), and results indicate that amylin may enhance the intake-suppressive effects of the adipose-derived hormone leptin through actions in the VMH (Turek et al. 2010; Le Foll et al. 2014).

Chronic amylin administration also reduces body weight, producing selective reductions in fat mass while sparing lean mass (Roth et al. 2006). This may be due to an amylin-induced reduction in R_q (Roth et al. 2006), although other studies see little to no effect of acute or chronic amylin treatment on R_q (Wielinga et al. 2007). The effects of amylin on body temperature are more consistent. Acute or chronic amylin increases body temperature (Wielinga et al. 2010); this effect may be caused by increased activity of brown adipose tissue, as central administration of amylin increases activity of the sympathetic nerve subserving this adipose depot (Fernandes-Santos et al. 2013). Acute peripheral administration of amylin prevents compensatory reductions in energy expenditure that arise as a consequence of amylin-induced hypophagia (Wielinga et al. 2007), and in an acute experiment where food was unavailable during testing, intracerebroventricular administration of amylin increased energy expenditure (Wielinga et al. 2007, 2010).

A unique feature of amylin receptor activation as a potential treatment for obesity is that it remains effective in its ability to suppress food intake and body weight in obese rodents and humans (Singh-Franco et al. 2007; Boyle et al. 2011). Studies using the amylin agonist pramlintide, which is FDA-approved for the treatment of diabetes (Singh-Franco et al. 2007), have shown that pramlintide treatment in obese humans reduces body weight and enhances control over feeding behavior (Chapman et al. 2005, 2007; Ravussin et al. 2009; Roth et al. 2008; Smith et al. 2007). This ability of amylin to exert its effects in obese individuals contrasts with other hormonal signals such as leptin and insulin, where sensitivity to their effects is reduced in the obese state (Munzberg et al. 2004; Ye and Kraegen 2008). Thus, the absence of amylin resistance in obesity has intensified interest in amylin-based pharmaceuticals as future potential treatments for obesity (Sadry and Drucker 2013; Roth et al. 2009; Mietlicki-Baase and Hayes 2014).

5 Conclusions and Future Directions for Obesity Treatment

Although this chapter considers the individual contributions of several gut-derived and pancreatic hormonal signals to energy balance control, it is crucial to reiterate that these signals do not act in isolation in mammals. Ingestion of food impacts many neural and hormonal processes, including those described here as well as numerous other peripheral and central systems, each of which contributes to the overall control of food intake and body weight. The redundancy of some of these signals is important for preserving and maintaining energy storage, but also has presented a major challenge to the development of pharmacological strategies for the treatment of obesity.

Historically, attempts to treat obesity by targeting a single neuroendocrine system have failed to produce meaningful and long-lasting suppression of body weight, and some have been plagued with serious side effects (Christensen et al. 2007; James et al. 2010; Arbeeny 2004; Gadde 2014). New monotherapeutic strategies continue to be developed and tested as potential antiobesity drugs; for example, the GLP-1R agonist liraglutide (Saxenda®) was recently approved

by the FDA for use in the treatment of obesity (Mordes et al. 2015), although its long-term efficacy remains to be determined. However, the notion that combination approaches will be more effective for producing sustained reductions in body weight has become increasingly accepted by the scientific community (Sarwer et al. 2009; Phelan and Wadden 2002). Such approaches include using pharmacotherapy in conjunction with behavioral intervention (Vetter et al. 2010) and/or pharmacologically targeting more than one neurotransmitter/neuropeptide system (Bray 2014; Rodgers et al. 2012; Glandt and Raz 2011). Indeed, the FDA has recently approved a few combination pharmacotherapies for obesity, including bupropion/naltrexone (Contrave) and phentermine/topiramate (Qsymia®) (Mordes et al. 2015), although again due to the relatively recent approval of these pharmaceuticals, we lack longitudinal data regarding their efficacy for weight loss.

Further development of effective, noninvasive pharmacological strategies for obesity treatment is urgently required, as the options currently available are clearly limited. Accordingly, several hormonal systems are under investigation for the development of novel pharmacological treatments for obesity. For example, amylin is currently considered one of the leading candidates for new antiobesity combination pharmacotherapies (Sadry and Drucker 2013) due to its ability to interact with and enhance the weight-reducing effects of other signals such as leptin (Chan et al. 2009; Ravussin et al. 2009; Roth et al. 2008), GLP-1 (Bello et al. 2010), and CCK (Bhavsar et al. 1998; Mollet et al. 2003), among others [see (Lutz 2013) for review]. Although further research is needed before clinical testing, the use of such combination pharmacotherapies hopefully will overcome some of the neurohormonal redundancies in energy balance control that have previously limited the success of monotherapies for obesity treatment, thus providing the basis for antiobesity pharmacotherapies that produce lasting weight loss.

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Gut Microbiome, Obesity, and Metabolic Syndrome

24

Herbert Tilg and Alexander R. Moschen

Contents

Abstract

Obesity, metabolic syndrome, and type 2 diabetes (T2D) reflect a major disease burden throughout the world. In all these disorders, low-grade chronic inflammation is commonly observed. The origin of this type of inflammation is currently unknown. Recent studies, however, suggest that the gastrointestinal tract with its enormous microbial world, i.e., the intestinal microbiota, could not only play a role in these disorders but also contribute to low-grade chronic inflammation. This microbiota affects many biological functions throughout the body including many immune and metabolic features. Data from animal models and humans support that obesity and associated disorders are characterized by a profound dysbiosis. Human metagenome-wide association studies mainly in obesity and T2D have demonstrated that there exists a "gut microbiota signature." Further, evidence for a major role of intestinal bacteria has been derived from studies in pregnancy and after Caesarean section. Antibiotic use in early life also affects the microbiota in a profound manner and might contribute to the development of childhood obesity and T2D in later life. Therefore, as a "gut" signature became evident in the last years in these diseases, a better understanding of these aspects is mandatory to gain further insights and define a basis for new therapeutic approaches.

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Abbreviations

AMPK	AMP-activated protein kinase
FFAR	Free fatty acid receptor
Fiaf	Fasting-induced adipose factor
FXR	Farnesoid X receptor
GLP-1	Glucagon-like peptide 1
GPCR	G-protein-coupled receptor
HFD	High-fat diet
HGC	High gene count
ILC	Innate lymphoid cells
LGC	Low gene count
LPL	Lipoprotein lipase
MLG	Metagenomic linkage group
SCFA	Short-chain fatty acid
T2D	Type 2 diabetes
TLR5	Toll-like receptor 5

1 Introduction

The human intestinal tract harbors an immense number of *microorganisms*, i.e., the intestinal microbiota consisting of at least 10^{14} bacteria, archaea, and viruses. These microorganisms generate a biomass of more than 1.5 kg, and their genomes (i.e., microbiome) exceed the human genome more than 100-fold (Lozupone et al. 2012; Shanahan 2012; Tremaroli and Backhed 2012; Lepage et al. 2013). Initial studies suggested that these genes encode mainly functions directing immune pathways and such ones needed for digestion of complex carbohydrates. Recent investigations, however, convincingly demonstrated that the microbiota may have key functions in regulating *metabolic pathways* in health and disease (Eckburg et al. 2005; Costello et al. 2009; Human Microbiome Project 2012; Tremaroli and Backhed 2012; Yatsunenko et al. 2012). High-throughput sequencing technologies have allowed in the last years to increase the understanding of the complexity and diversity of the microbiota (Qin et al. 2010). Importantly, most of the more than 1000 assumed bacterial species cannot be cultured currently.

An altered intestinal microbiota in metabolic diseases might play a role to initiate inflammatory processes throughout the organism. Such an altered microbiota might not only act "locally" but via an impaired *mucosal barrier* also systemically. This is in accordance with the recently proposed concept of "*metabolic infection*," where parts of the intestinal microbiota might act systemically and affect systemic including adipose tissue *inflammation* (Amar et al. 2011; Burcelin 2012). In many disorders such as inflammatory bowel disease, obesity, or type 2 diabetes (T2D), a "microbiotal signature" has been identified (Breen et al. 2013; Karlsson et al. 2013a; Tilg and Moschen 2014). In this chapter, we will discuss the current evidence for a role of the intestinal microbiota in obesity and T2D and thereby could contribute to the phenotype of these disorders.

2 Role of the Intestinal Microbiota in Obesity

Many studies from the last years, particularly using animal models, have shown that the microbiota might reflect one major player in the development of obesity (Backhed et al. 2004; Ley et al. 2005, 2006; Turnbaugh et al. 2006, 2009). Ridaura and colleagues showed that the microbiota derived from discordant obese twins affects metabolism in mice (Ridaura et al. 2013). These investigators transferred the microbiota collected from human female twin pairs discordant for obesity into *germ-free mice* showing that obesity can indeed be transferred to rodents. Importantly, co-housing of mice containing cultured bacteria from an obese twin with mice containing bacteria from a lean twin prohibited the development of the obese phenotype. Diet appeared as a critical cofounder in these experiments highlighting the dominant role of diet on the microbial community. When mice were treated with a low-fat, high-fiber diet even when harboring the obese microbiota and were co-housed with mice containing the lean

microbiota, the lean microbiota dominated in the obese mice preventing adiposity.

The gene count of the intestinal microbiota might play a key role in human obesity as demonstrated recently (Le Chatelier et al. 2013). Le Chatelier and colleagues observed that in case of low *bacterial richness* (low gene count, LGC), obesity and related disorders such as insulin resistance, fatty liver, and *low-grade inflammation* were more common compared to subjects characterized by high gene count (HGC). Individuals with this LGC in their microbiota gained more weight and had a higher rate of systemic inflammation as demonstrated by higher levels of *C-reactive protein*, a higher rate of insulin resistance and dyslipidemia. Whereas *Bacteroides* and some *Ruminococcus* species were more dominant in LGC, *Faecalibacterium prausnitzii*, *Bifidobacterium*, *Lactobacillus*, *Alistipes*, *Akkermansia*, and others were significantly associated with HGC. At phylum levels, *Bacteroidetes* and proteobacteria were more commonly observed in LGC, whereas *Verrucomicrobia* (e.g., *Akkermansia muciniphila*) and *Actinobacter* were more dominant in HGC. Findings of this study overall support a concept that in case of obesity, potential pro-inflammatory bacteria may dominate, e.g., *Ruminococcus gnavus* or *Bacteroides* and anti-inflammatory such as *F. prausnitzii* are less prevalent. Further, studies from this cohort of patients showed that LGC subjects contained a more pro-inflammatory microbiotal profile accompanied by an increase in oxidative stress. Dietary interventions by using an energy-restricted diet improved this microbial richness and clinical phenotype in LGC subjects, although subjects with an already high microbial richness responded less well to dietary treatment (Cotillard et al. 2013). These studies support the current belief that microbial composition and potentially the richness of these bacterial genes in our gut might be able to define obese people with metabolic and inflammatory complications.

It has been less well studied until recently how the gut microbiota changes in obese subjects after weight loss. Remely and colleagues investigated obese people receiving a *dietary intervention* proposed by the German, Austrian, and Swiss Society of Nutrition over 3 months (Remely et al. 2015). Here, fecal microbiota and bioelectrical impedance analysis were performed before, during, and after the dietary intervention. After weight loss, the ratio of *Firmicutes/Bacteroidetes* significantly decreased, whereas *Lactobacilli*, *Clostridium cluster IV*, *F. prausnitzii*, and *Akkermansia muciniphila* increased significantly. Increase in these bacteria is of relevance, as these strains have been demonstrated to exert beneficial and anti-inflammatory properties (Sokol et al. 2008; Everard et al. 2013). The use of *pre-* and *probiotics* besides weight loss reflects another important treatment approach as they might be able to cause beneficial shifts in the intestinal microbiota. Dewulf and colleagues recently demonstrated that the administration of certain prebiotics (i.e., inulin-type fructans) changed the gut microbiota composition in obese women with an increase in *Lactobacilli*, *Bifidobacteria*, and *Clostridium* cluster IV resulting in modest changes in *host metabolism* (Dewulf et al. 2013). Many preclinical studies have also focused on the use of certain probiotics to affect an obese phenotype. *Lactobacillus casei*, *Lactobacillus rhamnosus*, and *Bifidobacterium animalis* subsp. *lactis* are able to shift the microbiotal structure in mice after receiving a high-fat diet (HFD) toward a lean phenotype (Wang et al. 2015). Whereas *Lactobacillus casei* and *Lactobacillus rhamnosus* in this study mainly increased the concentration of the short-chain fatty acid acetate, *Bifidobacterium animalis* subsp. *lactis* failed such an effect but still was able to decrease adipose tissue inflammation.

Overall, all these studies have gathered convincing evidence that the gut microbiota plays a role in human obesity and intervention via *weight loss* strategies and/or pre-/probiotics might not only affect phenotype but also the composition of this microbiota. It has to be stated though that some reports in the past have shown different findings by suggesting that *Bacteroides* are more abundant in obese subjects compared to lean counterparts (Duncan et al. 2008; De Filippo et al. 2010; Schwiertz et al. 2010; Wu et al. 2011). Despite these discrepant findings

between certain studies, the model proposed by Ridaura and colleagues might become attractive in the future to study the effects of human microbiota under certain diets in germ-free animals and to test anti-inflammatory and potentially beneficial bacterial mixtures (Ridaura et al. 2013).

3 Gut Microbiota and Diabetes

As most of *T2D* patients are obese, it has been expected that also in this condition a microbiotal signature might exist. The first study using high-throughput sequencing was performed by analyzing stool samples from Chinese T2D patients, and metagenomic analysis was combined with clinical data (Qin et al. 2012). T2D patients showed a modest *intestinal dysbiosis* characterized by a decrease in butyrate-producing *Roseburia intestinalis* and *F. prausnitzii*. In this study, the concept of metagenomic linkage group (MLG) analysis has been applied, and thereby they observed that in the healthy control samples especially various butyrate-producing bacteria were enriched (e.g., *Clostridiales* sp. SS3/4, *Eubacterium rectale*, *F. prausnitzii*, *Roseburia intestinalis*, and others), whereas in T2D most MLGs belonged to more opportunistic pathogens such as *Bacteroides caccae*, various *Clostridiales*, *and Escherichia coli*. When assessing potential associated functions of this gut dysbiosis in T2D, T2D microbiota showed enrichment in membrane transport of sugars, branched-chain amino acid transport, and sulfate reduction and decreased *butyrate biosynthesis* but even more importantly also an increase in oxidative stress response. This could become of special relevance as one could speculate that the gastrointestinal tract with its microbiota could reflect a starting point for the observed low-grade inflammation in T2D. Overall, more than 3 % of the gut microbial genes differed between T2D patients and healthy subjects. Another study was recently reported from Denmark (Karlsson et al. 2013b). Here, the authors applied shotgun sequencing studying only postmenopausal female T2D patients. T2D patients showed increases in the abundance of four *Lactobacillus* species including *L. gasseri*, *Streptococcus mutans*, and certain *Clostridiales* such as *Clostridium clostridioforme* and again decreases in at least five other *Clostridium* species. ***Roseburia intestinalis*** and *F. prausnitzii*, both prototypic butyrate producers, were highly discriminant for T2D. It has to be stated that the number of analyzed T2D patients in the Scandinavian study was rather low and study design was not able to detect whether a diabetes-specific drug might have influenced microbiota composition. These two studies reflect an important initiative in this field and support the notion that not only a "gut signature" might exist, but more importantly functional analysis also revealed that a *pro-inflammatory* tone might be initiated in the intestine which could reflect the starting point of low-grade systemic inflammation as commonly observed in T2D and related disorders such as nonalcoholic fatty liver disease (Fig. 1).

In summary, the results from the presented studies here suggest that T2D patients show evidence of gut dysbiosis. Reasons for some discrepancies in these two studies may be numerous and include various confounding factors such as different study populations, different used sequencing techniques, use of various diets, and medications. All these studies can only be considered as a starting point, and many more well-designed clinical trials are needed to prove an association between the gut microbiota and T2D.

4 Involved Immunometabolic Pathways and Role of Certain Bacteria

4.1 Short-Chain Fatty Acids

One important activity of the gut's microbiota is to digest dietary fibers (Flint et al. 2008). The main end products of this digestion by enzymes derived from the gut microbiota reflect *short-chain fatty acids* (SCFAs) such as *acetate*, butyrate, and *propionate*. SCFAs constitute 5–10 % of energy source in healthy people. There is certain evidence that lean subjects exhibit higher stool levels of SCFA compared to obese people. Interestingly,

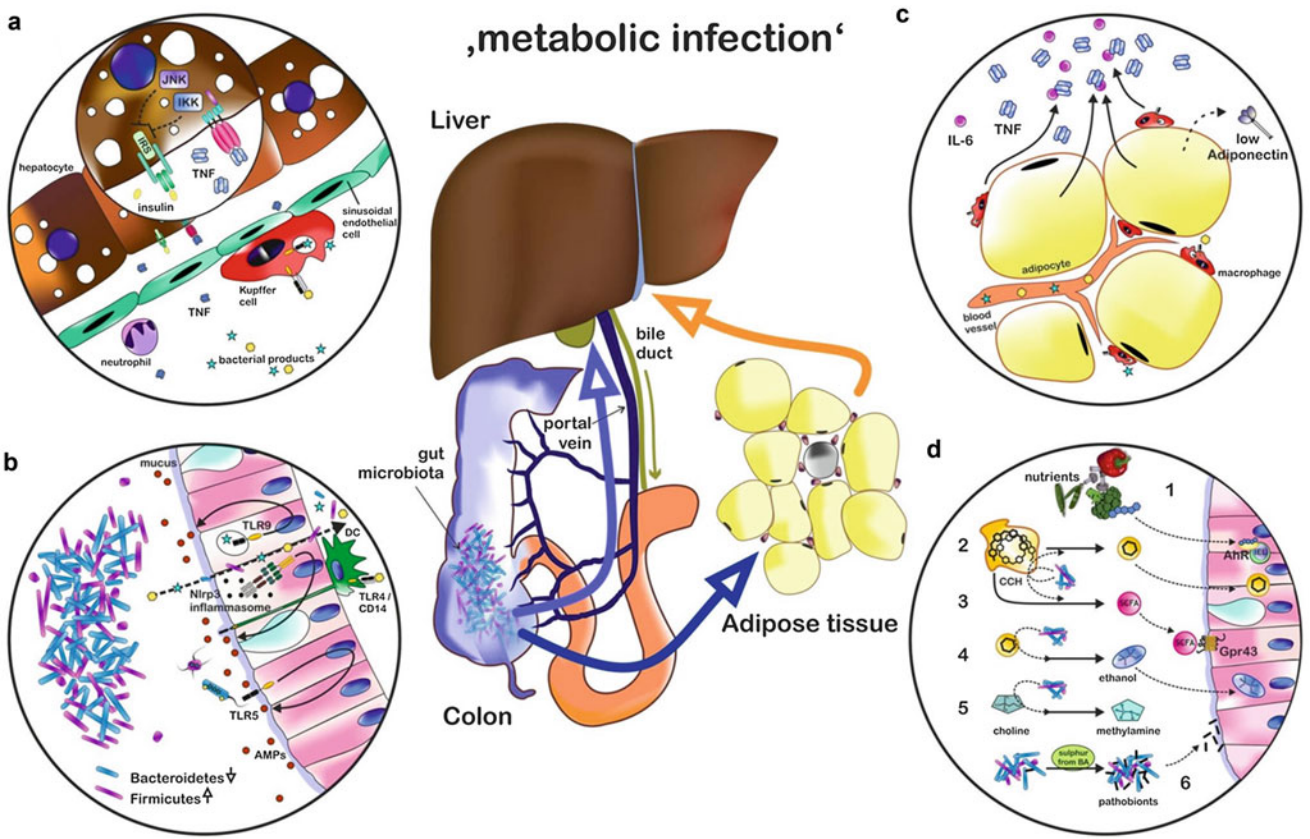

Fig. 1 NAFLD and metabolic infection. (**a**) In nonalcoholic fatty liver disease (*NAFLD*), hepatocytes accumulate various amounts of intracellular lipids. NAFLD is part of the metabolic syndrome and characterized by hepatic insulin resistance which again is triggered by inflammatory mediators, particularly TNFα. Evidence is increasing that the transition from NAFLD to nonalcoholic steatohepatitis (*NASH*) is driven by systemic factors. Bacterial products, both TLR-ligands and metabolic products, enter the liver via the portal vein. Adipose tissue-derived pro-inflammatory cytokines accumulate in the liver via the hepatic artery. (**b**) Obesity is associated with profound alterations of the microbial composition with reductions in the phylum *Bacteroidetes* and increases in the phylum *Firmicutes*. The functional capacity of the "obese" microbiome is optimized to extract energy from food. The resulting "extra"-oversupply of energy further substantiates metabolic stress, particularly in the energy-storing tissues (D1). High-fat diet has been associated with an increased permeability of the intestinal epithelium for bacteria or bacterial components which can be detected in the portal vein and the systemic circulation. The fine-tuned communication between the intestinal epithelium and the gut microbiota becomes dysbalanced. While the gut microbiota stimulates epithelial cells by engaging cell surface (TLR4,

fiber-enriched diets are also able to improve insulin sensitivity in lean and obese diabetic subjects (Robertson et al. 2003, 2005). SCFAs diffuse passively, are recovered via monocarboxylic acid transporters, or act as signaling molecules by binding to *G-protein-coupled receptors (GPCRs*) such as Gpr41 (free fatty acid receptor 3, FFAR3) and Gpr43 (FFAR2) (Brown et al. 2003; Le Poul et al. 2003). These GPCRs are expressed by many cell types including gut epithelial cells, adipocytes, and immune cells. Gpr43-deficient mice are obese even when consuming a normal diet, whereas mice overexpressing this receptor specifically in the adipose tissue remain lean independent of calorie consumption (Kimura et al. 2013). In this study, when mice were raised germ-free or were treated with certain antibiotics, both types of mice exhibited a normal phenotype. Gpr43 activation also enhances insulin sensitivity by promoting *GLP-1 secretion* in the gut (Tolhurst et al. 2012). Gpr43 is neither expressed in the liver nor in the muscle, and therefore, it seems that adipose tissue-derived Gpr43 is able to modulate all the metabolic effects after engagement with microbiota-derived products such as SCFAs. Therefore, SCFAs are not only an important energy source for the host, but also act as signaling molecules especially in the adipose tissue thereby maintaining energy balance. Data also suggest that the microbiota is the major source for *Gpr43 agonists* and biological functions of Gpr43 are completely dependent on the gut's microbiota.

Therefore, SCFAs could reflect a missing link between the microbiota and systemic inflammatory diseases as they (especially butyrate) regulate the development of extrathymic anti-inflammatory regulatory T cells (Arpaia et al. 2013). SCFAs also control the generation of colonic *regulatory T cells* and protect against colitis in a Gpr43-dependent manner (Smith et al. 2013). Trompette and colleagues recently demonstrated that mice fed a high-fiber diet have an altered microbiota and are protected from allergic airway inflammation (Trompette et al. 2014). These data are supportive for the current notion that microbiota-derived products are important players in the generation of local and systemic immunity/inflammation. As studies in T2D especially and consistently revealed that production of

Fig. 1 (continued) CD14, TLR5) and intracellular (TLR9, NLRP3⁄6–ASC–Caspase1 inflammasome) pattern recognition receptors, conversely, the epithelium shapes the microbiota by modifying its antibacterial strategies such as mucus and antimicrobial-peptide (*AMP*) production. Disruption of the NLRP3⁄6–ASC–Caspase1 inflammasome resulted in profound changes of the gut microbiota and barrier leakage which contributed to exacerbation of hepatic steatosis and inflammation (Dominguez-Bello et al. 2010). (**c**) Cytokines are major players in the pathophysiology of NAFLD/NASH. The "obese" adipose tissue accumulates large numbers of inflammatory cells, especially macrophages, and produces enormous amounts of pro-inflammatory cytokines such as TNFα and IL-6. Conversely, anti-inflammatory mediators such as adiponectin are diminished. Adipose tissue-derived mediators such as TNFα and IL-6 promote hepatic insulin resistance, an important feature of NASH. Recent evidence suggests that gut microbes and/or microbial products not only affect the liver via the portal vein but also peripheral organs such as the adipose tissue proposing **metabolic infection** as an important driver of NAFLD/NASH. (**d**) Nutritional components have been shown to impact intestinal and hepatic homeostasis in several ways: (*1*) Certain dietary molecules directly activate host receptors, collectively designated as **dietary pattern recognition receptors (DPRR)**. (*2*) Exemplary, a derivate of indole-3-carbinole (*I3C*), contained in cruciferous vegetables, stimulates the aryl-hydrogen receptor (*AhR*), and genes regulated by I3C–AhR interaction play a crucial role in the development of a balanced gut immune system (Wang et al. 2014; Wu et al. 2011). (*3*) Bacterial enzymes facilitate unique processing of dietary molecules. Complex carbohydrates can be fermented into short-chain fatty acids (*SCFA*) which in turn activate specific host receptors such as the G-protein-coupled receptor 43 (*Gpr43*). SCFA–Gpr43 interaction has been implicated in the control of intestinal inflammatory immune responses. (*4*) Increased endogenous ethanol produced by bacterial enzymes has been implicated in NAFLD development. (*5*) Conversion of dietary choline to methylamines by microbial enzymes has been suggested to cause choline deficiency and to promote NAFLD. (*6*) Certain food components promote expansion of otherwise low-abundant pathobionts. Milk-derived saturated fats promote taurine conjugation of hepatic bile acids, thereby increasing the availability of organic sulfur. This milieu facilitates a bloom of the sulphite-reducing pathobiont *Bilophila wadsworthia* which promotes a pro-inflammatory intonation (Yang et al. 2010) (The figure is reproduced from Moschen AR, Kaser S, Tilg H. *Non-alcoholic steatohepatitis: a microbiota-driven disease*. Trends Endocrinol Metab 2013;24:537–45 (Cell Press))

SCFAs, especially butyrate, is impaired, it sounds reasonable to assume that such mechanisms might contribute to low-grade inflammation observed in those disorders.

Several other mechanisms may allow the microbiota to interact with the host. The gut microbiota affects the composition and abundance of certain bile acid species through a variety of mechanisms resulting commonly in low levels of various *bile acids* in case of obesity (Swann et al. 2011). Obese mice demonstrate increased expression of *farnesoid X receptor* (FXR) and fibroblast growth factor 15, whose expression is regulated by bile acids, and directly regulate various metabolic effects. Conventionally, raised mice contain much more total body fat compared to those raised under germ-free conditions (Backhed et al. 2004). Conventionalization of mice suppresses intestinal expression of *fasting-induced adipose factor (Fiaf)* specifically in differentiated villous epithelial cells in the ileum. Fiaf acts as a circulating lipoprotein lipase (LPL) inhibitor (Yoon et al. 2000). Another metabolic pathway apart from Fiaf involves *AMP-activated protein kinase (AMPK)* (Backhed et al. 2007). Germ-free mice remain lean despite high-calorie intake, and this state is accompanied by increased activity of phosphorylated AMPK levels both in the liver and skeletal muscle and enhanced insulin sensitivity in the liver (Backhed et al. 2007). In summary, several pathomechanisms have been identified in the last years which could help to explain how the microbiota directs metabolic processes in health and disease (Fig. 1).

4.2 Innate Immunity

Metabolic syndrome might develop through the interaction of various genetic and environmental factors and includes a complex and yet poorly understood interaction between the intestinal microbiota and the *innate immune system* (Tilg and Kaser 2011). *Toll-like receptors* might play an important role in the development of a metabolic syndrome as demonstrated for the pattern recognition receptor *TLR5* (Vijay-Kumar et al. 2010). TLR5$^{-/-}$ mice exhibit hyperphagia; developed hyperlipidemia, hypertension, insulin resistance, and obesity; and an altered microbiota. Transfer of intestinal microbiota of TLR5$^{-/-}$ mice into germ-free mice led to metabolic syndrome. These data suggest that innate immune signaling is critical in the development of the metabolic syndrome, and alterations in the intestinal microbiota are able to induce the metabolic syndrome. Inflammasomes consist of an upstream sensor NLR protein, the adaptor protein Asc, and the effector protein caspase-1. Various groups have recently shown that the inflammasome may play an important role in metabolic inflammation, and some inflammasomes might affect the intestinal microbiota, metabolic syndrome, and fatty liver disease (Stienstra et al. 2010; Henao-Mejia et al. 2012). Whether similar phenomena are also relevant in human disease is currently unclear (Fig. 1).

4.3 "Metabolic Cytokines": A Role for Interleukin-22

It has long been assumed that certain cytokines might be crucially involved in the cross talk between metabolic processes and inflammation. *Interleukin-22* (IL-22) is an IL-10 family cytokine and mainly expressed by certain lymphoid cells (innate lymphoid cells, ILCs) and specialized T helper (Th) cells such as Th17 or Th22 (Colonna 2009). IL-10 family cytokines exert mainly anti-inflammatory actions, and the biological functions of IL-22 are focused on control of innate immune defense, tissue protection, and regenerative functions. Furthermore, IL-22 maintains epithelial integrity and homeostasis of commensals (Tilg 2012), as mice deficient in IL-22 show evidence of systemic dissemination of bacteria and chronic inflammation (Sugimoto et al. 2008; Zheng et al. 2008). Importantly, conditions of obesity are associated with a *leaky gut* and an impaired epithelial integrity suggesting that certain mediators might be involved in this process (Bischoff et al. 2014). A recent elegant study investigated the role of IL-22 in metabolic disorders and *mucosal immunity* (Wang

et al. 2014). Here, the authors observed that IL-22 production in ILCs and $CD4^+$ T cells is impaired in obese mice and after challenge with an HFD. Interestingly, infection with *Citrobacter rodentium* resulted in a dramatic reduction of peak IL-22 synthesis in the colon of *ob/ob* mice or in animals after HFD feeding. IL-22 is dispensable for a successful mucosal defense of *C. rodentium* (Zheng et al. 2008), and administration of exogenous IL-22-Tc reduced mortality, restored epithelial damage and inflammation, and inhibited dissemination of *C. rodentium* in leptin-receptor-deficient (*db/db*) mice. Surprisingly, exogenous IL-22-Fc treatment of obese mice reduced body weight and epididymal fat mass, decreased blood glucose levels, and improved insulin resistance under both fed and fasting conditions clearly proving that IL-22 is a metabolically beneficial cytokine. In addition, IL-22-Fc therapy improved metabolic functions in *db/db* mice with hyperglycemia. As IL-22 reflects a prototypic barrier cytokine, the authors investigated in their models effects of IL-22-Fc administration on the intestinal microbiota and could indeed observe that this therapy increased the *Firmicutes/Bacteroidetes* ratio although beneficial effects of this treatment could not be transferred to control mice via *fecal transplant*. Furthermore, IL-22-Fc also regulates lipid metabolism in the liver (Yang et al. 2010) and adipose tissue. These studies clearly highlight that certain cytokines such as IL-22, which are mainly active at barriers such as in the gut, link various aspects observed in obesity and related disorders such as impaired epithelial integrity, mucosal inflammation, systemic inflammation, and metabolic dysfunction. These connections are exciting as they offer new therapeutical possibilities.

4.4 Role of Certain Commensals: Akkermansia Muciniphila

Knowledge in this area is still in its infancy. *Akkermansia muciniphila* has been recently characterized as a mucin-degrading bacterium residing in the mucus layer (Derrien et al. 2004). *A. muciniphila*, a Gram-negative bacterium, is highly prevalent and constitutes 3–5 % of the gut's microbiota, and its concentrations are inversely correlated with the presence of overweight and diabetes in murine and human studies (Santacruz et al. 2010; Everard et al. 2011; Karlsson et al. 2012). Dietary supplementation with *fibers*, i.e., oligofructose, to genetically obese mice dramatically increases abundance of *A. muciniphila* (Everard et al. 2011). Several studies have shown that *A. muciniphila* might play a key role in the integrity of the mucous layer and has the potential to reduce inflammation and offer protection against the development of obesity and T2D. The most convincing report suggesting such a function for *Akkermansia* was recently presented by Everard et al. (2013). The authors demonstrated that both in genetic and dietary models of murine obesity, concentrations of *A. muciniphila* were highly decreased. A prebiotic therapy with *oligofructose* restored levels of *A. muciniphila* and improved metabolic functions including metabolic endotoxemia. Endotoxemia has been demonstrated to be of importance in metabolic dysfunction (Cani et al. 2007), and recent studies have corroborated this as increased levels of *lipopolysaccharide*-binding protein, an indirect surrogate of increased endotoxin activity, correlated with later development of metabolic syndrome in middle-aged and older Chinese individuals (Liu et al. 2014). Metformin, an antidiabetic drug, results in an increase in *Akkermansia* concentrations, and also in this study, administration of *A. muciniphila* resulted in an improvement of various metabolic functions including glucose tolerance and adipose tissue inflammation (Shin et al. 2014). NOD mice treated with vancomycin exhibit an increase in the abundance of *Akkermansia* accompanied by improved metabolic parameters further supporting a protective function for this bacterium (Hansen et al. 2012). *A. muciniphila* might exert anti-inflammatory functions also in other disease models as it has been shown

that administration of this bacterium improves DSS-induced colitis (Kang et al. 2013).

5 Early-Life Manipulation of the Microbiota: Role of Antibiotics

As stated, obese and lean humans differ in their microbiota, and disease phenotypes can be transferred to germ-free mice (Ridaura et al. 2013). A seminal study from 1963 by Dubos and colleagues described that antibiotic therapy might affect the body weight of mice (Dubos et al. 1963). This was paralleled by the observation and practice of farmers to expose livestocks to low doses of antibiotics to promote growth of respective animals (Cromwell 2002). All these facts have been rather ignored by medicine, namely, that these effects can be pronounced and especially are dependent on the time of use, e.g., in early life as interventions might have a profound impact in later life. Antibiotic therapy causes dramatic shifts in the microbiota with certain long-term effects (Dethlefsen et al. 2008; Antonopoulos et al. 2009; Morgun et al. 2015). Especially exposure in early life might have a major impact (Greenwood and Hirsch 1974). Several large prospective clinical studies have now also shown that "disturbance" of the intestinal microbiota by either mode of delivery or *antibiotic usage* might lead to childhood obesity (Ajslev et al. 2011; Trasande et al. 2013). Elegant experimental studies recently have demonstrated that early-life subtherapeutic antibiotic therapy not only affected the intestinal microbiome but also resulted in obesity (Cho et al. 2012). In this study, this intervention also resulted in a significant increase of SCFA, important energy substrates for the organism. Another recent study by Martin Balser's group has brought further insight into this topic. Low-dose penicillin (LDP) therapy, initiated at birth, induced major metabolic alterations in the host accompanied by changes in the expression of ileal innate immunity genes finally resulting in a substantially perturbated microbiota (Cox et al. 2014). Early penicillin exposure especially already to adult mice before birth resulted in enhanced metabolic phenotypes including total abdominal, visceral, and liver adiposity. LDP treatment had a major impact on the intestinal microbiota, and it suppressed multiple taxa that typically peak early in life. Furthermore, LDP and an *HFD* had independent selective effects, with LDP consistently affecting specific microbial strains. This important study overall clearly shows that at least in mice, early life is the critical window with respect to host-microbe metabolic interactions, and even exposure limited to infancy resulted in adiposity later in early to mid-adulthood. Importantly, they also observed that the altered microbiota alone, not continued LDP exposure, showed causality. Interestingly and this fits with this study, germ-free chickens do not demonstrate weight gain when treated with low-dose penicillin (Coates et al. 1963), and animals were especially responsive to an HFD, and importantly this "disease" phenotype was transferrable via antibiotics-selected microbiota to a healthy host. All these important studies clearly suggest that interference with the microbiota in early life especially antibiotic therapy may have a profound effect finally resulting in an increased risk for obesity and metabolic dysfunction in later life. Further, studies are needed to define key members of the early-life microbiota and also to prove whether similar mechanisms take place in humans.

6 Gut Microbiome and Pregnancy

Pregnancy is accompanied by massive hormonal, immunological, and metabolic changes. Metabolic alterations during pregnancy are substantial, and approximately 20 % of patients develop prediabetes or manifest T2D. Earlier studies have revealed that the composition of the gut microbiota is changing over the course of gestation (Collado et al. 2008). A major study providing robust insights into the relationship between microbiotal evolution and pregnancy and associated metabolic consequences has been recently reported (Koren et al. 2012). During pregnancy, many metabolic parameters changed significantly with an increase in serum leptin levels,

cholesterol, insulin, and HbA1c levels. From the first trimester (T1) to the third trimester (T3), the relative abundance from *Proteobacteria* and *Actinobacteria* increased in approximately 2/3 of women. Levels of *Bacteroidetes* and *Firmicutes* were not significantly different between trimesters. T1 was characterized by a high rate of the *Clostridiales* order of the *Firmicutes* (e.g., butyrate producers *F. prausnitzii* and *Eubacterium*), whereas T3 was characterized by members of the *Enterobacteriaceae* and *Streptococcus* genus. *Proteobacteria*, enriched in T3 stools, have been shown to exert pro-inflammatory effects (Mukhopadhyay et al. 2012). The authors transferred T1/3 microbiotas to germ-free wild-type mice, and only after 2 weeks of inoculation, inflammatory mediators in the stool and cecal samples including lipocalin were significantly higher in the T3 versus T1 recipients. This was paralleled by more adiposity and an *impaired glucose tolerance*. Overall, this fascinating translational work clearly suggests that pregnancy is associated with major shifts in the gut's microbiota characterized by a switch toward a pro-inflammatory tonus.

Mode of delivery might be crucial as a vaginal birth has been demonstrated to have a major impact on the establishment and development of the intestinal flora (Dominguez-Bello et al. 2010). In contrast, *Caesarean section* results in a markedly altered child microbiota, and this may have consequences with respect to disease patterns (Huurre et al. 2008; Biasucci et al. 2010; Dominguez-Bello et al. 2010; Pandey et al. 2012). Indeed, studies suggest an increased risk of childhood obesity after Caesarean section (Huh et al. 2012; Blustein et al. 2013; Li et al. 2014). Although these associations are probably more correlative at the moment, these findings indirectly also favor the concept that altered intestinal microbiota has metabolic consequences. In summary, pregnancy and mode of delivery have recently appeared as major confounders of the gut's microbiota, and consecutive microbiotal changes might contribute to various metabolic diseases including obesity and metabolic dysfunction.

7 Conclusions

Host phenotypes are dependent on interactions between diet, intestinal microbiota, and immunity. Until recently, it appeared that the direct interaction between food and immunity drives health and disease, and only recently evidence accumulated that "the big elephant" in us, i.e., the intestinal microbiota, has been ignored and has now been recognized as crucial player at this interphase. Over the last years, the intestinal microbiota has been defined as a fascinating "new organ" which affects many biological systems throughout the body including the immune system, metabolic functions and development, and programming of the nervous system. Fascinating recent data have now demonstrated an important role for this microbiota in metabolic diseases such as obesity and T2D. A "microbiotal gut signature" is present not only in human obesity but also in T2D, and it will become fascinating to define bacterial species in the near future which are metabolically beneficial or detrimental. Several interesting candidates have already been defined, and *A. muciniphila* reflects such a promising candidate. Mechanistically SCFAs, especially butyrate and propionate, have evolved as attractive pathways on how the microbiota might digest food and thereby shape immunological and metabolic functions. An exciting new area has been started in medicine bringing metabolic inflammation, food, and microbiota research to the forefront of biomedical research.

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Pancreatic Islet Adaptation and Failure in Obesity and Diabetes

25

Nicolai M. Doliba

Contents

Abstract

Normally, the insulin secretion is increased in response to insulin resistance in order to maintain glucose homeostasis. Pancreatic islet beta-cells respond to glucose, fatty acids, amino acids, autonomic innervation, incretins, and adipokines. Metabolic syndrome is associated with a failure of pancreatic islets to respond appropriately to nutrient, neuronal, and hormonal signals, resulting in glucose intolerance or type 2 diabetes. Pancreatic islet dysfunction in type 2 diabetes is characterized by increased glucagon secretion; impaired insulin response to secretagogues, e.g., glucose, arginine, and isoproterenol; blunted first-phase insulin secretion; irregular oscillations of plasma insulin levels; and impaired conversion of proinsulin to insulin. In addition, type 2 diabetes may be associated with reduced beta-cell mass, partly mediated by enhanced islet apoptosis due to glucolipotoxicity. Understanding of normal pancreatic islet physiology and molecular pathways linking islet adaptation to diabetes pathophysiology would facilitate the development of novel treatment modalities.

Keywords

Obesity • Diabetes • Pancreas • Islet • Insulin • Glucose • Lipid

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1 Nutrient Sensing in Pancreatic Islets

The prevalence of the metabolic syndrome is dramatically increasing and has emerged as a major threat to public health worldwide. The metabolic syndrome consists of a cluster of metabolic conditions including hypertriglyceridemia, insulin resistance, abnormal glucose tolerance or diabetes, and hypertension (Reaven 1988, 1995). These conditions combined with genetic susceptibility and abdominal obesity are risk factors for type 2 diabetes, vascular inflammation, atherosclerosis, and renal, liver, and heart diseases. Insulin resistance is at the core of metabolic syndrome, because the altered metabolism of nutrients by insulin-sensitive target tissues (muscle, adipose tissue, and liver) can result in high circulating levels of glucose and various lipids, which increase demands on pancreatic islet function to compensate for insulin resistance. Pancreatic islets are highly vascularized structures that monitor the nutrient content of the blood stream and consist of mainly five cell types: alpha cells, beta-cells, delta cells, ghrelin cells, and pancreatic polipeptide (PP) cells which produce the hormones glucagon, insulin, somatostatin, ghrelin, and PP, respectively (Wierup et al. 2014; Newsholme et al. 2014). Insulin-secreting pancreatic beta-cells play a central role in the physiology and in the pathology of obesity and diabetes by regulating glucose homeostasis. A critical role of pancreatic beta-cells is consistent with the observation that diabetes does not develop in obese insulin-resistant persons unless pancreatic beta-cell function or its adaptation is compromised.

Pancreatic beta-cells account for about 50 % of the islet cell mass in humans and are able to react to elevated dietary nutrients on a moment-to-moment basis and secrete insulin into the blood stream at rates that are appropriate for the maintenance of optimal glucose levels. Carbohydrates are normally the primary source of fuel in food, and glucose is the primary insulin secretagogue. An increase in blood glucose concentration leads to glucose transport into beta-cells by Na^+-independent facilitated glucose transporters (GLUTs) with a capacity markedly higher than the beta-cell glycolytic rate. GLUT-2 is expressed in rodent islets (Newgard et al. 2001) and has a Km for glucose and the capacity for glucose transport higher than other members of the family. Human islets express GLUT-2, but at lower levels than rodent islets (Newgard et al. 2001). In addition, human islets express significant levels of the low Km glucose transporters GLUT-1 and GLUT-3. Upon entry of glucose into beta-cells, the glucose is phosphorylated to glucose-6-P by glucokinase which is the rate determinant of glycolysis (Matschinsky 1996). Glucokinase, also known as hexokinase IV, contributes more than 90 % of the glucose-phosphorylating capacity in beta-cells. Enhanced flux through the glycolytic pathway and tricarboxylic acid (TCA) cycle results in elevated mitochondrial ATP generation. ATP can be produced by three different mechanisms in beta-cells (Newgard et al. 2001): (i) a large fraction of NADH produced in the glyceraldehyde phosphate dehydrogenase reaction can be transferred to mitochondria for entry into electron transport chain via alpha-glycerophosphate and aspartate/malate shuttles, (ii) ATP is generated in the phosphoglycerate kinase and pyruvate kinase reaction of glycolysis, and (iii) ATP is produced in mitochondria from oxidation of pyruvate. The increased ATP/ADP ratio induces plasma membrane depolarization by closure of beta-cell K_{ATP}-sensitive channels and subsequently leads to the opening of voltage-gated calcium channels. The resultant influx of Ca^{2+} leads to insulin export through the fusion of a readily releasable pool of insulin-containing vesicles with the plasma membrane (Henquin 2009; Ashcroft et al. 1984; Wollheim and Pralong 1990; Fig. 1). This triggering mechanism of K_{ATP}-dependent glucose-stimulated insulin release is responsible for the first phase of insulin secretion (over 5–10 min). The second phase insulin release is longer (30–60 min) and dependent on metabolic stimulus-secretion coupling (Newsholme et al. 2014; Henquin 2000).

Pancreatic beta-cells respond to other nutrients such as amino acids, fatty acids (FAs), and ketones. Amino acids administrated alone at

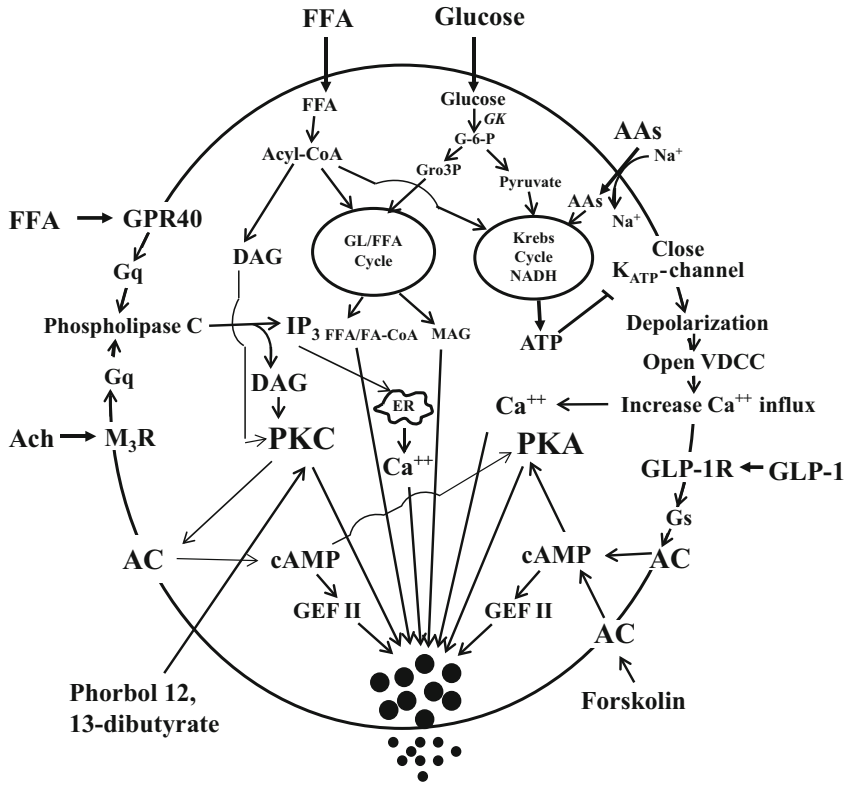

Fig. 1 Signaling in pancreatic islet beta-cell. Free fatty acid (*FFA*), glucose, amino acids (*AAs*), acetylcholine (*Ach*), and GLP-1 signaling pathways in pancreatic beta-cells are depicted. *GPR40* G-protein-coupled receptor for FFA, *M_3R* muscarinic receptor type 3, *GLP-1R* glucagon-like peptide-1 receptor, *VDCC* voltage-dependent Ca^{2+} channels, *IP3* inositol triphosphate, *G-6-P* glucose-6-phosphate, *Gro3P* glycerol-3-phosphate, *GL/FFA* glycerolipid/FFA cycle, *PKC* protein kinase C, *PKA* protein kinase A, Ca^{2+}, *ATP* adenosine triphosphate, *AC* adenylate cyclase, phosholipase C, *IP_3* inositol triphosphate, *MAG* monoacylglycerol, *DAG* diacylglycerol, cAMP-*GEF II* cAMP-guanine nucleotide exchange factor II, *ER* endoplasmic reticulum

physiological concentrations do not affect glucose-stimulated insulin secretion (GSIS), but interact with glucose to increase GSIS (Newsholme et al. 2007a, 2014; Doliba et al. 2007). Amino acids regulate both triggering and amplification pathway of insulin secretion by acting as a substrate for the TCA cycle and/or redox shuttles with subsequent generation of ATP (Newsholme et al. 2007a; Li et al. 2003), direct depolarization of plasma membrane by the transport of positively charged amino acids into the cell via specific amino acid transporter (Newsholme et al. 2007a), and cotransport of Na^+ ions resulting in plasma depolarization (Newsholme et al. 2007a) and through amino acid receptors of the plasma membrane, in particular the glutamate receptor expressed in beta-cells (Inagaki et al. 1995; Wollheim and Maechler 2015).

Fatty acids (FAs) alter pancreatic beta-cell function by signaling through the free FA (FFA) receptor: GPR40/FFAR1 (G-protein-coupled receptor 40) that has been shown to be a physiologically relevant receptor for long-chain FAs (Itoh et al. 2003; Soga et al. 2005; Kristinsson et al. 2013). GPR40/FFAR1 belongs to a family of G-protein-coupled receptors that are highly expressed in beta-cells and mediate approximately

half of the FFA-induced secretion (Ferdaoussi et al. 2012; Kebede et al. 2008; Latour et al. 2007; Nolan et al. 2006) where it increases insulin secretion by signaling via Gαq and phospholipase C, IP3-mediated Ca^{2+} release from ER, and stimulation of PKC by increased level of diacylglycerol (DAG) (Kristinsson et al. 2013; Fujiwara et al. 2005; Fig. 1). The second pathway involves FAs entering into the intermediary metabolism of beta-cell (Prentki et al. 2013). At a low glucose concentration, the FAs are converted into long-chain acyl-CoA by the enzyme acyl-CoA synthetase (ACS) and enter the mitochondria through carnitine palmitoyltransferase I (CPT-1), where they are oxidized via the β-oxidation pathway for energy production. When the glucose concentration increases in pancreatic β-cells, FA oxidation is decreased and glucose oxidation fulfills a larger part of the cellular energy needs. The shift in fuel utilization occurs due to a high substrate flux to the TCA cycle that leads to an increase in anaplerosis and efflux of citrate from the mitochondria. Cytosolic citrate is converted into malonyl-CoA by citrate lyase and acetyl-CoA carboxylase (ACC). Malonyl-CoA is a potent allosteric inhibitor of mitochondrial CPT-1 and therefore inhibits the transport of long-chain acyl-CoA into the mitochondria to be oxidized (Prentki et al. 1992; Liang and Matschinsky 1991). The malonyl-CoA/CPT-1/FA-CoA interaction is connected to the glycerolipid/free fatty acid cycle (GL/FFA) (Prentki et al. 2013; Prentki and Madiraju 2008, 2012). At a high glucose concentration, a substantial portion of glucose utilization by pancreatic β-cells (about 30 %) is incorporated into glycerol (GL) via glycerol-3-phosphate (Gro3P) and enters GL/FFA cycling (Peyot et al. 2010; Fig. 1). The GL/FFA cycle consists of lipogenesis (esterification) and lipolysis components that generate many lipid intermediates, some of which serve as signaling molecules, e.g., monoacylglycerol (MAG), diacylglycerol (DAG), phosphatidate, lysophosphatidate, FA-CoA, and FFA (Prentki and Madiraju 2008). Specifically, DAG and LC-CoA enhance the exocytotic function of key vesicle priming and docking proteins such as MUNC13, synaptosomal-associated protein 25 (SNAP-25), and synaptotagmin and also modulate signal transduction by PKC activity (Nolan and Prentki 2008; Newsholme et al. 2007b; Rorsman and Braun 2013).

What is the interaction between the GL/FFA cycle and the malonyl-CoA/CPT-1/FA-CoA network? Elevated blood glucose, occurring in the fed condition, enhances GL/FFA cycling by increasing malonyl-CoA that inhibits β-oxidation, providing Gro3P for the esterification arm of the cycle, and activating lipolysis via covalent modification of lipolytic enzymes. Amino acids also enhance anaplerosis and malonyl-CoA production, and exogenous FFAs provide substrate for the GL/FFA cycle. These nutrients act together with glucose to promote GL/FFA cycle activity and production of metabolic coupling factors (Prentki et al. 2013). Thus, the malonyl-CoA/FA-CoA-GL/FFA cycle metabolic signaling network likely plays an integrating role in modulating insulin secretion in response to all classes of fuel stimuli to adjust insulin secretion as a function of the nutritional state (Prentki and Madiraju 2012). Thus malonyl-CoA acts to switch pancreatic islet beta-cell metabolism from FA oxidation to glucose oxidation.

In addition, pancreatic islets express hormone-sensitive lipase (HSL) which may activate endogenous lipolysis and also participate in the regulation of insulin secretion (Prentki et al. 2013). Therefore, triacylglycerol (TAG) stored in pancreatic islet beta-cells plays an important role in stimulus-secretion coupling mechanism of GSIS. It has been shown that both glucose and FA metabolism are needed for normal islet beta-cell function (Prentki et al. 1992). If malonyl-CoA accumulation is blocked by the inhibition of acetyl-CoA carboxylase (ACC), GSIS is markedly reduced.

The mechanisms described above are related to acute exposure to FFA. In contrast, chronic exposure of pancreatic islet beta-cells to FFA results in inhibition of insulin secretion as shown in vitro in isolated perfused pancreas and islets (Sako and Grill 1990; Zhou and Grill 1995; McGarry 2002) and in vivo studies in humans (Kashyap et al. 2003). This phenomenon has been termed lipotoxicity (Prentki et al. 2002; Poitout and

Robertson 2002). Chronic exposure to FFA enhances the basal insulin secretion but decreases the response to glucose. Chronic elevation of FFA also decreases insulin gene expression, proinsulin processing, and induction of islet apoptosis (Newsholme et al. 2007b; El-Assaad et al. 2003; Lupi et al. 2002). Chronic exposure to high glucose and FFA may also lead to ceramide formation and/or NO-mediated apoptosis (Newsholme et al. 2007b; Boslem et al. 2012). This pathway plays a role in the development and pathogenesis of pancreatic islet beta-cell dysfunction in type 2 diabetes (McGarry 2002; McGarry and Dobbins 1999).

FA receptors may also play a role during prolonged exposure to FFA (Kristinsson et al. 2013). Indeed, it was shown that GPR40/FFAR1 knockout (KO) mice generated by Steneberg et al. (2005) did not develop metabolic abnormalities seen in wild-type animals when given a high-fat diet. When islets isolated from the GPR40/FFAR1-KO mice were chronically exposed to elevated levels of FFAs, subsequent GSIS was not impaired. In another study, FFAR1-KO mice generated by another laboratory showed better glucose tolerance after 1 week of high-fat diet compared to wild-type mice (Brownlie et al. 2008). In contrast to these results, FFAR1-KO mice generated by Kebede et al. (2008) and Lan et al. (2008) developed obesity and hyperglycemia. Islets isolated from FFAR1-KO mice were not protected from impairment of GSIS caused by prolonged exposure to elevated levels of FFAs (Latour et al. 2007). Overexpression of FFAR1 in rats was favorable for glycemic control on a high-fat diet (Nagasumi et al. 2009). A number of FFAR1 agonists have been shown to stimulate insulin secretion in a glucose-dependent manner and to lower glucose levels in obese and diabetic rats and mice (Lin et al. 2011; Houze et al. 2012; Luo et al. 2012; Tsujihata et al. 2011; Yashiro et al. 2012). These results demonstrate that pancreatic islet beta-cells are adversely affected by chronic exposure to high glucose and FFA levels which predisposes to impaired insulin secretion and the development of glucose intolerance and type 2 diabetes.

2 Neuroendocrine Regulation of Pancreatic Islets

In addition to various nutrients, insulin secretion is stimulated by hormones and neurotransmitters. Acetylcholine, the neurotransmitter of the parasympathetic nervous system, plays a key role in the regulation of insulin secretion in pancreatic islet β-cells (Gilon and Henquin 2001; Ahren 2000; Teff and Townsend 1999). Mutant mice lacking the M_3 muscarinic acetylcholine receptor subtype in beta-cells display impaired glucose tolerance and reduced insulin release (Gautam et al. 2006; Zawalich et al. 2004). In contrast, transgenic mice overexpressing M_3 receptors in β-cells showed an improvement in glucose tolerance and insulin secretion (Gautam et al. 2007). The secretory response of β-cells to fuel stimulation is also markedly enhanced by the gut hormone GLP-1, an incretin released into the portal circulation when a meal is digested (Holz and Habener 1992). These neuroendocrine signals are mediated by specific G-protein-coupled receptors (GPCRs) of the beta-cells (Ahren 2009; Regard et al. 2007; Fig. 1). The binding of various ligands activates specific subgroups of heterotrimeric G proteins, Gs, Gi, and Gq, involved in distinct pathways of signal transmission (Regard et al. 2007; Lagerstrom and Schioth 2008; Kimple et al. 2014).

Signaling by Gs (activated by the GLP1 receptor) (West et al. 2014; Doyle and Egan 2007) and Gq (activated by M_3 acetylcholine receptor) (Gilon and Henquin 2001; Ahren 2000; Nakajima et al. 2013; Jain et al. 2013) potentiates fuel-stimulated insulin release during the course of a meal and also stimulates beta-cell proliferation and enhances beta-cell mass (Baggio and Drucker 2006, 2007) as compensation for insulin resistance associated with obesity, the major precipitating factor for type 2 diabetes (Baggio and Drucker 2006). Various lines of evidence suggest that defects of the neuroendocrine regulation of beta-cells play an important role in the molecular pathogenesis of type 2 diabetes (Lee et al. 2012). There is evidence that both release and action of incretin hormones are disrupted in type 2 diabetes (Drucker and Nauck 2006; Drucker 2006;

Vilsboll et al. 2001). This defect is partly attributed to reduced expression of GLP1 receptor in pancreatic beta-cells (Rajan et al. 2015). Activation of the vagal afferent pathway is also impaired in a rodent model of type 2 diabetes (Lee et al. 2012; Rocca and Brubaker 1999). Previously we demonstrated in vitro with isolated mouse islets that palmitic acid acutely reduced the glucose-dependent acetylcholine stimulation of insulin release, the total oxygen consumption response to glucose, the Ca^{2+} response, and cAMP metabolism in isolated mouse islets, while the effects of GLP-1 on these parameters were not altered or potentiated (Doliba et al. 2010). These effects occurred at concentrations of albumin-bound palmitic acid as low as 50 μM, thus implicating the activation of GPR-40 receptors. We have also shown that chronic exposure of pancreatic islets to high glucose and FA concentrations decreased the ability of acetylcholine to potentiate GSIS (Doliba et al. 2015). This effect strongly depends on the glucose concentration in the culture medium with a delayed onset of potentiation at 10 mM glucose and a delayed onset plus reduced maximal effectiveness of the neurotransmitters at 16 and 25 mM concentrations of glucose. Based on the significant contribution of cholinergic regulation to insulin secretion and glucose homeostasis in humans (Gilon and Henquin 2001; Ahren 2000), it was proposed that impairment of this pathway by FA may contribute to the lack of compensatory insulin release in response to insulin resistance.

3 Pancreatic Islet Adaptation in Pregnancy and Obesity

The endocrine pancreas is a unique organ that can adapt to physiological and pathological conditions by changing its mass and function to ensure glucose homeostasis (Steiner et al. 2010; Lingohr et al. 2002; Karaca et al. 2009). Two types of compensation can occur: a functional one in which beta-cells secrete more insulin and the second one in which there is a change in beta-cell mass (Bonner-Weir 2000). Functional adaptations, including changes in the threshold for glucose-induced insulin secretion (Sorenson et al. 1987) and glucose-induced increase in glucokinase activity (Chen et al. 1994), are involved in the maintenance of glucose homeostasis. After stimulation by high glucose levels, the proinsulin synthesis in beta cells is increased by more than tenfold, with hormone synthesis approaching 50 % of the total protein production (Schuit et al. 1988). The beta-cell mass is a major determinant of the amount of insulin that can be secreted, and experimental evidence shows that the beta-cell mass can increase or decrease (Bonner-Weir 2000). An adaptive increase in beta-cell mass is well illustrated in pregnancy and obesity (Rhodes 2005; Bernard-Kargar and Ktorza 2001; Sorenson et al. 1997). In mammals, including humans, pregnancy results in profound changes in maternal metabolism and insulin secretion to allow an optimal nutrient supply to the fetus. During the last trimester, there is marked insulin resistance accompanied by a dramatic increase in the insulin response to glucose and doubling of the beta-cells mass (Parsons et al. 1992). Failure to compensate for the high insulin demand during pregnancy leads to gestational diabetes.

Pancreatic beta-cell plasticity also occurs in obesity. Although obesity is associated with insulin resistance, most obese individuals remain normoglycemic because of a compensatory increase in beta-cell function and mass to cope with the increase in metabolic status (Sorenson et al. 1997) (Ackermann and Gannon 2007). This may explain why 70–75 % of obese individuals do not develop diabetes (Mokdad et al. 2001). Pancreatic islet beta-cell adaptation has been documented in several animal models. Placing normal rats on a high-fat diet for 6 weeks results in a modest increase in body weight, mild insulin resistance, and a 30–40 % increase in islet density and beta-cell size (Buettner et al. 2000). Pancreatic islet beta-cell compensation and expansion of beta-cell mass is also well demonstrated in Zucker fatty (ZF) rats, which possess a leptin-receptor defect that results in obesity and insulin resistance (Clark et al. 1983). However, these animals

remain normoglycemic via compensatory hyperinsulinemia. Adaptation to insulin resistance occurs via a fourfold increase in the beta-cell mass (Pick et al. 1998) together with enhanced insulin secretion (Milburn et al. 1995; Zhou et al. 1999), thereby allowing the maintenance of glucose homeostasis. However, as the animals get older, more obese, and glucose intolerant, there is a deficit in the beta-cell population that no longer adequately compensates for the insulin resistance. This worsens with age, so the animals eventually become diabetic (Pick et al. 1998; Unger and Orci 2001).

Previously we have studied pancreatic islet adaptation in diet-induced obese (DIO) C57BL/6 J mice (Roat et al. 2014; Imai et al. 2008). This mouse strain mimics human obesity (Surwit et al. 1988) and develops hyperinsulinemia and mildly elevated blood glucose levels indicating a substantial capacity to compensate for insulin resistance (Roat et al. 2014). Hyperinsulinemia in DIO C57BL/6 J mice is associated with an increase in islet mass and size and increased BrdU incorporation in beta-cells, indicating hyperplasia (Roat et al. 2014). Although studies in humans are limited, a morphometric study of autopsy pancreases from diabetic and nondiabetic patients (Kloppel et al. 1985) has showed that the β-cell mass was increased by 40 % in the obese subjects as compared with lean subjects. These results suggest that there is a compensatory growth of beta-cell mass in response to insulin resistance in obesity.

Glucose, FFA, and some hormones and neurotransmitters are the most physiologically relevant stimuli for beta-cell proliferation and mass increase in vitro and in vivo (Baggio and Drucker 2006; Hugl et al. 1998; Shimabukuro et al. 1998; Brubaker and Drucker 2004; Thorens 2014). A prolonged (48-h) glucose infusion in normal rats led to a twofold increase in beta-cell mass as a result of both hypertrophy and hyperplasia (Bernard et al. 1998), and it was associated with a marked increase in islet responsiveness to glucose (Bernard et al. 1998). In the obese and/or insulin-resistant state, chronic hyperglycemia and hyperlipidemia can evoke beta-cell apoptosis leading to decreased beta-cell mass (Pick et al. 1998; Donath et al. 1999). In rodent models, FFAs can cause a modest increase in beta-cell proliferation at basal glucose concentrations (Shimabukuro et al. 1998). However, long-term exposure of beta-cells to FFAs inhibits beta-cell mitogenesis and induces beta-cell apoptosis (Cousin et al. 2001). These adverse effects of FFAs on beta-cell growth could be mediated via intracellular accumulation of long-chain CoA or ceramides (Shimabukuro et al. 1998).

GLP-1 increases beta-cell mass by activating beta-cell proliferation and differentiation and inhibiting beta-cell apoptosis (Baggio and Drucker 2006; Brubaker and Drucker 2004). These actions are associated with GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors (Drucker and Nauck 2006; Drucker 2013). However, it should be noted that the majority of experiments were carried out in younger animals (Campbell and Drucker 2013) whereas older rodent beta-cells exhibit a substantially diminished or absent proliferative response to multiple regenerative stimuli, including GLP-1 receptor agonists (Rankin and Kushner 2009). Human beta-cells are less responsive to the proliferative action of GLP-1 compared to rodent beta-cells (Parnaud et al. 2008). More work is required to understand whether older diabetic human beta-cell retain the capacity to proliferate, resist cell death, or retain a functionally differentiated state in response to GLP-1 agonists (Drucker 2013).

It has been also shown that both parasympathetic and sympathetic nervous systems influence the postnatal development and plasticity of the endocrine pancreas (Thorens 2014). Defects in these autonomic pathways impair beta-cell mass expansion during the weaning period and beta-cell mass adaptation in adult life (Thorens 2014). Various growth factors have been implicated in increasing adult pancreatic beta-cell proliferation and beta-cell neogenesis (Lingohr et al. 2002). The best characterized and physiologically relevant growth factors that increase beta-cell proliferation are insulin-like growth factor (IGF-1), growth hormone (GH), and GLP-1. The IGF and GH signal transduction pathway is described in detail in a review article by Lingohr et al. (2002).

4 Glucolipotoxicity and Diabetes

Hyperglycemia develops when pancreatic islet beta-cells fail to synthesize and secrete sufficient insulin for maintaining the physiological glucose concentration of 5 mM. Glucolipotoxicity, the operationally defined condition resulting from caloric overload, is proposed to worsen or cause beta-cell damage which eventually leads to type 2 diabetes. The term "glucolipotoxicity" implies that repeated or continued exposure to high blood glucose and lipid levels is required for beta-cell damage and functional dysfunction to occur. However, a compelling mechanistic molecular explanation of glucolipotoxicity effecting pancreatic beta-cells is still lacking. In an attempt to model glucolipotoxicity in vitro, pancreatic islets are usually cultured for several days in high glucose and FA concentrations. Studies have described multiple cellular processes involved in the pathogenesis of beta-cell dysfunction, including changes in gene expression (Biden et al. 2004; Gremlich et al. 1997), intermediary metabolism (Iizuka et al. 2002), mitochondrial function (Koshkin et al. 2003), ion channel activity (Branstrom et al. 1997, 1998; Reimann et al. 2003), insulin synthesis, and exocytosis (Somesh et al. 2013). Different molecular mechanisms of FA-induced beta-cell dysfunction have been proposed including accumulation of ceramide (Boslem et al. 2012), apoptosis of beta-cells due to oxidative (Gehrmann et al. 2010; Morgan et al. 2007) and ER stress (Kharroubi et al. 2004; Cnop et al. 2008), as well as others mechanisms (Joseph et al. 2004; Cnop et al. 2005). Many of these mechanisms remain controversial. For example, the exposure of human islets for 24 h in elevated FA and glucose conditions was found in one study to initiate apoptosis (El-Assaad et al. 2003), but other studies have failed to find evidence of any significant apoptosis following long-term exposure to FAs (Kelpe et al. 2003). Olofsson et al. (2007) reported that inhibition of GSIS by long-term exposure to the FAs oleate and palmitate was not related to any signs of increased beta-cell death, reduced insulin synthesis, and impaired glucose metabolism, K_{ATP} channel regulation, or Ca^{2+} signaling. These discrepancies could be due to differences in acute or chronic islet experimentations. In vitro albumin/FA ratios are often not optimal, glucose concentrations are often excessive to be meaningful (i.e., >16 mM), there are significant limitations inherent in animal models, and there is a lack of a clear definition of the glucolipotoxicity phenomenon (Poitout et al. 1801). While various molecular and cellular mechanisms of glucolipotoxicity and their roles in obesity and diabetes have been described (Prentki et al. 2013; Prentki and Madiraju 2012; Poitout et al. 1801; Poitout and Robertson 2008), it is unclear whether these models recapitulate the pathogenesis of human type 2 diabetes.

5 Pancreatic Islet Bioenergetics and Diabetes

A faulty bioenergetic process is a plausible explanation for defective insulin secretion in type 2 diabetes. Normally the ATP, generated by metabolism of glucose, amino acids, and probably FAs, serves as the obligatory coupling factor in fuel-stimulated insulin release involving beta-cell-specific mechanisms (Ashcroft et al. 1984). The unique role of ATP as a critical messenger in the stimulus-secretion coupling was clearly shown in our previous studies with mouse, rat, and human islets where oxygen consumption, glycolysis, and glucose oxidation were related to insulin secretion (Doliba et al. 2012). Such measurements allowed us to calculate the ATP production rate in beta-cells as a function of the glucose concentration and insulin secretion. Making a reasonable assumption that islet glycogen stores are negligible (Matschinsky et al. 1971) and that coupling of oxidative phosphorylation is intact, we were able to develop an islet "ATP production/insulin secretion" curve (Fig. 2). Despite major differences in insulin profiles (Fig. 2a), the ATP production/insulin secretion curves were similar for mouse, rat, and normal human islets, and the data for all species fit a single sigmoidal curve (Fig. 2b), showing a clear

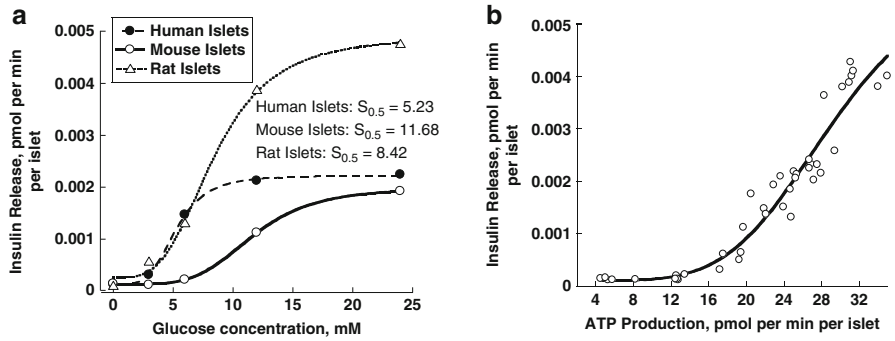

Fig. 2 Mouse, rat, and human islet ATP production/insulin secretion curves. Panel A: Secretion profiles of mouse, rat, and human islets as a function of the glucose concentration. *Panel B*: combined energy production/insulin secretion curve with data on ATP production and insulin release from all three types of islets projected on a single continuous sigmoidal curve. The ATP production was calculated based on oxygen consumption and glucose usage data

relationship between the pancreatic islet energy (ATP) production rate and insulin secretion (Doliba et al. 2012).

The ATP production/insulin secretion curve is steeply sigmoidal and has a threshold for glucose-stimulated insulin secretion at about 15 pmole/islet/min, a Hill coefficient of about 11 – which is an indication of highly cooperative coupling mechanisms – and a half-maximal effective rate (ER_{50}) of about 25 pmole/islet/min. These values imply that ATP turns over about twice at the threshold and about four times at maximal glucose stimulation, but that ATP turnover is changed relatively little (perhaps not more than 30 %) in the physiologically important segment of the curve. We speculate that the "ATP production/insulin secretion" curve has clinical significance comparable to that of the classical "Frank/Starling" curve of the heart. In the heart, it is the venous return and the ensuing muscle fiber stretch which determines cardiac output maintaining the match between the pump rate and body oxygen requirements. In pancreatic islet beta-cells, it is the fuel load and the ensuing ATP turnover that determines the insulin output and maintains glucose homeostasis. We also showed that ATP production/insulin secretion curve is modified by GLP-1 and a glucokinase activator piragliatin (Doliba et al. 2012). We speculate that the "ATP production/insulin secretion" curve is modified in type 2 diabetic islets.

The literature proposes various ways by which mitochondrial energy metabolism can be altered due to fuel overload. It has been shown that FAs may act as uncouplers and inhibitors of mitochondrial respiration (Wojtczak and Schonfeld 1993), operating as protonophors and by inhibiting the electron transport, respectively (Schonfeld and Reiser 2006; Schonfeld and Wojtczak 1767, 2008). In addition, FAs induce uncoupling protein (UCP2) in pancreatic islets (Joseph et al. 2004; Chan et al. 2004; Zhang et al. 2001). FAs may act as complex-I-directed inhibitors (Loskovich et al. 2005) and can also serve as a substrate for transport by the ANT inhibiting ATP and ADP exchanges (Klingenberg 1778). FAs may alter mitochondrial membrane permeability by opening of the permeability transition pore (Scorrano et al. 2001; Bernardi et al. 2002; Penzo et al. 2002; 2004).

Fatty acids (FAs) increase the expression of PGC-1 alpha which may alter bioenergetics in pancreatic beta-cells (Yoon et al. 2003). PGC-1 alpha is elevated in islets from different animal models of diabetes and in human studies (Yoon et al. 2003; Ek et al. 2001; Oberkofler et al. 2004, 2009). PGC-1 alpha promotes mitochondrial biogenesis in brown tissue (Puigserver et al. 1998); however, adenovirus-mediated expression of PGC-1 alpha to levels similar to those present in diabetic rodents produces a marked inhibition of GSIS in isolated islets and in mice

(Yoon et al. 2003), by suppressing glucose oxidation or decreasing the cell's ability to drive ATP production. PGC-1 alpha increases the transcription of UCP2 (Oberkofler et al. 2006) by PGC-1-mediated upregulation of beta-cell sterol element binding protein (SREBP) gene expression. Since UCP2 modulates the efficiency of ATP production (Klingenberg and Huang 1999) by catalyzing the translocation of protons across the mitochondrial membrane, one should expect changes in oxygen consumption and oxidative ATP synthesis. However, such data are limited and related to insulinoma cells (Barlow and Affourtit 2013). Only measurements of total ATP concentration in islets exposed to FA have been reported (Somesh et al. 2013). Since insulin granules contain ATP, which is co-secreted with insulin, it is difficult to dissociate between the effects of FA on ATP syntheses and changes of ATP content in insulin granules. In fact, the insulin content is decreased in islets chronically exposed to FFA (Somesh et al. 2013), which may result in concomitant decreased total ATP concentration which says little about the functional ATP.

In order to access beta-cell bioenergetics and its relationship to insulin secretion, we performed two sets of experiments: (i) the bioenergetics, ionic, and secretion profiles of pancreatic islets isolated from healthy and type 2 diabetic organ donors were examined and (ii) isolated normal human islets were exposed to a glucolipotoxicity condition (high glucose and FFAs) in organ culture, and the bioenergetics and insulin secretion were studied in perifusion experiments. When islets were exposed to a "staircase" glucose stimulus in the perifusion setup, the glucose dependency curves of insulin secretion (Fig. 3a) and respiration (Fig. 3c) of diabetic islets showed decreased maximal rates and a right shift for the oxygen consumption rate (OCR) as compared to the control islets. It is worthy of note that the baselines for both parameters are comparable. In the insulin secretion profiles, the difference is most pronounced at the 6 and 12 mM glucose steps (Fig. 3b) showing decreased rates of rise and a decreased extent and loss of biphasicity. The glucose dependency of the OCR of the diabetic islets was flat and reduced by 50 % at 24 mM glucose (Fig. 3c). Addition of a mitochondrial uncoupler, FCCP (5 μM), blocked insulin release instantly and transiently increased OCR in control and diabetic islets to the same level, indicating that strong coupling exists between islet respiration and oxidative phosphorylation in both types of islets (Fig. 3c).

Oxygen consumption (VO_2) of healthy and type 2 diabetic human islets increased sigmoidally as a function of a stepwise rise of glucose concentrations (Fig. 3d). In islets from type 2 diabetics, the maximal stimulation of respiration (V_{max}) by glucose was reduced from 0.4 ± 0.02 in control to 0.32 ± 0.01 nmol/min/100 islets, and the $S_{0.5}$ rose from 4.39 ± 0.01 in control to 5.43 ± 0.13 mM (Fig. 3d). Panel E of Fig. 3 presents changes in intracellular $[Ca^{2+}]_i$ of human islets. 3 mM glucose caused a transient and 9 mM glucose a biphasic sustained increase in $[Ca^{2+}]_{i.}$ of control islets. Diabetic islets responded only to 9 mM and this response was delayed and significantly lower than in controls.

Together, these data indicate that impaired pancreatic islet beta-cell bioenergetics resulting in reduced ATP production is critical in the molecular pathogenesis of type 2 diabetes. Importantly, the glucokinase activator piragliatin was able to correct the defect of respiration and GSIS (Doliba et al. 2012). In our second experiment, the glucolipotoxicity, which is a hallmark of type 2 diabetes, was mimicked in vitro by culturing the islets for 3 or 5 days with 0.5 mM palmitic acid or a mixture of palmitic and oleic acid at 1 % albumin and different concentrations of glucose: 10, 16, and 25 (Doliba et al. 2015). We found that chronic exposure of mouse islets to FA with a glucose leads to bioenergetic failure, as evidenced by decreased OCR and reduced insulin secretion upon stimulation with glucose or amino acids. These changes were associated with reduced islet ATP levels, impaired glucose-induced ATP rise, a trend for reduced mitochondrial DNA, and reduced expression of mitochondrial transcription factor A (Tfam). We also discovered accumulation of carnitine esters of hydroxylated long-chain FA (Doliba et al. 2015) that have been shown to uncouple the heart and brain mitochondria (Tonin

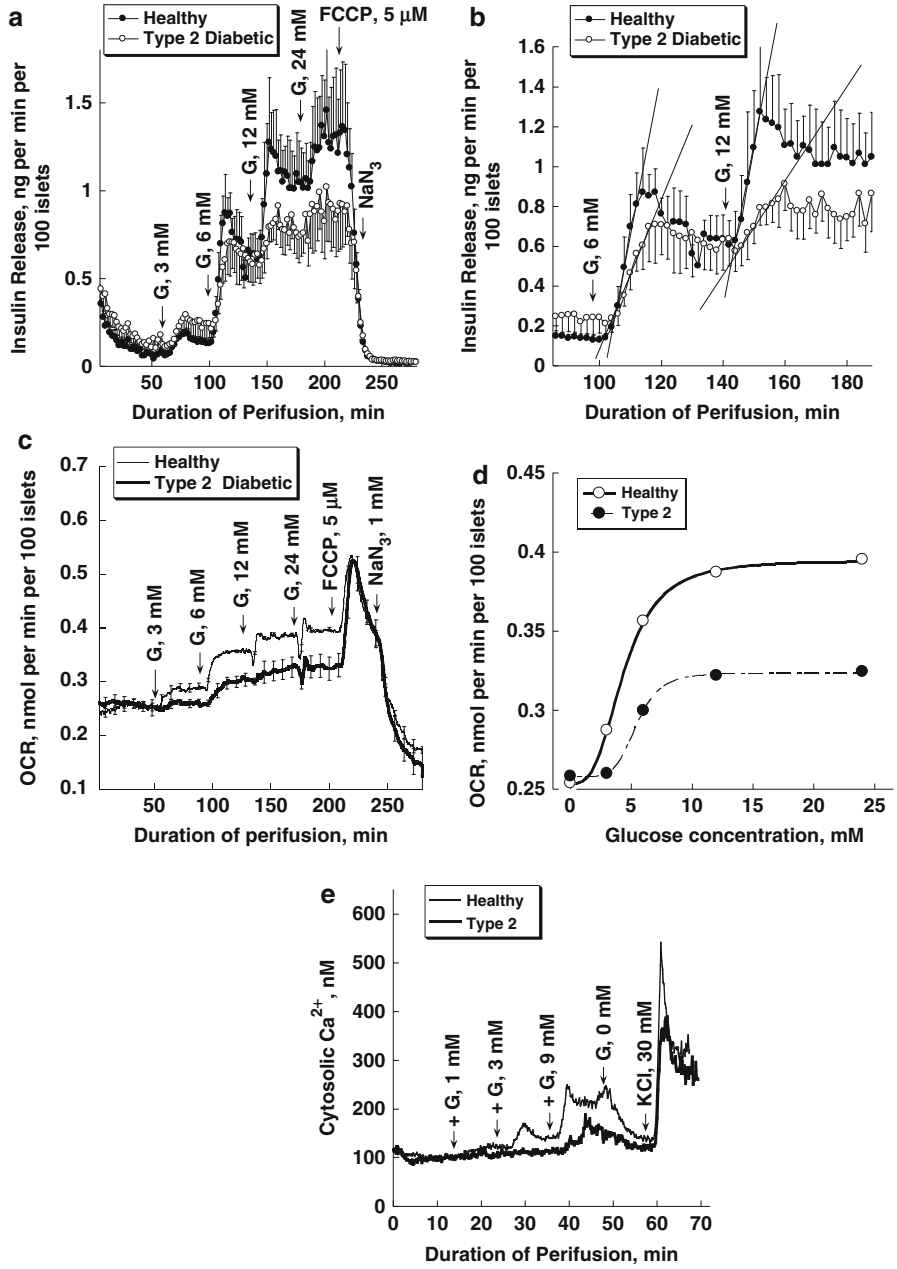

Fig. 3 Impaired insulin release (*A* and *B*), oxygen consumption (*C* and *D*), and intracellular calcium (*E*) of isolated islets from control and type 2 diabetic organ donors. *Panel A*: shows the insulin release patterns with glucose stimulation using stepwise increases of glucose from zero to 3, 6, 12, and 24 mM. *Panel B*: magnified view of selected section (85–190 min) of the experiment presented in *A* to show the loss of the first phase of insulin release in type 2 diabetic islets. *Panel C*: islet respiration during stepwise of glucose concentration followed by treatment with 5 μM of the uncoupler of Ox/Phos FCCP and 1 mM Na-azide. O_2 consumption was determined with a method based on phosphorescence quenching of metalloporphyrins by oxygen (Doliba et al. 2006). *Panel D*: oxygen consumption rate as function of glucose concentration. *Panel E*: represents corresponding changes in intracellular Ca^{2+} of human islets due to stepwise increases of glucose from zero to 1, 3, and 9 mM. The Fura-2 method was employed. Typical experiments are presented (n of the series = 3). Hb A1c levels for the pancreas donors with T2DM were 9.3, 11.0, and 7.4 %. Results are presented as means ± SE (SE when applicable) of three experiments

et al. 2010, 2013). We propose that mitochondrial accumulation of unsaturated hydroxylated long-chain FA uncouples and ultimately inhibits pancreatic islet beta-cell respiration and that this effect of the toxic FA metabolite causes a slow deterioration of mitochondrial function, progressing to bioenergetic failure as the main cause of impaired insulin secretion and reduced beta-cell mass, both hallmarks of type 2 diabetes.

6 Effects of Fatty Acids in Humans

FAs play an important role in the regulation of pancreatic beta-cell function in humans (McGarry 2002). In the fasting state, free FAs sustain basal insulin secretion and assume efficient nutrient-stimulated insulin secretion when the fast is terminated. Elevated plasma FFA levels have been reported to play an important role in maintaining chronic hyperinsulinemia in insulin-resistant obese subjects, and removal of this FFA stimulus by overnight reduction of plasma FFAs with nicotinic acid impairs glucose-induced insulin secretion (Dobbins et al. 1998). Despite the evidence from in vivo studies, the effects of prolonged elevation of FFA on insulin secretion in humans remain controversial. Boden and colleagues demonstrated that 48-h elevation of plasma FFA potentiated GSIS in healthy subjects at glucose levels clamped at 8.6 mM (Boden et al. 1995) but insulin secretion was defective in type 2 diabetic patients (Boden and Chen 1999). In contrast, Carpentier et al. (1999) have shown that acute enhancement of insulin secretion by FA in healthy humans is lost with prolonged FA elevation. This loss of insulin secretion was specific to glucose and the response to arginine was normal (Carpentier et al. 2001). Interestingly, obese but not diabetic subjects are more susceptible to the inhibitory effect of lipids on GSIS (Carpentier et al. 2000). Kashyap et al. (2003) have examined insulin secretion and insulin action during a 4-day lipid infusion in nondiabetic subjects with and without a family history of type 2 diabetes. The most striking finding is that a 4-day intralipid infusion enhances insulin secretion in control subjects but inhibits GSIS in individuals with family history of type 2 diabetes (Kashyap et al. 2003). These data suggest that in subjects with a high risk of developing type 2 diabetes, beta-cell lipotoxicity may play an important role in the progression from normal glucose tolerance to overt hyperglycemia. Of note, a reduction in plasma FFA concentration with the antilipolytic agent acipimox enhanced first-phase insulin secretion in nondiabetic patients with a family history of type 2 diabetes (Paolisso et al. 1998).

Recently a new strategy was applied to study the functional impairment of human pancreatic islets (Rosengren et al. 2012). The goal of this approach was to calculate a genetic risk score for islet dysfunction leading to type 2 diabetes that involved impaired insulin exocytosis, decreased docking of insulin-containing secretory granules, and reduced insulin secretion (Rosengren et al. 2012). Such calculations were based on correlation analysis of function and genotype of human islets obtained from diabetic and nondiabetic donors. Rosengren et al. (2012) analyzed a panel of 14 gene variants robustly associated with type 2 diabetes susceptibility. This work resulted in the identification of four genetic variants that confer reduced beta-cell exocytosis and six variants that interfere with insulin granule distribution. It is of interest that this study showed that the negative impact of type 2 diabetes loci on beta-cell function was evident in islets from nonobese individuals. This suggests that the functional effects of the type 2 diabetes-associated SNPs may be more pronounced in lean than in obese individual. It may seem counterintuitive that obese individuals with type 2 diabetes exhibit greater insulin secretion than their lean counterparts. This may reflect an adaptation, albeit insufficient to prevent diabetes, in the obese donors. In addition, the lean donors who developed diabetes were likely to be those with the lowest insulin secretory capacity. These data suggest that there may be considerable heterogeneity in the cellular pathways that lead to reduced insulin secretion, which may explain why the reduction of exocytosis is evident only in genetic subgroups and not in the entire type 2 diabetes cohort (Rosengren et al. 2012).

7 Conclusions

To conclude, based on the existing literature, it is clear that excessive glucose and FAs levels have time-dependent deteriorating effects on pancreatic beta-cell pathophysiology in diabetes. These effects are different at the various stages of beta-cell dysfunction during the course of type 2 diabetes. When insulin resistance develops, for instance, as a result of obesity, the beta-cells mount a compensatory response that increases beta-cell mass, insulin biosynthesis, and insulin secretion. The magnitude of the compensatory beta-cell response is genetically determined (Kashyap et al. 2003; Rosengren et al. 2012; Fadista et al. 2014), and this is a major determinant of the long-term ability of an individual to maintain glucose homeostasis in the face of insulin resistance. In genetically predisposed individuals, pancreatic beta-cell compensation eventually becomes insufficient to sustain a secretory response that matches the high demand imposed by insulin resistance.

The failure of beta-cells to compensate for insulin resistance is a major component of impaired glucose homeostasis and overt diabetes. This defect is the consequence of a decline of insulin response to glucose due to functional beta-cell deficiency. It is also the consequence of an inability of the endocrine pancreas to adapt the beta-cell mass which eventually leads to a decrease in functional beta-cells. This idea has resulted in considerable attention being paid to the development of new therapeutic strategies aimed toward preserving or regenerating functional beta-cell mass (Karaca et al. 2009). GLP-1 enhances beta-cell survival by activating beta-cell proliferation and differentiation and inhibiting beta-cell apoptosis and thus contributing to the long-term regulation of insulin secretion by maintaining a functional beta-cell mass. It should be pointed out that any intervention to improve insulin secretion should start early in the disease when the endogenous insulin secretion and presumably the number of functional beta-cells have not decreased excessively (Grill and Bjorklund 2002; Karvestedt et al. 2002).

8 Cross-References

- ▶ Adipokines and Metabolism
- ▶ Genetics of Obesity
- ▶ Genetics of Type 2 Diabetes
- ▶ Insulin Resistance in Obesity
- ▶ Overview of Metabolic Syndrome
- ▶ Pharmacotherapy of Obesity and Metabolic Syndrome
- ▶ Type 2 Diabetes: Etiology, Epidemiology, Pathogenesis, Treatment

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Insulin Resistance in Obesity

26

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Abstract

Obesity is pandemic in population worldwide over the past decades, largely owing to overnutrition. Excess energy stores in the adipose tissue and other organs as lipids, promoting lipotoxicity and metabolic inflammation, activating intracellular protein kinases to impair insulin signaling components, and resulting in insulin resistance. Insulin resistance is the key etiologic defect that defines "metabolic syndrome," a group of interrelated disorders, including obesity, hyperglycemia, dyslipidemia, and hypertension. Following insulin resistance, many of patients with the metabolic syndrome eventually developed pancreatic β-cell failure, which triggers the onset of type 2 diabetes mellitus (T2DM) and its complications. Cell- and animal-based studies demonstrate that insulin and its signaling cascades normally control cell growth, metabolism, and survival through activation of mitogen-activated protein kinases (MAPKs) and phosphatidylinositol-3-kinase (PI3K), of which activation of PI3K associated with insulin receptor substrates 1 and 2 (IRS1, IRS2) and subsequent Akt→Foxo1 phosphorylation cascade have a central role in control of nutrient homeostasis and organ survival. Inactivation of Akt and activation of Foxo1, through suppression IRS1 and IRS2 in a variety of organs following overnutrition, lipotoxicity, and inflammation, may form a fundamental mechanism for insulin resistance in humans. This chapter discusses the basis of insulin signaling and resistance and how excess nutrients and lipid signaling from obesity promote inflammation and insulin resistance promoting organ failure, with emphasis on the IRS and the *forkhead*/*winged-helix* transcription factor Foxo1.

Keywords

Insulin resistance • Obesity • Lipotoxicity • Inflammation • Insulin receptor substrates 1 and 2 (IRS1, IRS2) • *Forkhead*/*winged*-helix transcription factor Foxo1

1 Introduction

The prevalence of obesity has globally increased over the past decades. Currently, at least 10 % of the world's population and two-thirds American are obese or overweight, significantly contributing to the prevalence of type 2 diabetes mellitus (T2DM) (Eckel et al. 2005; Roger et al. 2011). An estimated 366 million people around the world had diabetes in 2011, and nearly 80 % of the patients are obese (Whiting et al. 2011). Thus, obesity and associated diseases have become critical healthcare problems worldwide (Finucane et al. 2011; Haslam and James 2005).

Obesity is a problem because it is a major driver for insulin resistance, the key underlying mechanism for a common metabolic disorder – the "metabolic syndrome," formerly known as "insulin resistance syndrome" (Reaven 1988; Moller and Kaufman 2005). The features of metabolic syndrome include obesity, hyperglycemia, dyslipidemia, hyperinsulinemia, and hypertension (Eckel et al. 2005). Following the insulin resistance, many patients eventually develop pancreatic β-cell failure, which triggers the onset of T2DM and develops diabetes complications including cardiovascular disorders, fatty liver, infertility, renal failure, neuropathy, retinopathy, and certain cancers, resulting in high morbidity and mortality rates (Eckel et al. 2005). Owing to an imbalance between intake and expenditure of energy, energy excessively stores in the adipose tissue as lipids during obesity development. The genetic factors, such as mutations in *leptin and melanocortin receptor 4* (*MCR4*) genes (Allison and Myers 2014; Spiegelman and Flier 2001), can result in overeating and obesity, but the environmental and behavior factors, such as food availability and physical inactivity, are now believed to be major contributors to the epidemic of obesity (Eckel et al. 2005) (Fig. 1).

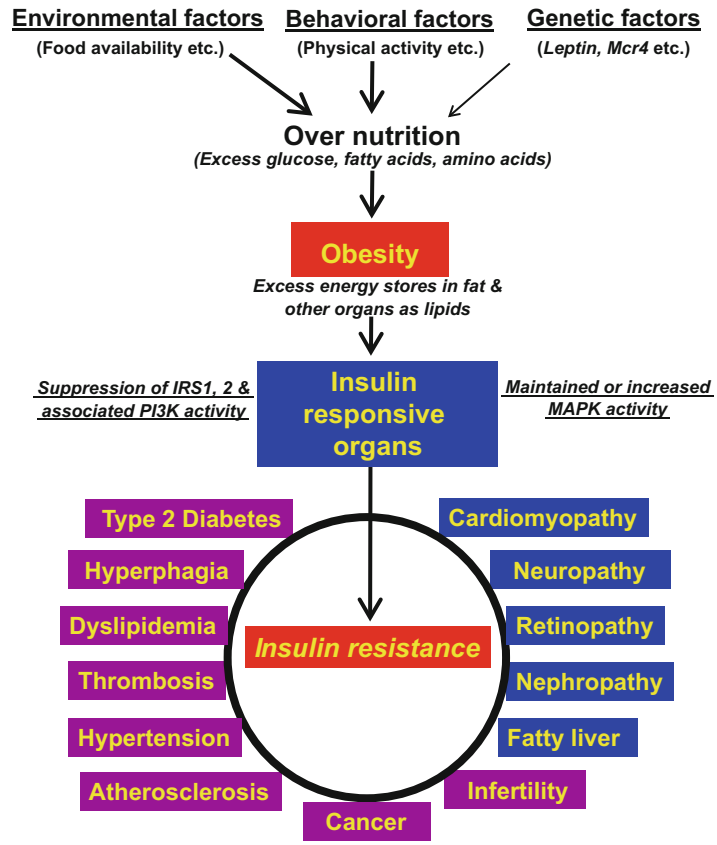

Fig. 1 Over nutrition-driven obesity plays a central role in induction of insulin resistance, liking to a number of diseases, including systemic diseases, such as type 2 diabetes, dyslipidemia, thrombosis, hypertension, atherosclerosis, infertility, and cancer, as well as special organismal diseases, such as fatty liver, nephropathy, retinopathy, nephropathy, and cardiomyopathy. Insulin resistance in tissues are associated with a selective PI3K inactivation and MAPK activation, which is tightly controlled by IRS1,2 suppression. *MC4R* melanocortin receptor 4, *IRS1, 2* insulin receptor substrate 1, 2, *PI3K* phosphatidylinositol-3-kinase, *MAPK* mitogen-activated protein kinases

Currently, obesity is accepted as a chronic inflammatory state, in which lipid accumulation in adipose tissue initiates inflammation and insulin resistance (Johnson and Olefsky 2013). Moreover, ectopic lipid accumulation in non-adipose tissues, such as the pancreas, the liver, muscles, and vessels, also triggers intracellular protein kinases, synthesis and secretion of cytokines/hormones, and induction of cellular damage and inflammation, hence impairing insulin signaling cascades to promote failure of many organs (Fig. 2). This chapter will focus on how excess lipid and signaling during obesity trigger lipotoxicity and inflammation to promote insulin resistance and associated diseases.

2 Insulin and Insulin Signaling: The Molecular Basis

Insulin is the most important hormone controlling nutrient homeostasis and growth in the body. During the postprandial state, insulin is secreted from the pancreatic β cells lowering blood glucose concentration and promoting anabolic processes and survival in a variety of target tissues. Insulin

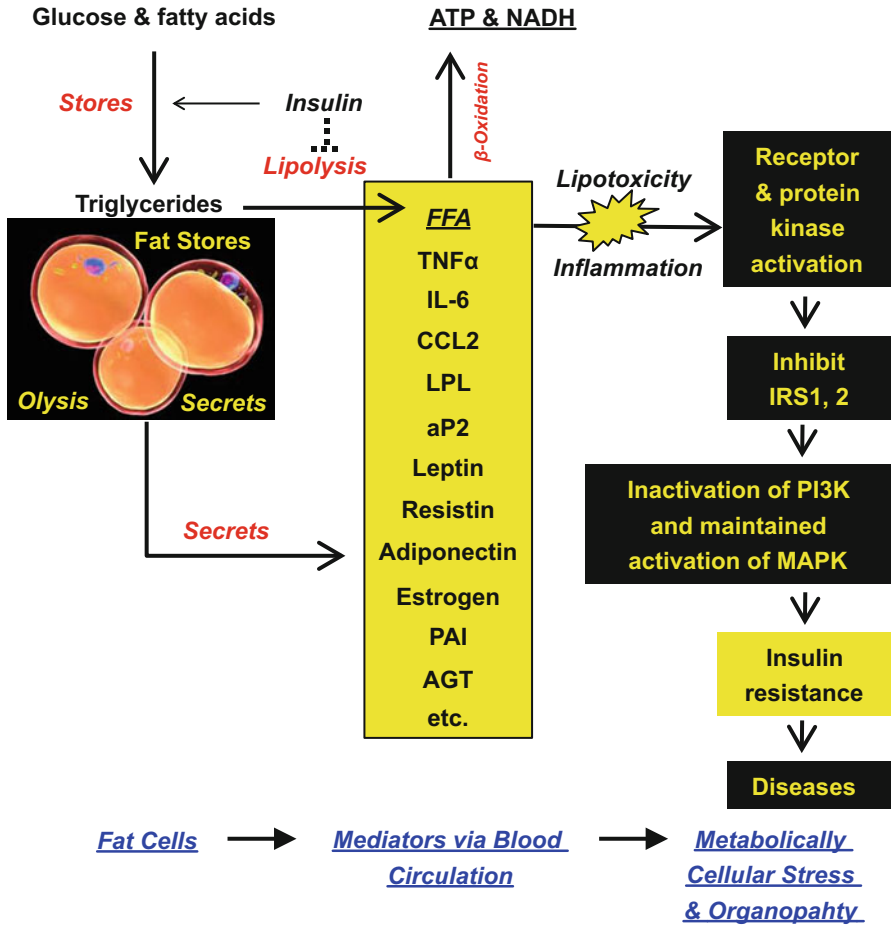

Fig. 2 Excess nutrient storage in adipose tissue promotes spillover of excess free fatty acids into the bloodstream and enhances adipocytes' metabolic activity for synthesis and secretion of adipokines and hormones, triggering lipid toxicity and metabolic inflammation in adipose tissue itself and other organs. *FFA* free fatty acids, *CCL2* chemokine C-C motif ligand 2, *PAI* plasminogen activator inhbitor-1, *AGT* angiotensinogen

stimulates glucose oxidation and influx into the muscle and fat, glycogen and protein synthesis in the muscle and liver, and lipid synthesis and storage in the liver and fat, while insulin inhibits fatty acid oxidation, glycogenolysis, gluconeogenesis, apoptosis, and autophagy in target tissues. During the fasting state, insulin secretion decreases so that tissues coordinate with counter-regulatory hormones, such as glucagon, favoring fatty acid oxidation and glycogenolysis and gluconeogenesis for supply of cellular ATP and maintenance of glucose homeostasis. The substrate preferences for metabolic adaptation, during the transit from postprandial state to fasting, are tightly controlled by the pancreatic hormones insulin and glucagon (Randle et al. 1963). This adaptive transition is dominantly controlled by insulin, which is blunted in the target tissues during insulin resistance preceding the development of type 2 diabetes (Johnson and Olefsky 2013).

The actions of insulin are mediated by insulin signaling cascades. The most important components in the insulin signaling cascades have been identified over the past decades, including the insulin receptor (IR), insulin receptor substrate proteins (IRS), PI3-K, Akt, and *the forkhead/winged-helix* transcription factor Foxo1 (Kasuga et al. 1983; White et al. 1985; Guo et al. 1999, 2009; Guo 2014a, b).

2.1 Insulin Receptor and Insulin Receptor Substrates 1 and 2

Insulin signaling is triggered by insulin binding to the α-subunit of insulin receptor on the cell membrane, resulting in dimerization to the β-subunit of the receptor and forming the $\alpha_2\beta_2$ complex and subsequent autophosphorylation of a number of tyrosine residues in the β-subunit of the insulin receptor. The insulin receptor, a protein tyrosine kinase, is then activated and recruits and phosphorylates several downstream substrates, including IRS1-4, Shc, Grb2-associated protein (Gab1), Dock1, Cbl, and APS adaptor proteins, all of which provide specific docking sites for recruiting further downstream signaling proteins, leading to activation of both Ras→MAP kinases and PI-3K→Akt signaling cascades (White 2003).

Activation of Ras→MAP kinases mediates the effect of insulin on mitogenesis and cellular growth; however, activation of PI3K generates phosphatidylinositol (3,4,5)-triphosphate (PIP3), a second messenger activating 3-phosphoinositide-dependent protein kinases 1 and 2 (PDK1 and PDK2), which mediate the effect of insulin on metabolism and pro-survival. PDK1 and PDK2, in turn, activate protein serine/threonine kinase Akt, formerly known as protein kinase B (PKB), by inducing phosphorylation at T^{308} and S^{473}, respectively. Both PDK1 and PDK2 are crucial for Akt activation for survival and metabolic regulation (Fig. 3).

2.2 PDK1 and TORC2 (PDK2)→ Akt→TORC1 Signaling Cascades

PDK1 phosphorylates the T^{308} of Akt, resulting in Akt activation and a profound effect on cellular survival and metabolism (Dong and Liu 2005). PDK2 is recognized as mTORC2 that interacts with rictor adaptor protein phosphorylating S^{473} of Akt, which is required for Akt full activation (Sarbassov et al. 2006). mTOR (mammalian target of rapamycin), including two distinct complexes called complex 1 (mTORC1) and complex 2 (mTORC2), is a highly conserved protein kinase that controls cell growth and metabolism in response to nutrients, growth factors, and energy status (Sengupta et al. 2010).

mTORC1 is rapamycin-sensitive raptor-mTOR and activated by RhebGTPase, via suppression of tuberous sclerosis protein 2 (TSC2) following Akt activation (Sengupta et al. 2010). mTROC1 is distinct from mTORC2 and is not required for hepatic gluconeogenesis (Li et al. 2010); it has substrates ribosomal protein S6 kinase (S6K) and eukaryotic initiation factor 4E-binding protein (4E-BP), both of which control protein synthesis; it also promotes lipogenesis via phosphorylating a phosphatidic acid phosphatase lipin 1, and nuclear translocation of lipin

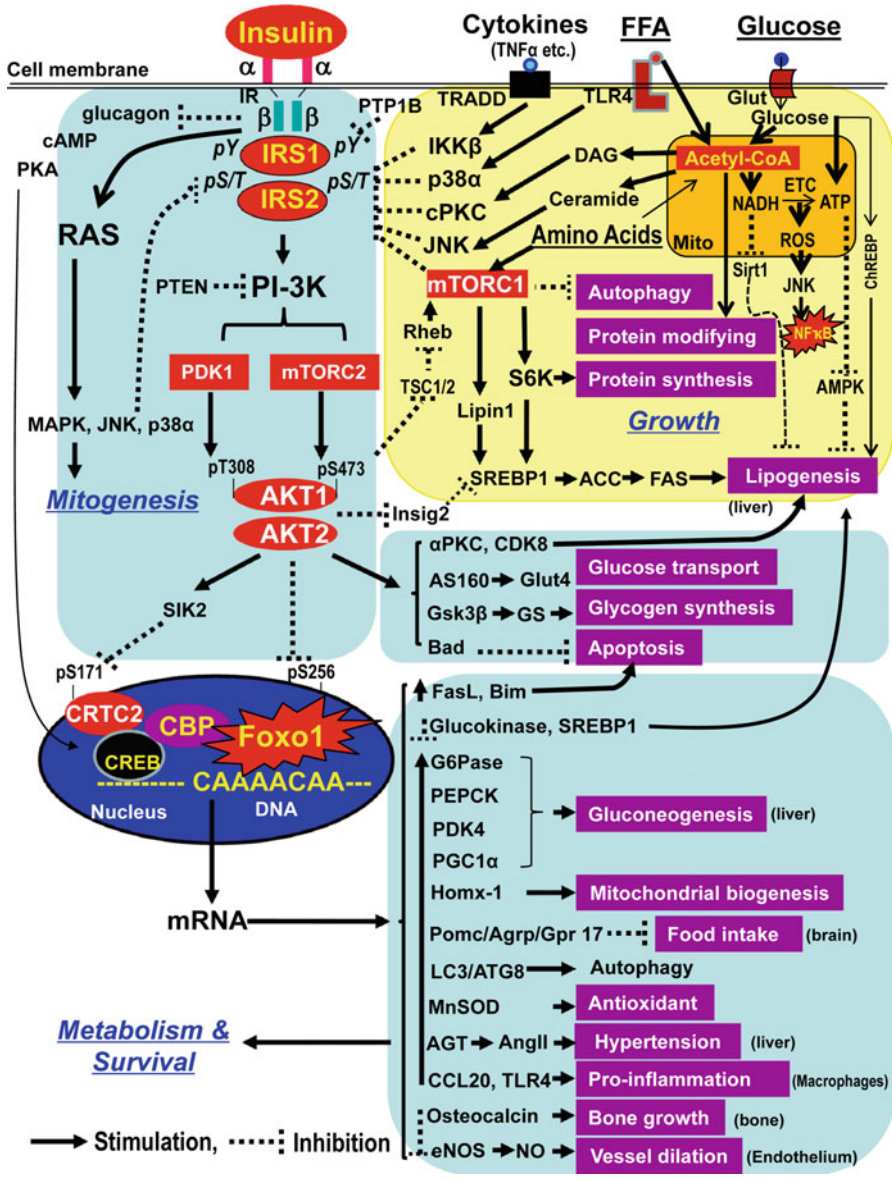

Fig. 3 IRS1, 2-centered mechanisms for insulin resistance in obesity. Insulin signaling cascade and interaction with intracellular signaling components from nutrients and cytokines in control of cellular metabolism, including synthesis of glucose, glycogen, lipids and proteins, as well as other biological responses, such as autophagy, apoptosis, mitochondrial biogenesis, food intake, anti-oxidant, calcium handling, bone growth, vascular dilation, and hypertension. Abbreviation: *IR* insulin receptor, *IRS* insulin receptor substrate, *PI3K* phosphatidylinositol (PI)-3-kinase, *PDK* phosphoinositide-dependent protein kinase, *CREB* cAMP response element binding protein, *CBP* CREB binding protein, *CRTC2* CREB regulated co-factor 2, *SIK2* salt-induced protein kinase 2, *Foxo1* forkhead/winged helix transcription factor O-class member 1, *JNK* c-Jun terminal end protein kinase, *DAG* diacylglycerol, *SREBP1* sterol response element binding protein 1, *Insig2* insulin induced gene 2, *S6K* ribosome protein p70 S6 kinase, *GSK3* glycogen synthase kinase-3, *GS* glycogen synthase, *mTORC* mammalian target of rapamycin complex, *TSC1/2* tuberous sclerosis complex 1/2, *aPKC* atypical protein kinase C, *AS160* Akt substrate 160kD protein, *PDK4* pyruvate dehydrogenase kinase-4, *ACC* acetyl-CoA carboxylase, *PEPCK* phosphoenolpyruvate carboxykinase, *G-6-Pase* glucose-6-phosphatase, *FAS* fatty acid synthase, *MnSOD* manganese superoxide dismutase, *TLR* toll-like receptor, *FFA* free fatty acids, *ChREBP* carbohydrate responsive element binding

1 stimulates sterol regulatory element-binding protein 1 (SREBP1) gene expression and lipogenesis (Li et al. 2010; Peterson et al. 2011; Owen et al. 2012); additionally, it is also activated by nutrients, such as amino acids, suppressing cellular autophagy. Autophagy is a basic catabolic mechanism that involves cell degradation of unnecessary or dysfunctional cellular components through lysosomal machinery and expression of a number of autophagy genes (Klionsky 2007). The breakdown of cellular components ensures cellular survival during starvation by maintaining cellular energy levels (Liu et al. 2009a). Thus, mTORC1 serves as a sensor and mediator for the action of both hormones and nutrients in cells.

mTROC2 phosphorylates and activates Akt and other protein kinases, such as PKC, controlling cell survival and energy homeostasis (Sarbassov et al. 2006; Hagiwara et al. 2012). mTROC2, through Akt, promotes expression and activation of the SREBP1 that promote lipid and cholesterol synthesis (Yecies et al. 2011). Moreover, mTORC2 (PDK2) and PDK1 suppress the forkhead transcription factor Foxo1 that promotes gluconeogenesis, mediating the effect of insulin on suppressing hepatic glucose production (Hagiwara et al. 2012) (Fig. 3).

2.3 Targets of Akt in Metabolic Control

Akt phosphorylates a number of downstream targets, including inhibitors of macromolecular synthesis as follows:

1. It phosphorylates and inhibits glycogen synthase kinase-3β (Gsk3β), which in turn dephosphorylates and activates glycogen synthase (GS) promoting glycogen synthesis.
2. It inhibits TSC2, thereby activating Rheb, a small GTPase, for mTORC1 and S6K activation that stimulate protein synthesis (Inoki et al. 2002).
3. It phosphorylates AS160 for Rab10GTPase activation and Glut4 translocation for glucose transport.
4. It phosphorylates Bad for inhibition of apoptosis.
5. It phosphorylates phosphodiesterase 3B (PDE3B) for induction of cAMP degradation.
6. It phosphorylates salt-induced kinase 2 (SIK2) that inhibits gluconeogenesis, by suppressing cAMP response element-binding protein (CREB)-regulated transcription coactivator 2 (CRTC2), a CREB coactivator that increases hepatic gluconeogenesis (Wang et al. 2010).
7. Akt regulates metabolism and survival by controlling expression of a number of genes through transcription factors, such as SREBP1c and Foxo1.

Akt phosphorylates and stimulates SREBP1c, promoting lipogenetic gene expression through suppression of insig2, a protein of the endoplasmic reticulum that blocks processing of SREBP1c activation, by binding to SCAP (SREBP cleavage-activating protein) and preventing it from escorting SREBPs to the Golgi (Yabe et al. 2002). By contrast, Akt phosphorylates Foxo1 at S^{256} and inhibits Foxo1 transcriptional activity, suppressing hepatic glucose production in the liver and promoting cell survival in the heart (Guo et al. 1999; Zhang et al. 2012; Matsumoto et al. 2007; Hannenhalli et al. 2006; Battiprolu et al. 2012; Evans-Anderson et al. 2008). Many

Fig. 3 (continued) protein, *AMPK* AMP-dependent protein kinase, *pY* phosphorylated tyrosine, *TNFα* tumor necrosis factor α, *pS/T* phosphorylated serine or threonine, *Pomc* pro-opiomelanocortin, *Agrp* Agouti-related peptide, *Serca2A* sarco/endoplasmic reticulum Ca^{2+}-ATPase, *PGC1α* peroxisome proliferator-activated receptor gamma coactivator 1-alpha, *Homx-1* heme oxygenase 1, *ATG8* autophagy regulated gene 8, *LC3* microtubule-associated protein 1A/1B-light chain 3, *eNOS* endothelial nitric oxide synthase, *Glut* glucose transporter, *AGT* Angiotensinogen, *AngII* Angiotensin II. Adapted and modified from Guo S: Insulin signaling, resistance, and the metabolic syndrome: Insights from mouse models into disease mechanisms. J Endocrinology 2014; 220:T1–T23

of these phosphorylation events are indicators of insulin signaling, and Akt→Foxo1 phosphorylations serve as powerful indicators for insulin sensitivity on metabolic regulation (Guo et al. 2006, 2009; Gonzalez et al. 2011; Qi et al. 2013) (Fig. 3).

2.4 The Forkhead Transcription Factor Foxo1

Foxo1, a member of the O-class of *forkhead/winged-helix* transcription factors (Foxo), was first identified as an Akt substrate in insulin signaling (Guo et al. 1999; Rena et al. 1999). Insulin suppresses gene expression, such as insulin-like growth factor-binding protein-1 (IGFBP-1), through a conserved insulin response element (IRE: CAAAACAA), located on the target gene promoter region (Guo et al. 1999). A similar sequence is present in the promoter regions of a number of genes, including phosphoenolpyruvate carboxykinase (Pepck) and glucose-6-phosphatase (G6pc), two rate-limiting enzymes for gluconeogenesis in hepatocytes (Schmoll et al. 2000; Yeagley et al. 2001). Mice lacking hepatic Foxo1 exhibited lower level of hepatic glucose production and blood glucose (Zhang et al. 2012; Matsumoto et al. 2007). Thus, Foxo1 has been identified as a trans-acting factor for the cis-acting element IRE, serving as an endogenous mediator for insulin suppression on gluconeogenesis and hepatic glucose production (Guo et al. 1999; Zhang et al. 2012).

Foxo1 has three Akt phosphorylation sites at T^{24}, S^{256}, and S^{319} (Rena et al. 1999), which are phosphorylated and inhibited by insulin in a PI3K-dependent manner (Rena et al. 1999). Phosphorylation of these residues by PI3K/Akt activation promotes Foxo1 nuclear export and cytoplasmic accumulation and interaction with Skp2, a subunit of the Skip1/Cul1/-F-box protein, promoting Foxo1 ubiquitination and degradation and hence impairing Foxo1-mediated gene transcription (Matsuzaki et al. 2003; Rena et al. 2001; Huang et al. 2005). This provides a molecular link by which insulin integrates cell surface insulin receptor signaling into the nuclear gene transcriptional programming via Foxo1, targeting a number of genes in control a variety of physiological functions, such as hepatic glucose production and cell apoptosis (Guo et al. 1999) (Fig. 3).

Other members of O-class of forkhead family include Foxo3, Foxo4, and Foxo6, sharing the conserved Akt phosphorylation motif RXRXXS/T (R, arginine; X, any amino acid; and S/T, Akt phosphorylation site of serine or threonine) (Guo 2014b). Foxo1 null mice exhibited incompletion of embryonic angiogenesis and embryonic lethality. Foxo3 or Foxo4 knockout mice survived beyond parturition (Hosaka et al. 2004). Thus, each of Foxo members has distinct roles in regulating physiological functions, the mechanisms of which are incompletely understood. Regardless, inhibiting Foxo transcription factors may mediate many effects of insulin on metabolism and survival control (Fig. 3).

3 Insulin Resistance: Molecular Mechanisms

3.1 Suppression of IRS and Associated PI3K Inactivation in Metabolism and Survival Control During Insulin Resistance

Insulin resistance is defined as an impaired response to the physiological effect of insulin, including glucose, lipid, and protein metabolism. A breakthrough discovery achieved recently is that IRS1 and IRS2 are tightly associated with PI3K and Akt activation and minimally with MAP kinase activity. Deficiency of IRS1 and IRS2 causes selective PI3K inactivation but sustains MAP kinase activation. Liver-specific inactivation of IRS1 and IRS2 genes in mice (L-DKO mice) promotes hyperglycemia and T2DM, while heart-specific inactivation of IRS1 and IRS2 in mice (H-DKO mice) promotes heart failure and animal death (Guo et al. 2009; Qi et al. 2013; Dong et al. 2008). These studies underscore the roles of IRS1 and IRS2 in control of endogenous PI3K and Akt activities, governing energy

metabolism and organ survival. The biased or selective PI3K inactivation and MAPK activation are also observed in tissues of animals with insulin resistance and T2DM (Jiang et al. 1999). Thus, the IRS signaling couples to PI3K/Akt activation, providing a fundamental mechanism for insulin signaling in control of metabolism and survival. However, a resistance to this branch of insulin signaling has crucial roles in disease development and eventually organ failure. In support of this concept, mice lacking either PI3K catalytic subunit or Akt2 exhibited insulin resistance and type 2 diabetes (Brachmann et al. 2005), while mice lacking Gab1, which is an ERK activator, enhanced insulin sensitivity with elevated hepatic Akt activity (Bard-Chapeau et al. 2005).

3.2 Central Roles of Foxo1 Activation Following PI3K→Akt Inactivation in Insulin Resistance

Upon PI3K inactivation during insulin resistance, many PI3K downstream targets are not under control. A failure of Akt activation promotes metabolic dysfunction and disease development when PI3K activity is lost. Several lines of evidence demonstrated that PI3K or Akt inactivation causes diabetes, organ failure, or animal death. Inactivation of PI3K, PDK1, mTORC2, or both Akt1 and Akt2 in mouse liver is sufficient for induction of hyperglycemia, hyperinsulinemia, and hypolipidemia (Hagiwara et al. 2012; Mora et al. 2005; Miyake et al. 2002; Lu et al. 2012), and mutation in Akt2 gene has been found in patients with T2DM (George et al. 2004).

Upon Akt inactivation following PI3K inactivation, a failure to suppress Foxo1 or Foxo1 activation may have a central role in disease development and organ failure. Foxo1 is suppressed by insulin through Akt-activated serine/threonine phosphorylation, while Akt inactivation promotes Foxo1 stability and functionality during insulin resistance and T2DM. Liver-specific Foxo1 deletion in mice with T2DM, such as db/db mice, prevented diabetes and mitochondrial dysfunction, and heart-specific Foxo1 deletion in db/db mice prevented cardiac dysfunction (Zhang et al. 2012; Battiprolu et al. 2012; Lu et al. 2012; Qi et al. 2015). By contrast, overexpression of a constitutively active form of Foxo1 where the three Akt phosphorylation sites were mutated to alanine blocking insulin suppression, in the liver caused insulin resistance and in the heart resulted in embryonic heart failure in mice, respectively (Evans-Anderson et al. 2008; Zhang et al. 2002). Collectively, these data suggest that Foxo1 activation is sufficient and necessary for induction of insulin resistance and organ failure.

3.3 Foxo1 Promotes Hepatic Glucose Production, Apoptosis, Mitochondrial Degeneration, and Inflammation During Insulin Resistance

Foxo1 controls expression of a number of genes that govern cellular metabolism and survival. First, as mentioned above, Foxo1 promotes hepatic glucose production via enhancing expression of genes encoding gluconeogenic enzymes (Zhang et al. 2006, 2012). Second, Foxo1 promotes cell apoptosis by stimulating Bim gene expression, as well as mediates the effect of TNFα on promotion of cell death (Alikhani et al. 2005). Third, Foxo1 promotes mitochondrial degeneration. We recently demonstrated that Foxo1 stimulates gene expression of hemeoxygenase-1 (Hmox-1), an enzyme catalyzing degradation of heme to produce biliverdin, iron, and carbon monoxide. Heme is a component of the mitochondrial electron transport chain complexes III and IV; hence, Foxo1 activation promotes heme degradation and then impairs mitochondrial biosynthesis and function reducing fatty acid oxidation and ATP synthesis, as observed in the liver db/db mice (Qi et al. 2013; Cheng et al. 2009). Fourth, Foxo1 promotes gene expression of angiotensinogen, which is the precursor of angiotensin II (AngII), a bioactive peptide that promotes renin-angiotensin system elevating the blood pressure (Qi et al. 2014). Recently, it is shown that Foxo1 promotes toll-like receptor 4 (TLR4) gene expression accelerating the

inflammatory response in microphages of the liver (Fan et al. 2010) and stimulates expression of chemokine ligand 20 (CCL20) in hepatocytes inducing fatty liver (Miao et al. 2012).

4 A Unification of Insulin Resistance at the IRS Level

Insulin resistance occurs at multiple levels in cells, from the cell surface membrane to the nucleus, including insulin receptor desensitization, suppression of IRS protein and functionality, inhibition of PI3K cascades, and failure to restrain Foxo1-activated gene transcriptional profiling. Given that PI3K→Akt signaling serves as a common platform for multiple hormone and growth factor signaling cascades (Sussman et al. 2011), IRS1 and IRS2 are recently identified as the major mediators activating endogenous PI3K→Akt signaling cascade (Guo et al. 2009; Qi et al. 2013). Normal expression and functionality of IRS that couples to PI3K and Akt signaling pathway are essential for maintenance of nutrient homeostasis and organ survival. Thus, understanding the mechanisms that regulate IRS gene expression and functionality would be a key to decipher the mechanism of insulin resistance.

IRS proteins have about 20 tyrosine residues, and tyrosine phosphorylation of these residues is required for insulin signaling in activating PI3K and Akt. On the other hand, IRS proteins also have about 40 serine/threonine residues, and their phosphorylation can suppress insulin signaling for inactivation of PI3K/Akt, since IRS serine/threonine phosphorylation links to IRS protein ubiquitination and degradation. A number of intracellular protein kinases, including p38α, JNK, mTOR, IKKβ, and protein kinase Cθ (PKCθ), stimulate IRS serine/threonine phosphorylation coupling with IRS degradation and inhibiting IRS-associated PI3K/Akt activity following overnutrition, such as high-fat diet (HFD) feeding (Guo 2014b; Qi et al. 2013; Copps and White 2012; Sun and Liu 2009). Therefore, investigating how IRS gene expression is regulated by environmental factors provides us novel insights into understanding the molecular mechanism of insulin resistance (Fig. 3).

5 Etiology of Insulin Resistance in Obesity

Insulin is the most important hormone controlling glucose and lipid homeostasis in the body. In adipose tissue, insulin promotes fat cell differentiation, enhances adipocyte glucose uptake, but inhibits lipolysis, a breakdown of lipid involving hydrolysis of triglycerides into glycerol and free fatty acids. Mice lacking insulin receptor or its downstream protein kinase mTORC2 in adipocytes exhibited hyperglycemia, hyperinsulinemia, and a failure to suppress lipolysis in response to insulin, resulting in hyperlipidemia, fatty liver, and insulin resistance (Kumar et al. 2010; Boucher and Kahn 2013). These data suggest that when insulin action fails in the adipose tissue, adipocyte development is retarded and free fatty acids and carbohydrate unable to synthesize triglycerides for storage, and then fatty acids spill over into the blood circulation and infiltrate into the liver and muscle, resulting in hyperlipidemia and fatty organs. These studies significantly underscore the contribution of insulin resistance in the adipose tissue, via mTORC2→Akt inactivation.

Apart from the energy storage, adipose tissue is also a prolific endocrine organ that can secrete a number of cytokines, called adipokines, such as TNFα, IL6, leptin, angiotensinogen, and adiponectin, influencing the whole body insulin sensitivity. Upon the development of fat expansion and obesity, excess adipokines and fatty acid release into the bloodstream and infiltration of adipokines and fatty acids into many individual tissues triggering metabolic inflammation and insulin resistance (Fig. 2).

5.1 Lipid Toxicity and Insulin Resistance

Following overnutrition, excess energy intake will likely exceed energy expenditure in the body, resulting in excess energy storage in the fat as lipids. The lipid and its signaling might be the primary factors triggering cellular malfunction to initiate insulin resistance in the adipose tissue

first and extend to other tissues simultaneously. The following evidence supports excess lipid and signaling exert toxic functions in cells impairing intracellular signaling to tackle the insulin action:

1. Excess lipid generates excess supply of ATP and nicotinamide adenine dinucleotide (NADH) through the fatty acid oxidation process in the mitochondria, resulting in suppression of AMP-activated protein kinase (AMPK) and Sirt1 that inhibit lipogenesis and lipid accumulation in cells (Fig. 3). AMPK, an energy sensor to energy deprivation, promotes fatty acid oxidation. Sirt1, a NAD^+-activated protein deacetylase that is suppressed by NADH, deacetylates a number of proteins suppressing lipogenesis and increasing insulin sensitivity (Li et al. 2011).
2. Excess NADH promotes mitochondrial oxidative phosphorylation, enhancing generation of reactive oxygen species (ROS). ROS promotes oxidative stress and JNK-mediated NFκ-B activation that enhances PTP1B expression antagonizing PI3K activity and promoting cell death (Panzhinskiy et al. 2013). Thus, both lipid and glucose toxicity can merge and share similar mechanisms by activating oxidative stress and cell damage from excess fuel substrate and mitochondrial activity (Fig. 3).
3. Saturated fatty acids induce cell apoptosis and suppress IRS signaling, resulting in Akt inactivation. One mechanism of lipid-induced toxicity is through activating TNF-related apoptosis-inducing ligand (TRAIL) and death receptor signaling cascade, in which JNK is required for induction of cell death (Malhi et al. 2007; Cazanave et al. 2009; Idrissova et al. 2014). Another mechanism of lipotoxicity is through suppression of IRS protein and associated inactivation of PI3K and Akt. An acute lipid infusion or chronic high-fat diet induces insulin resistance in mice, via activation of protein kinase C that attenuates IRS signaling, limiting glucose oxidation and utilization in target tissues (Griffin et al. 1999). In hepatocytes and pancreatic β-cells, saturated free fatty acid palmitate induces apoptosis by activating JNK, PKC, and oxidative stress (Malhi et al. 2006; Wrede et al. 2002; Wong et al. 2009; Galbo et al. 2013). Lipid intermediate diacylglycerol (DAG) and ceramide are potent activators for PKCθ and JNK, respectively, inducing IRS serine/threonine phosphorylation and insulin resistance (Holzer et al. 2011; Oh et al. 2010). Ceramide can directly enhance protein phosphatase 2A activity that suppresses Akt activation resulting in Foxo1 activation and induction of cell apoptosis (Yan et al. 2008). Clinically, lipid accumulation in hepatocytes or fatty liver is a high risk factor not only for insulin resistance but also for nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and liver cancer (Kumashiro et al. 2011).

5.2 Chronic Inflammation and Insulin Resistance

A current prevailing concept on lipotoxicity is that excess saturated fatty acids trigger chronic inflammation, and obesity is regarded as low-grade and chronic inflammation state and promotes insulin resistance (Samuel and Shulman 2012). Lipid accumulation excessively in the fat or ectopically in the liver, muscle, heart, and blood vessels can trigger tissue inflammatory responses. Recent evidence demonstrated that saturated fatty acids bind to a liver-secreted glycoprotein fetuin A that interacts and activates toll-like receptor 4 (TLR4), resulting in NFκB activation (Pal et al. 2012), JNK activation in microphages, and insulin resistance by inducing PTP-1B (Panzhinskiy et al. 2013; Holzer et al. 2011). Recruitment of macrophages and other immune cells, including M1 microphages that promote inflammation and neutrophil, $CD8^+$ killer T cells, and B cells, is increased in the adipose tissue and liver of HFD and ob/ob mice, while that of anti-inflammatory M2 microphages reduced (Glass and Olefsky 2012). By contrast, unsaturated fatty acids do not inhibit insulin sensitivity by interacting with the G-protein-coupled receptor GRP120, thereby inhibiting cellular inflammation and increasing insulin sensitivity (Ichimura et al. 2012).

Apart from that saturated fatty acids inhibit IRS signaling and PI3K/Akt activation, the recruitment of microphages and immune cells in tissues promotes the generation of cytokines that also suppress the IRS-associated PI3K/Akt signaling. Fat expansion in obesity promotes synthesis and secretion of adipokines in adipocytes, disrupting a proper balance of adipokine generation and promoting inflammation (Fig. 2). In obese conditions, pro-inflammatory factors, such as TNFα, IL-6, angiotensinogen, and leptin, are markedly increased (Hotamisligil and Erbay 2008; Yiannikouris et al. 2012), while the anti-inflammatory factor adiponectin is reduced (Romeo et al. 2012). Adiponectin, which is expressed specifically in adipocytes and its expression suppressed by TNFα, enhances insulin sensitivity by stimulating IRS1 and IRS2 binding to the insulin receptor, via intracellular adaptor protein APPL1 (Ryu et al. 2014). In addition to reducing gene expression of adiponectin, TNFα also activates JNK, resulting in IRS degradation and insulin resistance (Gao et al. 2002; Zhang et al. 2008a). Moreover, overexpression of IKKβ, a key mediator of TNFα, in mouse liver, is sufficient for suppressing IRS and inducing insulin resistance and type 2 diabetes (Cai et al. 2005). Accordingly, suppression of inflammation increases insulin sensitivity and improves metabolic dysfunction in T2DM (Hotamisligil et al. 1996).

However, the outcome of anti-inflammatory therapy in treating insulin resistance so far has been a challenge, and several concerns deserve a cautionary note:

1. Inflammation is involved in deploying and mobilizing immune cell leukocytes to defend against infections or toxins. Many inflammatory actors, such as TNFα, reduce body weight and increase energy expenditure (Ye and McGuinness 2013). Overexpression of IL6, in the liver, increased energy expenditure and insulin sensitivity in mice (Sadagurski et al. 2010).
2. During some physiological conditions such as exercise, inflammatory factors including TNFα and IL6 are secreted inhibiting anabolic metabolism (insulin action) and promoting catabolic metabolism (fat lipolysis) to meet fuel requirements, such as muscular contractility.
3. NFκB is essential for hepatocyte proliferation and survival. Mice lacking the p65 subunit of NFκB died of liver failure (Malato et al. 2012). Taken together, a balance between inflammation and anti-inflammation is required for proper insulin actions and nutrient homeostasis. Thus, correcting the imbalance of nutrients and inflammation may provide opportunities and challenges for prevention and treatment of insulin resistance, obesity, and T2DM.

5.3 Hyperinsulinemia and Insulin Resistance

Obesity is associated with abnormal hormone secretions, one of which is hyperinsulinemia occurring along with the development of obesity. It is likely that excess energy storage impairs insulin signaling gradually in the peripheral tissues, such as the fat, liver, and muscle, promoting pancreatic β-cells to increase insulin secretion and capacity to counteract the elevation of blood glucose. Therefore, hyperinsulinemia takes place preceding the onset of diabetes. Obese mice fed with HDF developed hyperinsulinemia prior to development of hyperglycemia with significant decreases in IRS2 protein expression in many tissues, including the liver and heart (Qi et al. 2013). Thus, hyperinsulinemia can have profound effects on inducing insulin resistance following obesity.

Chronic insulin treatment inhibits IRS2 gene transcription and promotes IRS2 ubiquitination in cells, including fibroblasts and hepatocytes (Guo et al. 2006; Zhang et al. 2001; Rui et al. 2001). mTORC1 activation following insulin stimulation is a pathway that can result in IRS2 ubiquitination, and mTORC1 inhibitor rapamycin completely prevented insulin or IGF-1-induced IRS2 degradation (Guo et al. 2006; Rui et al. 2001). Furthermore, deletion of mTORC1 downstream protein kinase S6K increased IRS1 and IRS2 gene expressions, improved insulin sensitivity, and prevented age- or diet-induced obesity in mice

(Um et al. 2004). Conversely, deletion of mTORC2 in mouse liver resulted in a diabetic phenotype, similar to the L-DKO mice (Guo et al. 2009; Hagiwara et al. 2012).

Prolonged insulin treatment also activates intracellular protein kinases suppressing IRS to prevent acute insulin signaling on Akt→Foxo1 phosphorylation and Glut4 membrane trafficking, as shown in myocardium and adipocytes (Gonzalez et al. 2011; Qi et al. 2013). The effect of hyperinsulinemic induction on insulin resistance was also observed in mice subjected to type 1 diabetes (Liu et al. 2009b). Given that p38 MAP kinase is a key mediator of TNFα promoting insulin resistance (Li et al. 2005) and that increased p38 MAPK activity and decreased IRS expression were found in tissues of animals and patients with hyperinsulinemia and T2DM (Qi et al. 2013; Kerouz et al. 1997; Rondinone et al. 1997), we expect that cytokine (TNFα)→p38α MAPK→IRS suppression has an important role in developing insulin resistance following obesity and inflammation (Qi et al. 2013).

There exist about 1100 protein kinases in mouse or human genome. It will be important to identify these kinases and activation mechanisms under different cellular and environmental conditions for induction of IRS serine/threonine phosphorylation, degradation, and insulin resistance. Of note, even under a physiological condition, a 50 % reduction in IRS2 protein was found in the liver during feeding, compared to the fasting condition (Ide et al. 2004). This observation suggests that tissues, such as the liver, are less sensitive to insulin during feeding than a fasting state since IRS2 expression decreases.

6 Clinic Perspectives of Insulin Resistance

6.1 Hapothalamic Insulin Resistance, Hyperphagia, and Obesity

Appetite is tightly controlled by insulin action through the central nervous system (CNS). The hypothalamus at the base of the forebrain is comprised of numerous small nuclei, each with distinct connections and neurochemistry, which regulate food intake, hormone release, circadian rhythms, and other biological functions (Myers and Olson 2012). A low dose of insulin injection to intracerebroventriculum decreased both food intake and hepatic glucose production, effects which were blocked by PI3K inhibitors (Woods et al. 1979; Obici et al. 2002). Combined with evidence from mice with neuron-specific insulin receptor deletion are obese and insulin resistant (Bruning et al. 2000), current data indicate that neuronal insulin signaling is required for both body weight control and glucose homeostasis.

The functional significance of brain insulin signaling is further evidenced by that deletion of IRS2 in the hypothalamus resulted in hyperglycemia and obesity in mice (Taguchi et al. 2007; Lin et al. 2004). Similar to the action of leptin, an adipocyte-derived hormone that inhibits food intake through the leptin receptor neurons in CNS activating the Jak2→Stat3 signaling cascade (Allison and Myers 2014; Myers and Olson 2012; Bates et al. 2003), brain insulin signaling reduced food intake by activation of PI3K via IRS2 and inactivation of Foxo1, which can be independent of the Jak2→Stat3 pathway (Taguchi et al. 2007). However, both leptin and insulin promoted IRS2 tyrosine phosphorylation and PI3K activation in the brain (Warne et al. 2011). IRS2 deletion in leptin receptor-expressing neurons caused diabetes and obesity, in which Foxo1 inactivation completely reversed the metabolic dysfunction (Sadagurski et al. 2012).

Hypothalamic neurons expressing agouti-regulated peptide (Agrp) stimulate food intake (orexigenic: appetite stimulant) during the fasting state. Foxo1 stimulates orexigenic Agrp expression, an effect reversed by leptin delivery, of which activation of Stat3 abrogates Foxo1 occupancy on the Agrp promoter region (Kitamura et al. 2006). Foxo1 deletion in Agrp neurons of mice resulted in reduced food intake, leanness, and decreased hepatic glucose production, involving suppression of a G-protein-coupled receptor Gpr17, a Foxo1 target gene in Agrp neurons (Ren et al. 2012). By antagonizing the effect of Agrp, hypothalamic neurons expressing pro-opiomelanocortin (Pomc) inhibit food intake during

feeding (anorexic: lack of appetite). Foxo1 deletion in Pomc neurons also resulted in reduced food intake and leanness, by increasing the obesity susceptibility gene, carboxypeptidase E (Cpe), and subsequent β-endorphin production that mediates anorexigenic effects in mice (Plum et al. 2009). Thus, Foxo1 activation in neurons likely promotes food intake and obesity.

High-fat diet induces hypothalamic inflammation for NFκB activation and ER stress that is necessary for diet-induced obesity (Zhang et al. 2008b). HFD also induces brain injury by losing POMC neurons in both rodents and humans (Thaler et al. 2012). However, Foxo1 inactivation in the ventromedial hypothalamus prevented HFD-induced obesity, improved glucose intolerance, and increased insulin sensitivity (Kim et al. 2012), suggesting that Foxo1 activation has key role in the brain resulting in insulin resistance and obesity.

6.2 Insulin Resistance and Retinopathy

Loss of IRS2 resulted in retinal degeneration and photoreceptor cellular dysfunction (Yi et al. 2005). IRS2 is mainly localized to the outer plexiform layer and photoreceptor inner segments. IRS2 is required for maturation and survival of photoreceptors in mouse retina immediately after birth because IRS2 null mice lost 10 % photoreceptors a week after birth and up to 50 % by 2 weeks of age due to increased apoptosis. Since apoptosis is the final common pathway in photoreceptor degeneration, pharmacological strategies that increase IRS2 expression or function in photoreceptor cells could be a general treatment for blindness, such as retinitis pigmentosa (Yi et al. 2005).

6.3 Pancreatic β-Cell failure and T2DM

β-Cell failure is essential for the development of hyperglycemia in type 1 diabetes; but β-cell failure is also present in type 2 diabetic patients (Rhodes 2005; Rhodes et al. 2013). The β-cells secrete insulin reducing blood glucose, and the α-cells secrete glucagon increasing the blood glucose level to meet bodily energy requirements and maintain glucose homeostasis. Recent studies showed that insulin enhances glucose-stimulated insulin secretion in healthy humans (Bouche et al. 2010), and insulin secretion in the β-cells was impaired in mice lacking the insulin receptor gene (Kulkarni et al. 1999). However, whether insulin has a direct autocrine action on β-cells in promoting insulin secretion is unclear (Rhodes et al. 2013).

Foxo1 inactivation by IRS signaling is required for β-cell survival and differentiation. IRS2 null mice resulted in Foxo1 activation and diabetes owing to the pancreatic β-cell failure (Withers et al. 1998). Genetic Foxo1 deletion in the IRS2 null mice prevented β-cell apoptosis and diabetes (Nakae et al. 2002). Conversely, Foxo1 activation following IRS2 inactivation in β-cells may promote β-cell regeneration or differentiation since deletion of IRS2 in β-cells triggered β-cell repopulation or regeneration, leading to a restoration of insulin secretion and resolution of diabetes in aged mice (Lin et al. 2004). Foxo1 inactivation in β-cells resulted in reduced β-cell mass, hyperglycemia, and hyperglucagonemia, probably owing to dedifferentiation of β-cells into progenitor-like cells or pancreatic α-cells (Talchai et al. 2012).

Glucagon receptor action in both T1DM and T2DM was markedly increased, and suppression of glucagon receptor reduced blood glucose and completely rescued diabetes (Lee et al. 2011; Sorensen et al. 2006; Liang et al. 2004; Ali and Drucker 2009). High levels of glucagon in HFD and db/db mice were found (Edgerton and Cherrington 2011). Thus, abnormality of the pancreatic hormones is critical for development of diabetes and correcting the imbalance of insulin in β-cells, and glucagon in α-cells may provide a potential strategy to prevent diabetes mellitus.

6.4 Hepatic Insulin Resistance, Hyperglycemia, and Dyslipidemia

Hepatic insulin signaling has key roles in control of whole body glucose and lipid homeostasis.

Deletion of either IRS1 or IRS2 in the liver barely impaired glucose homeostasis; but liver-specific deletion of both IRS1 and IRS2 in L-DKO mice resulted in unrestrained gluconeogenesis and hyperglycemia, with a reduction in hepatic lipogenesis and blood lipids (Guo et al. 2009). HFD suppressed IRS2 expression and functionality in the liver, as evidenced by that mice lacking hepatic IRS1 with HFD-treatment severely impaired hepatic IRS2 expression and tyrosine phosphorylation, and then mice developed severe diabetes (Guo et al. 2009).

Hepatic insulin defects further result in insulin resistance in other tissues. The L-DKO mice not only displayed an inhibition of hepatic insulin→Akt signaling but also blunted brain intracerebroventricular (ICV) insulin action on reducing hepatic glucose production (Guo et al. 2009). Moreover, L-DKO mice exhibited cardiac IRS1 and IRS2 suppression and cardiac dysfunction, probably secondary to hyperinsulinemia (Qi et al. 2013). Likewise, mice lacking hepatic insulin receptor displayed pro-atherogenic lipoprotein profiles with a reduction in high-density lipoprotein (HDL), cholesterol, or very low-density lipoprotein (VLDL) particles and developed severe hypercholesterolemia, within 12 weeks of being placed on an atherogenic diet (Biddinger et al. 2008). These data suggest that hepatic insulin resistance is sufficient to produce hyperinsulinemia, dyslipidemia, and increased risk of cardiovascular dysfunction.

6.5 Cardiac Insulin Resistance and Heart Failure

The heart is an insulin-responsive and energy-consuming organ that requires a constant fuel supply to maintain intracellular ATP for myocardial contraction. Deletion of IRS1 and IRS2 genes in the heart diminished cardiac Akt and Foxo1 phosphorylation and resulted in heart failure and death of male mice, in which Foxo1 activation promoted cardiac dysfunction and heart failure (Qi et al. 2013, 2015). Foxo1 overexpression in the heart of mice caused heart failure and embryonic death (Evans-Anderson et al. 2008), and an increase of Foxo1 expression was found in the failing human hearts (Hannenhalli et al. 2006). In the hearts of obese animals, p38α MAPK activation following hyperinsulinemia contributes to IRS1 and IRS2 degradation (Qi et al. 2013). Thus, sensitizing myocardial IRS→Akt→Foxo1 signaling may provide new treatment modality for heart failure, during insulin resistance, obesity, and T2DM (Guo 2014b; Qi et al. 2013).

6.6 Insulin Resistance in Skeletal Muscle and Longevity

Skeletal muscle is an important fuel storage tissue in response to insulin, increasing glucose uptake and converting carbohydrates to glycogen, protein, and triglycerides. Skeletal muscle has remarkable metabolic flexibility to consume and store macromolecules. Muscle-specific insulin receptor deletion resulted in hyperlipidemia, with normal blood glucose, serum insulin, and glucose tolerance. Thus, insulin resistance in muscle may largely associate with an alteration in lipid metabolism (Bruning et al. 1998). Moreover, it was recently demonstrated that mice lacking mTORC2 in muscle exhibited decreased insulin-stimulated phosphorylation of Akt-S^{473} and glucose uptake and mild glucose intolerance (Kumar et al. 2008). Mice lacking both IRS1 and IRS2 in skeletal and cardiac muscle died at 3 weeks of age, with a much shorter life span than mice lacking both IRS1 and IRS2 in cardiac muscle in H-DKO mice, the latter which died of heart failure at 7 weeks of age, in company with hyperlipidemia (Qi et al. 2013), suggesting deletion of IRS1 and IRS2 in skeletal muscle shortened life span and muscular inactivation of mTORC1 may play a role in the longevity control since mice lacking mTRORC1 in skeletal muscle not only developed dystrophic muscle with mild glucose intolerance but also shortened life span (Bentzinger et al. 2008). Collectively, insulin action in skeletal muscle has an unrecognized role of longevity control by which muscular IRS→mTORC1 signaling cascade involves. Currently, muscles are regarded as active organs that secrete hormones (myokines), such as irisin, a hormone in skeletal muscle

systemically regulating glucose homeostasis and obesity (Bostrom et al. 2012). Cardiac muscle also can regulate systemic energy homeostasis through miR-208a, a heart-specific microRNA, controlling MED13, a subunit of the mediator complex which modulates gene transcription of nuclear hormone receptors. Genetic deletion of MED13 in the heart of mice enhanced HFD-induced obesity and systemic insulin resistance (Grueter et al. 2012). Thus, it would be of interest to identifying muscle-derived mediators and related mechanisms in control of longevity, systemic insulin resistance, and obesity in animals and humans.

6.7 Vascular Insulin Resistance and Endothelial Dysfunction

Insulin signaling in the vascular system of obese Zucker rats also documented a selective suppression of PI3K, rather than MAP kinase compared to lean rats (Jiang et al. 1999). In the aorta of obese rats, insulin-stimulated tyrosine phosphorylation of IRS1 and IRS2 and IRS-associated PI3K/Akt activities were significantly decreased, even though MAPK activity was equal or higher.

Insulin resistance in vascular endothelium stimulates vasoconstriction and promotes hypertension and atherosclerosis. Vasodilator actions of insulin are mediated by PI3K-dependent signaling pathways stimulating expression of nitric oxide (NO) gene in endothelium (Xu and Zou 2009). Inactivation of insulin receptor in endothelium diminished insulin-induced eNOS phosphorylation and blunted aortic vasorelaxant responses to acetylcholine and calcium ionophore in normal mice (Duncan et al. 2008) and accelerated atherosclerosis in apolipoprotein-E null mice (Rask-Madsen et al. 2010). Endothelium-specific deletion of IRS2 resulted in reduction in endothelial Akt activity and eNOS phosphorylation (Kubota et al. 2011).

Foxo activation following loss of IRS2 may play a key role in stimulating endothelial dysfunction. In HFD mice or low-density lipoprotein receptor (LDLR) null mice, deletion of Foxo1, Foxo3, and Foxo4 in endothelium enhanced eNOS phosphorylation and NO production, reduced inflammation and oxidative stress in endothelial cells, and hence prevented atherosclerosis (Tsuchiya et al. 2012). Clinical and epidemiological studies also support that decreased PI3K and Akt activities following insulin resistance are linked to a reduction in NO, exacerbating endothelial dysfunction and atherothrombosis (Samad and Ruf 2013).

6.8 Insulin Resistance and Renal Failure

The prevalence of nephropathy or chronic kidney disease (CKD) is increasing, and the epidemic of obesity is one of the causes. Obesity induces hypertension, causing vasoconstriction and salt and water retention and accelerating CKD. Moreover, obesity damages the kidney by recruiting immunologic cells to trigger intra-renal inflammation (Prasad 2014).

Possible mechanisms for renal injury include insulin resistance, oxidative stress, increased pro-inflammatory cytokine production, profibrotic factor production, and microvascular injury and renal ischemia (Prasad 2014). Insulin resistance is associated with CKD, including reduced glomerular filtration rate, proteinuria, and histopathological markers, such as tubular atrophy and interstitial fibrosis. Although the relationship between insulin resistance and CKD is complex and bidirectional, CKD is viewed as a common progressive illness along the development of obesity and insulin resistance significantly intervenes. A decrease in PI3K activity appeared critical in the pathophysiology of CKD, and lipotoxicity from intra-renal accumulation of lipid moieties has recently emerged to CKD-associated insulin resistance through impairing insulin signaling (Prasad 2014).

6.9 Imbalanced Sex Hormones and Infertility in Obesity

Sex hormones are synthesized by fatty acid-derived cholesterol. Caloric restriction, a

catabolic state, and even short-term caloric deprivation can impair fertility in mammals. However, obesity is also associated with infertility. The db/db mice exhibit infertility, which may involve in suppression of IRS2 in the brain (Mauvais-Jarvis et al. 2013). IRS2 null mice increased food intake and obesity and elevated levels of leptin. Female mice lacking IRS2 exhibited small and anovulatory ovaries with reduced numbers of follicles; low levels of plasma concentrations of luteinizing hormone, prolactin, and sex steroids; and small size of pituitaries with reduced numbers of gonadotrophs. Thus, insulin, together with other neuropeptides, such as leptin, may modulate hypothalamic control not only on the appetite but also on the reproductive endocrinology (Burks et al. 2000).

Obesity is also associated with polycystic ovary syndrome (PCOS), linking to infertility (Diamanti-Kandarakis and Dunaif 2012). In humans, PCOS is an important metabolic and reproductive disorder conferring severe insulin resistance and high levels of androgen (Diamanti-Kandarakis and Dunaif 2012). The poorly understood PCOS serine kinase may involve in IRS suppression inhibiting metabolism but increasing mitogenesis (Diamanti-Kandarakis and Dunaif 2012). Distinct from androgen, estrogen is known to prevent insulin resistance, obesity, and T2DM in female, probably owing to activating PI3K and Akt in an IRS-independent pathway in some tissues (Mauvais-Jarvis et al. 2013). Obviously, dysregulation of sex hormones has important role in control of both metabolism and fertility.

6.10 Insulin Resistance and Cancer

Growing epidemiological and clinical evidence implicates insulin resistance to the cancer risk. Obesity has accounted for 14–20 % of cancer deaths, including breast, colorectal, and endometrial cancers in the USA (Calle et al. 2003). The mechanism by which insulin resistance increases cancer risk is yet to be fully understood (O'Neill and O'Driscoll 2015). In insulin resistant patients, hyperinsulinemia activates Ras→MAP kinase pathways promoting cell mitosis that may involve tumor development in the obese individuals. Moreover, free fatty acids and excess mitochondrial activities promote ROS production in obesity. Overproduction of ROS caused DNA mutagenesis and carcinogenesis (Goodwin and Stambolic 2014). Thus, hyperinsulinemia, selective intracellular RAS→MAPK activation, and ROS overproduction in obese individuals apparently have important roles in promoting cellular proliferation, tumor initiation, and progression (Goodwin and Stambolic 2014).

6.11 Hyperlipidemia

Insulin inhibits hepatic glucose production while stimulates lipid synthesis. Liver-specific deletion of insulin receptor or both IRS1 and IRS2 in mice resulted in hyperglycemia, hyperinsulinemia, and hypolipidemia (Guo et al. 2009; Michael et al. 2000). Many patients with the metabolic syndrome and T2DM exhibit hyperglycemia, hyperinsulinemia, and hyperlipidemia (Brown and Goldstein 2008), indicating a paradox in lipid profiles versus mice with hepatic insulin resistance.

A challenging question is whether disease mouse models created by genetic engineering approaches reasonably reflect clinical lipid features of metabolic syndrome. Given that IRS→PI3K→PDK1/2→Akt→Foxo1 branch of insulin signaling pathway has a central role in control of glucose homeostasis and organ survival, suppression of this branch signaling cascade not only results in unchecked hepatic glucose production and hyperglycemia but also limits the hepatic TORC2→Akt signaling for promotion of lipogenesis, resulting in hypolipidemia.

Alternatively, other insulin-independent or selectively insulin-stimulated pathways that promote lipogenesis may remain active in the liver and other organs following obesity. For example, carbohydrate-activated lipogenic gene expression profiles, via carbohydrate-responsive element-binding protein (ChREBP) and AMPK, facilitate

progression of lipogenesis in hepatocytes upon excess glucose upload (Fig. 3). Moreover, HFD also promoted hepatic oxidative stress, which oxidized and inactivated protein tyrosine phosphatase N2 to promote lipogenesis and hepatic steatosis, and selectively enhanced insulin-stimulated STAT5 signaling that promotes hepatic IGF-1 production, which couples suppression of pituitary growth hormone release, thereby promoting fatty liver, insulin resistance, and obesity (Gurzov et al. 2014). Identifying these and other novel mediators in control of lipid homeostasis is important to understand disease mechanisms and develop interventions treating insulin resistance, obesity, and dyslipidemia.

7 Is Insulin Resistance Always Bad?

Theoretically, insulin resistance is regarded as a mechanism promoting the disease development. However, under physiological conditions, insulin triggers phosphorylation of Akt and Foxo1 within a short period of time, and then the phosphorylation diminished rapidly or slowly, suggesting that insulin signaling will have to be attenuated or terminated in target cells, which allow other catabolic mechanisms suppressed by insulin begin to work. This is essential for cells to adapt from insulin to other counter hormone signals promoting energy utilization. Thus, cells would have an adaptive insulin inhibition mechanism in order to release energy meeting demands for metabolism and growth.

Similarly, Foxo1 activation has beneficial effects under certain conditions. During the fasting state with less amount of insulin, Foxo1 stimulates gluconeogenesis gene for hepatic glucose production to maintain glucose homeostasis. Moreover, Foxo1 stimulates expression of MnSOD and catalase and enhances antioxidant responses to protect cells from apoptosis. In rodents, Foxo1 activation following IRS2 deficiency, in the brain, enhanced longevity in spite of obesity and diabetes (Taguchi et al. 2007). In hearts, Foxo1 activation enhances myocardial survival upon induction of moderate oxidative stress (Sengupta et al. 2009, 2011, 2012) and promotes autophagy in control of cell size following serum starvation (Sengupta et al. 2009). Foxo1 is required for endothelial cell lineage during cardiovascular development since Foxo1 null mice are embryonic lethal (Hosaka et al. 2004; Sengupta et al. 2012).

Together, these data suggest that moderate Foxo1 activation is required for maintenance of a life cycle under some stress conditions, such as prolonged fasting in the liver for hepatic glucose production and activation of anti-oxidative mechanisms promoting survival. However, Foxo1 is over-activated at multiple layers upon environmental challenges, such as obesity. In this regard, Foxo1 signaling serves as a key mechanism for insulin resistance contributing to obesity, T2DM, and associated organ failure.

8 Other Considerations

8.1 Insulin Resistance in Bone Impairs Glucose Homeostasis

Insulin also exerts its function in non-classic organs in control of glucose homeostasis, which is far beyond of our expectation, such as insulin in the bone, controlling glucose homeostasis by suppressing Foxo1.

Insulin promotes bone formation and differentiation of osteoblasts that synthesize osteocalcin, a bone-derived insulin secretagogue which regulates pancreatic insulin secretion and systemically controls glucose homeostasis. Mice lacking insulin receptor in osteoblasts exhibited reduced bone formation, increased peripheral adiposity, and insulin resistance through decreasing osteocalcin gene expression (Ferron et al. 2010; Fulzele et al. 2010). Foxo1 activation decreased osteocalcin expression and activity by increasing expression of Esp, a protein tyrosine phosphatase, that inhibits osteocalcin bioactivity by favoring its carboxylation. Osteoblast-specific Foxo1 null mice have increased osteocalcin expression and

insulin production and reduced blood glucose (Rached et al. 2010). Collectively, these data suggest that the bone serves as an endocrine organ in control of glucose homeostasis, through bone-pancreas cross talk, in which Foxo1 plays a key role in insulin action regulating osteocalcin expression and activity in osteoblasts.

8.2 Microbiota, Inflammation, and Insulin Resistance

Recent studies indicate that gastrointestinal (GI) microbiota may trigger inflammation and insulin resistance (Johnson and Olefsky 2013; Nicholson et al. 2012). Increased levels of circulating bacteria or bacterial products derived from microbiota, such as lipopolysaccharides, initiate infection and metabolic inflammation that induce insulin resistance and promote metabolic syndrome (Cani et al. 2008). Comparisons of distal gut microbiota of genetically obese mice and their lean littermates, as well as those of obese and lean human volunteers, have revealed that obesity is associated with relative changes in two dominant bacterial divisions, bacteroidetes and firmicutes, and that the obese microbiome has an increased capacity to harvest energy from the diet. Thus, the gut microbiota is an additional factor to the pathophysiology of obesity and insulin resistance (Turnbaugh et al. 2006).

8.3 Bariatric Surgery

More than 80 % of patients with T2DM are obese; thus, body weight loss is an attractive but challenging therapeutic option (Dixon et al. 2012). Bariatric surgery, designed to achieve and sustain substantial weight loss and reduce food intake, effectively prevents and remediates T2DM (Sjostrom et al. 2012). Moreover, bariatric surgery reduces adverse cardiovascular events, not only in obese adults (Sjostrom et al. 2012) but also in patients with T2DM without severe obesity (Cohen et al. 2012). Although the mechanisms of bariatric surgery on metabolic control are unclear (Rubino et al. 2010), it is likely that the surgery resets metabolic parameters and hormones in a balanced way, such that energy intake and expenditure are controlled.

9 Conclusions

Mouse studies demonstrated that Foxo1 activation and Akt inactivation following suppression of IRS1 and IRS2 provide a fundamental mechanism for insulin resistance, impairing glucose and lipid homeostasis, and also serve as important mechanisms for the development of obesity. The metabolic syndrome is driven by insulin resistance in different organs, including the brain, liver, pancreas, fat, muscle, bone, and cardiovascular system. The IRS→Akt→Foxo1 signaling cascade and its regulatory network require further exploration under different cellular and environmental contexts. Notably, lipotoxicity, pro-inflammation, and hyperinsulinemia from overnutrition and microbiota all may affect this system, contributing to obesity and T2DM and failure of many organs (Fig. 4).

Genome-wide association analyses have identified some genes in control of development of obesity and diabetes (Doria et al. 2008; Wagner et al. 2013), but insulin resistance in obesity is a result of complex interactions among different tissues with genetic, environmental, and behavioral factors, all of which modify the IRS→Akt→Foxo1 branch at multiple levels in each organ. Other mediators for this pathway, such as SH2B, Grb10, and reactive nitrogen species, and CDK8 have not discussed here (Song et al. 2010; Liu et al. 2014; Zhao et al. 2012; Cao 2014; Zhou et al. 2015). We expect that current antidiabetic therapy (Tahrani et al. 2011), including glucagon-like peptide, pioglitazone and metformin, and bariatric surgery, may affect the IRS signaling directly or indirectly, facilitating a balance of hormones, nutrients, and inflammation. Thus, targeting the IRS→Akt→Foxo1 signaling cascade, associated protein kinases, and gene expression profiles may provide important therapeutic modalities for prevention or treatment of insulin resistance, obesity, T2DM, and associated organ failure.

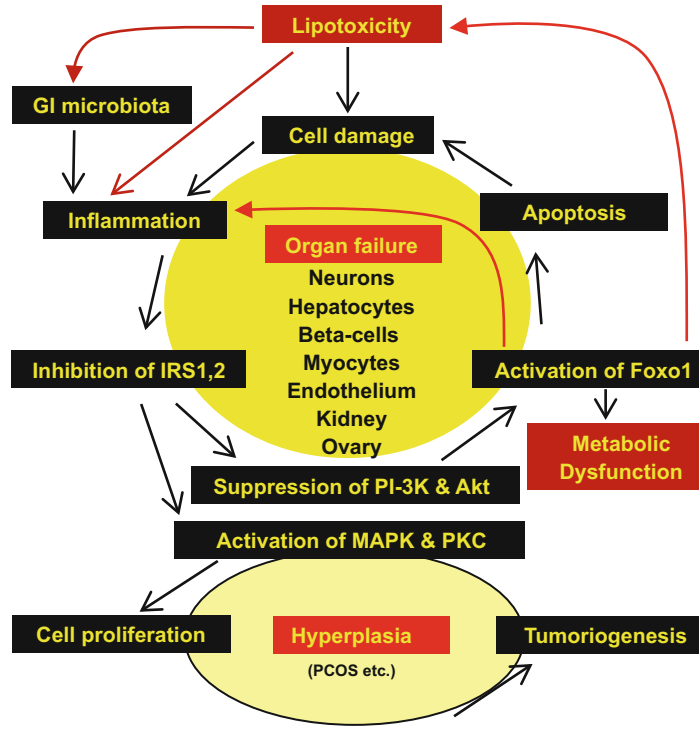

Fig. 4 Lipotoxicity promotes insulin resistance by suppressing IRS1, 2-associated PI3K/Akt activation and enhances Foxo1 activation, inducing cell damage/apoptosis and inflammation, and increases MAPK activation that may result in hyperplasia and development of certain cancers. *PCOS* polycystic ovary syndrome, *GI* gastrointestinal

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10 Cross-References

- Adipokines and Metabolism
- Adipose Structure (White, Brown, Beige)
- Bariatric Surgery
- Brain Regulation of Feeding and Energy Homeostasis
- Carbohydrate, Fat, and Protein Metabolism in Obesity
- Diet, Exercise, and Behavior Therapy in the Treatment of Obesity and Metabolic Syndrome
- Dyslipidemia in Obesity
- Endocrine Disorders Associated with Obesity
- Epidemiology of Obesity in the United States
- Gut Microbiome, Obesity, and Metabolic Syndrome
- Kidney Disease in Obesity and Metabolic Syndrome
- Linking Inflammation, Obesity, and Diabetes
- Myokines and Metabolism
- Nonalcoholic Fatty Liver Disease
- Obesity and Cardiac Disease
- Overview of Metabolic Syndrome
- Reproductive Disorders and Obesity in Males and Females and Focus on the Polycystic Ovary Syndrome
- Principles of Energy Homeostasis
- Social and Community Networks and Obesity

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Linking Inflammation, Obesity, and Diabetes

27

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Contents

Abstract

Overnutrition disrupts normal adipose tissue function. Dysfunctional lipid metabolism leads to an increase in circulating free fatty acids, initiating inflammatory signaling cascades and increased immune cell activity in metabolic tissue. A feedback loop of pro-inflammatory cytokines exacerbates this chronic inflammatory state, driving further immune cell infiltration, cytokine secretion, and activation of inflammasome complexes. This disrupts the insulin signaling cascade and is causative of defects in hepatic and skeletal muscle glucose homeostasis, resulting in systemic insulin resistance and ultimately the development of type 2 diabetes. This chapter will focus on the initiation of the inflammatory response in obesity and describe the impact of this on metabolic tissue, with a particular emphasis on the development of insulin resistance and type 2 diabetes. We will also review current and prospective treatment and intervention strategies and the biological mechanisms through which these function.

Keywords

Inflammation • Insulin resistance • Adipose tissue • Macrophage • Inflammasome

Abbreviations

ADP	Adenosine diphosphate
AMP	Adenosine monophosphate
AMPK	AMP-activated protein kinase

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ASC	Apoptosis-associated speck-like protein containing a CARD
ATM	Adipose tissue macrophages
ATP	Adenosine triphosphate
BAT	Brown adipose tissue
BMI	Body mass index
BMM	Bone marrow macrophages
CCR	C–C chemokine receptor
CLS	Crown-like structures
DAG	Diacylglycerols
DAMPs	Danger-associated molecular patterns
DC	Dendritic cell
DGAT	Diacylglycerol acyltransferase
DHA	Docosahexaenoic acid
DIO	Diet-induced obesity
ECM	Extracellular matrix
EPA	Eicosapentaenoic acid
FA	Fatty acids
FFA	Free fatty acids
Fiaf	Fasting-induced adipocyte factor
GLUT	Glucose transporter type
GPR	G protein-coupled receptor
HFD	High-fat diet
ICAM	Intercellular adhesion molecule
IKK	IκB kinase
IL	Interleukin
IR	Insulin resistance
IRS	Insulin receptor substrate
IS	Insulin sensitivity
IκB	Inhibitor of κB
JNK	c-Jun N-terminal kinase
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
MCP	Monocyte chemoattractant protein
MetS	Metabolic syndrome
MHC	Major histocompatibility complex
MUFA	Monounsaturated fatty acids
NF-κB	Nuclear factor kappa B
NLR	NOD-like receptor
PI3K	Phosphatidylinositol 3-kinase
PKB	Protein kinase B
PKC	Protein kinase C
PPAR	Peroxisome proliferator-activated receptor
PUFA	Polyunsaturated fatty acids
R	Receptor
RA	Receptor antagonist
SCFA	Short-chain fatty acid
SFA	Saturated fatty acids
SOCS	Suppressor of cytokine signaling
SVF	Stromal vascular fraction
T2D	Type 2 diabetes
TAG	Triacylglycerol
T_H	T helper
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TNFR	Tumor necrosis factor receptor
Treg	Regulatory T cell
TZDs	Thiazolidinediones
UCP-1	Uncoupling protein 1
WAT	White adipose tissue

1 Introduction

Metabolic syndrome (MetS) is a health condition that encompasses a number of factors including obesity and high blood glucose concentrations, which both are risk factors for the development of type 2 diabetes (T2D). It is projected that >420 million people will have prediabetes worldwide by 2030 (WHO/IDF 2006), with 5–10 % of pre-diabetic individuals progressing to develop T2D annually (Tabak et al. 2012). As prevalence figures continue on this upward trajectory, examination of the pathophysiological determinants underlying this condition is required.

The obese state is linked to the development of insulin resistance (IR), through the induction of an inflammatory response in insulin-sensing organs. Obesity-associated inflammation is described as being chronic, in that it fails to be resolved. A number of events can initiate this state of chronic inflammation, and these act synergistically to maintain an inflammatory environment. Such an inflammatory response can result from increased cell exposure to free fatty acids (FFA) which initiate inflammatory signaling, a shift in the cell population types present in metabolic tissues and changes in the gut microbiome (Fig. 1).

The immune system is necessary in promoting and resolving inflammation. This paradigm is

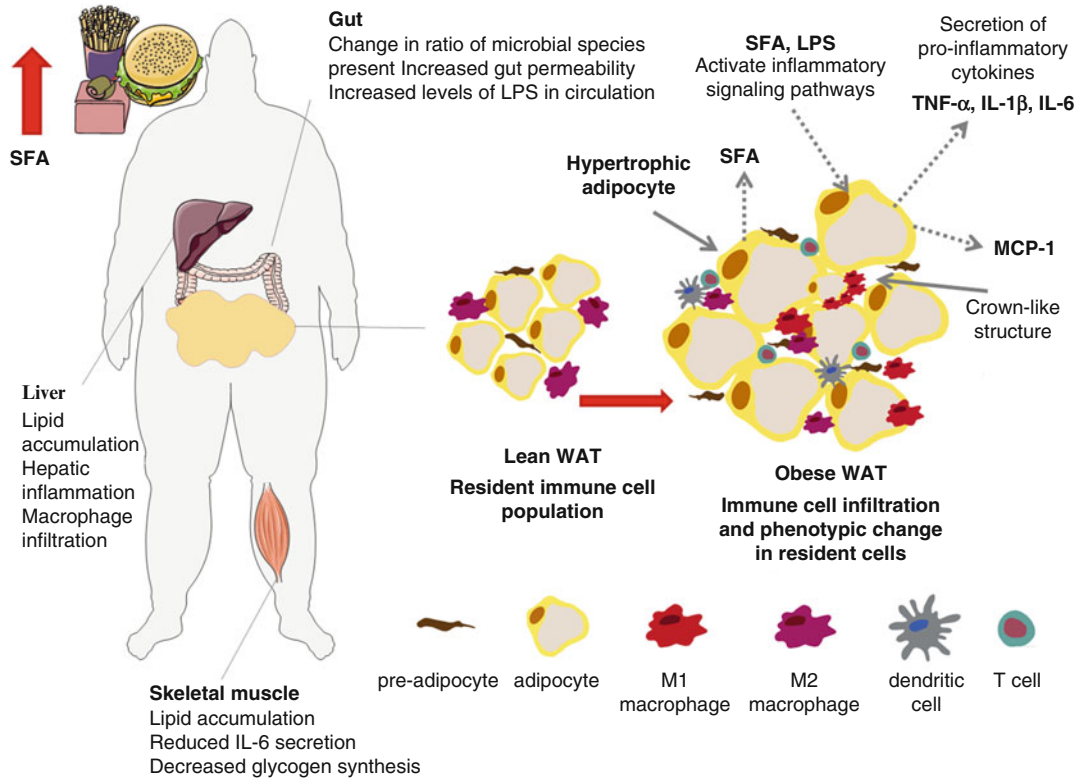

Fig. 1 Obesity – the impact on metabolic tissues and the gut. Excessive caloric intake has a negative impact on metabolic tissue. Increased exposure of metabolic cell types to circulating fatty acids results in lipid accumulation, the influx of immune cells, and a phenotypic switch in resident immune cell populations (M2 to M1 macrophages). Saturated fatty acids and LPS derived from the gut activate inflammatory pathways in metabolic tissue. This results in the production of pro-inflammatory cytokines (TNF-α (alpha), IL-1β (beta), IL-6); these signal within the tissue to sustain an inflammatory environment and promote the infiltration of immune cells. The release of FFA from adipocytes that have reached their expansion capacity further stimulates inflammatory signaling and thus chronic inflammation propagates

also true for obesity-associated inflammation. Immune cells, including macrophages and T cells, infiltrate metabolic tissue during the development of obesity. These immune cells secrete chemokines and cytokines. Chemokines function to attract additional immune cells into metabolic tissues. With obesity, there is increased production of the pro-inflammatory cytokines, tumor necrosis factor (TNF)-α (alpha), interleukin (IL)-6 and IL-1β (beta). These cytokines induce inflammatory signaling pathways in neighboring inflammatory and metabolic cells and impede insulin signaling. Insulin is a critical hormone that regulates glucose, lipid, and energy metabolism, in the liver, adipose tissue, and skeletal muscle. With IR, glucose is not taken up by metabolic tissues, circulating glucose levels increase, and this is an early indicator of T2D.

This chapter will focus on the link between obesity and inflammation. We will explore early events that initiate this process, from expanding adipocytes and increased levels of FFA to the deleterious impact of an altered gut microbiome. We examine how these factors alter metabolic tissue composition, cytokine secretion, insulin signaling, and glucose uptake. Finally, this chapter will highlight both nutritional and pharmacological strategies to counteract obesity-induced inflammation, IR, and T2D.

2 Metabolic Tissues

Multiple pathogenic factors have been implicated in the development of "metaflammation," a term coined to describe the synergy between metabolic and inflammatory pathways (Finucane et al. 2015). These pathways interact within the context of obesity, IR, and T2D, resulting in the deleterious effect of obesity at a systemic level (McGettrick and O'Neill 2013).

2.1 Adipose Tissue

There are different subtypes of adipose tissue: white adipose tissue (WAT), brown adipose tissue (BAT), and the recently identified beige adipose tissue. White adipose tissue is responsible for the storage of excess energy as triacylglycerol (TAG). These fatty acids (FA) can be oxidized by BAT and released as heat; however, the decreased BAT levels associated with obesity cause dysregulation in this response (Saito et al. 2009). Overproduction of WAT-derived TNF-α (alpha) has become a hallmark of obesity-induced IR and is associated with impaired insulin signaling (Hotamisligil et al. 1995). Chronic low-grade inflammation in WAT is characterized by increased inflammatory macrophage and T cell number (Talukdar et al. 2012). Conversely, lower levels of WAT-derived adiponectin are associated with IR (Yamauchi et al. 2001) and are inversely related to ectopic lipid accumulation (Samuel et al. 2010). Interestingly, despite WAT inflammation having unfavorable effects on IR, Asterholm et al. demonstrate that pro-inflammatory signaling is necessary for WAT functionality (Wernstedt Asterholm et al. 2014). If adipocytes fail to expand, then excess FA may end up being deposited in other cell types. Inflammation is also important for proper extracellular matrix (ECM) remodeling which facilitates adipogenesis (Cristancho and Lazar 2011). Both processes are likely mechanisms through which inflammation promotes WAT functionality (Wernstedt Asterholm et al. 2014).

Brown adipose tissue represents a small fat depot located in the neck and upper chest of adults (Tchkonia et al. 2005), and it has been associated with a protective effect against metabolic diseases such as T2D (Chondronikola et al. 2014). The protective effect of BAT has been attributed to the presence of uncoupling protein 1 (UPC-1) which is involved in the conversion of energy from food into heat (Cannon and Nedergaard 2004). Beige adipocytes express a distinct gene expression profile that distinguishes them from WAT and BAT. In the basal state, beige cells resemble WAT, demonstrating low levels of UCP-1; however, upon stimulation with cyclic adenosine monophosphate (AMP), UCP-1 levels increase, and these adipocytes demonstrate a BAT-like phenotype (Wu et al. 2012). It is suggested that BAT depots in adults may be composed of beige adipocytes. Beige and brown adipocytes exert a similar beneficial effect in terms of metabolic regulation (Harms and Seale 2013), and manipulation of these may open new opportunities for promoting metabolic health.

2.2 Liver

Hepatic steatosis refers to the accumulation of lipid in the liver; it is associated with obesity-induced inflammation and is a hallmark of nonalcoholic fatty liver disease (Angulo 2002). Accumulation of FA metabolites such as diacylglycerols (DAG), FFA, ceramides, and acylcarnitines, within insulin-sensitive tissues is one mechanism through which obesity causes IR (Samuel et al. 2010). Hepatic FA accumulation activates protein kinase C (PKC)-δ (delta); this interferes with insulin signaling by blocking insulin receptor substrate (IRS)-associated phosphatidylinositol (PI) 3-kinase activity (Lam et al. 2002). Similar to WAT, hepatic macrophage number increases with obesity (Obstfeld et al. 2010). Excess lipid derivatives in the liver induce endoplasmic reticulum stress and hepatic inflammation, evident by increased secretion of pro-inflammatory cytokines, acute-phase reactants, and activation of nuclear factor kappa B (NF-κ (kappa) B) and c-Jun N-terminal kinase (JNK)-mediated pathways (Cai et al. 2005; Tuncman et al. 2006). Specific deletion of *Ikbkb* from hepatocytes, the gene that encodes IKKβ (beta), showed an important role for this gene in the development of HFD-induced IR. Obese

HFD-fed hepatic *Ikbkb*$^{-/-}$ mice maintained hepatic insulin sensitivity (IS) but developed IR in muscle and WAT, with no overall improvement peripheral IS (Arkan et al. 2005). In contrast, myeloid-specific deletion of *Ikbkb* improved systemic IS.

2.3 Skeletal Muscle

Skeletal muscle is the main site for glucose uptake in the body, and muscle IR represents a core defect in T2D (DeFronzo and Tripathy 2009). Numerous defective mechanisms contribute to IR in skeletal muscle. These include impaired glycogen synthesis (Shulman 2000) and glucose transport (Abel et al. 2001), elevated IL-6 (Spranger et al. 2003) and FFA levels (Roden et al. 1996), with reduced AMP-activated protein kinase (AMPK) activity (Yamauchi et al. 2001). Skeletal muscle dysregulation plays a critical role in the development of IR, and glycogen synthesis is reduced by up to 50 % in T2D (Shulman 2000). Defects in glucose transport are also critical in the development of skeletal muscle IR (Rothman et al. 1992). Lower glucose-6-phosphate levels in diabetic individuals link defective glucose transport and decreased glycogen synthesis in skeletal muscle (Rothman et al. 1992).

Lipotoxicity with obesity is associated with the development of skeletal muscle IR. Myocyte lipid accumulation as FFA, fatty acyl-coenzyme A (CoA), DAG, and ceramides is a mechanism which potentiates skeletal muscle IR (Abdul-Ghani and Defronzo 2010). The pleiotropic cytokine IL-6 is considered a myokine; levels of IL-6 secretion from skeletal muscle increase following exercise, which promotes IS (Pedersen and Febbraio 2008). However, increased IL-6 expression is unfavorable in WAT and liver, and elevated plasma levels of IL-6 are predictive of T2D (Pradhan et al. 2001; Spranger et al. 2003).

3 Instigators of Inflammation

Traditionally, inflammation is considered to stem from infection and tissue injury. More recently, the impact of metabolic stress is considered to promote inflammation also. Weight gain places additional metabolic stress on the body initiating an inflammatory response. While the metabolic stressors are only beginning to be identified and understood, saturated fatty acids (SFA), lipotoxicity, and the altered gut microbiome are implicated in obesity-induced inflammation.

3.1 Lipotoxicity and Adipose Health

With increasing weight gain, adipocytes are faced with two fates, hypertrophy or hyperplasia, an increase in cell size or cell number, respectively. Hypertrophy naturally occurs prior to hyperplasia, in response to increasing adiposity (Jo et al. 2009). When excessive dietary intake persists over time, the expansion capacity of adipocytes is exceeded, and FFA are released (Sethi and Vidal-Puig 2007).

Circulating SFA can induce an inflammatory response similar to infectious agents. Both SFA and microbial lipopolysaccharide (LPS) signal via toll-like receptor (TLR) 4 and TLR2 present on the surface of adipocytes and immune cells (Glass and Olefsky 2012; Lee et al. 2001; Shi et al. 2006). Circulating FFA increase with obesity and promote IR through induction of inflammatory signaling pathways and downstream serine/threonine kinase phosphorylation of IRS-1 (Shulman 2000). The profound effect of SFA on IS has been confirmed through studies that induce transient IR within hours of TAG emulsions plus heparin infusion which elicits FFA release (Boden et al. 1991; Glass and Olefsky 2012).

Intracellular accumulation of TAG and other FA metabolites such as fatty acyl-Co-A, DAG, and ceramides interferes with insulin signaling and leads to IR (Shulman 2000). Intracellular accumulation of DAG activates PKC and initiates serine/threonine phosphorylation of IRS (Samuel et al. 2010). With obesity, inflammatory signaling induces the expression of genes involved in lipid metabolism, including enzymes that synthesize ceramide (Holland et al. 2011; McNelis and Olefsky 2014). Ceramide is a sphingolipid that has been shown to accumulate in response to HFD or infusion of SFA. Ceramides suppress insulin action by inhibiting phosphorylated protein kinase B (PKB) (Chavez and Summers 2012). Pharmacological

inhibition of ceramide by myriocin improves glucose tolerance (McNelis and Olefsky 2014). Data from studies investigating lipodystrophy in human and mouse models show that ectopic lipid accumulation may be a factor which potentiates IR, irrespective of peripheral and visceral adiposity (Samuel et al. 2010). This places intracellular lipid accumulation as an early instigator of chronic low-grade inflammation and IR.

3.2 Altered Gut Microbiome

The gut microbiome can modulate immune responses and therefore impact an inflammatory response (Kanneganti and Dixit 2012). The gut flora of obese individuals differs markedly from their lean counterparts, with circulating levels of LPS being significantly higher in the obese state (Baker et al. 2011). In murine and human studies, a change in the ratio of bacteroidetes/firmicutes has been shown with weight gain, and this may impact the levels of microbiome-derived LPS (Everard et al. 2014; Harley and Karp 2012; Moreno-Indias et al. 2014). Transport of LPS from the gut lumen to circulation is upregulated in response to HFD feeding (Erridge et al. 2007). High-fat diet feeding also increases gut permeability and reduces tight-junction integrity allowing for movement of LPS across the gut epithelium (Cani et al. 2008). The composition of the gut microbiome has been directly linked to the development of metabolic disorders associated with obesity (Baker et al. 2011; Dali-Youcef et al. 2013; Kanneganti and Dixit 2012). It has been established that the NLRP3 and NLRP6 inflammasomes and caspase-1 play a role in regulating gut microbiota. Deficiencies in these inflammasome components lead to gut microbiota dysregulation (Henao-Mejia et al. 2012). This interaction also provides a mechanism through which changes in gut microbiota exert a regulatory effect on obesity-associated inflammation (Dali-Youcef et al. 2013).

Gut microbiota also affects energy absorption via short-chain fatty acid (SCFA) metabolism and storage by inhibition of fasting-induced adipocyte factor (Fiaf) (Backhed et al. 2007). Elevated levels of the lipoprotein lipase inhibitor Fiaf is one mechanism responsible for the resistance to diet-induced obesity (DIO) in germ-free mice. The obese microbiome has increased energy absorption potential (Turnbaugh et al. 2006), and the suppression of Fiaf plays a critical role in this (Dali-Youcef et al. 2013). Additionally, suppression of Fiaf is vital for gut microbiota-associated deposition of TAG in adipocytes (Backhed et al. 2004).

The influence of TLRs on the gut microbiota also represents another important factor linking inflammation and obesity. Ablation of TLR5 alters gut microbiota and leads to metabolic complications such as IR (Vijay-Kumar et al. 2010). Whereas the absence of TLR4 exerts positive effects on metabolic health, reducing inflammatory signaling required for the development of obesity-associated IR (Baker et al. 2011). The influential function of the gut microbiota makes it an interesting target for future therapies aimed at reducing the inflammation associated with obesity.

4 "Metaflammation": Cells and Signaling

With obesity, the changes evident at a metabolic tissue level result from alterations in tissue composition and secretory profile. Increased circulating concentrations of TNF-α (alpha), IL-1β (beta), and monocyte chemoattractant protein-1 (MCP-1/CCL2) have been observed in T2D and are indicative of future disease risk (McNelis and Olefsky 2014).

4.1 Adipocytes and the Stromal Vascular Fraction

Adipose tissue is composed of adipocytes and a stromal vascular fraction (SVF). At a fundamental level, adipocytes function in the uptake and release of FA; however, they are more complex than simply lipid storage cells. They secrete proteins and hormones which influence satiety and immune cell infiltration. Proteins secreted from adipocytes are often referred to as adipokines

and include MCP-1 and IL-6 in addition to the hormones leptin and adiponectin. Additionally, adipocytes are involved in insulin signaling and glycemic control.

The SVF in turn is composed of adipose-derived stem cells, precursor preadipocytes, and immune cells that are crucial for normal tissue function. With obesity, the secretory profile of these cell types is altered toward an inflammatory response. The presence of inflammatory cytokines TNF-α (alpha), IL-1β (beta), and IL-6 halts the maturation of preadipocytes in vitro, characterized by reduced lipid accumulation (Gustafson and Smith 2006). Additionally, TNF-α (alpha) treatment of preadipocytes results in increased secretion of IL-6 and MCP-1 (Chung et al. 2006). Collagenase digestion of WAT separates the floating adipocyte layer from a SVF pellet. Analysis of the adipocyte layer from obese mice has shown that lipid-laden macrophages closely surround adipocytes (Ebke et al. 2014).

Adipogenesis is the process through which precursor preadipocyte cells become adipocytes, and it is crucial for the expansion of WAT. Once committed to differentiation, preadipocytes undergo growth arrest, and there is a concurrent increase in the expression of mature adipocyte genes such as fatty acid-binding protein and lipid-metabolizing enzymes (Gregoire et al. 1998). The transcription factor peroxisome proliferator-activated receptor (PPAR)-γ (gamma) is an important driver of this process, and for this reason (PPAR)-γ (gamma) is the target of the thiazolidinediones (TZDs) family of medication, used in the treatment of T2D.

Crucial to WAT function, adipocytes undergo hypertrophy and hyperplasia, which together contribute to an overall increase in WAT mass. When adipocytes become dysfunctional, cell death follows. The occurrence of adipocyte death is correlated with cell size, and adipocyte death is a pathologic marker of obesity (Cinti et al. 2005). These dying cells leak FFA, which are taken up by local adipose tissue macrophages (ATM) (Cinti et al. 2005). It has been demonstrated that lipolysis, the hydrolysis of TAG, acts in the recruitment of macrophages into obese WAT (Kosteli et al. 2010).

4.2 Macrophages

It has been estimated that up to 50 % of obese WAT is comprised of macrophages, a fivefold increase from the lean state (Kraakman et al. 2014; Weisberg et al. 2003). Three research papers are crucial to our current understanding of the role of macrophages in metaflammation. First, in 1993, Hotamisgil et al. published research that showcased the role of WAT-derived TNF-α (alpha) in obesity (Hotamisligil et al. 1993). A decade later, two research papers published in the Journal of Clinical Investigation highlighted that macrophages were crucial to obesity-associated inflammation and identified these cells as the main source of TNF-α (alpha) in obese WAT (Weisberg et al. 2003; Xu et al. 2003). Xu et al. demonstrate that inflammatory and macrophage-specific genes including *MCP-1* and macrophage markers F4/80 and CD11b were significantly upregulated in *ob/ob*, *db/db*, and high-fat diet (HFD)-fed murine SVF (Xu et al. 2003).

Additionally, TNF-α (alpha) acts to stimulate adipocyte lipolysis, thus contributing to elevated FFA concentrations in the serum (Cawthorn and Sethi 2008). In vitro treatment of 3T3-L1 adipocyte cells with TNF-α (alpha) leads to reduced expression of *Pparg* gene (Ye 2009). Circulating levels of TNF-α (alpha) have been shown to be increased in obese and T2D subjects, and expression is also increased in WAT and skeletal muscle (Hotamisligil et al. 1995; Kern et al. 1995; Zahorska-Markiewicz et al. 2000).

Lumeng et al. investigated the inflammatory profile of ATM from lean and obese mice (Lumeng et al. 2007). This research demonstrated a distinct difference in cell surface marker expression. Macrophages from obese mice have significantly increased expression of the cell surface marker CD11c. This CD11c population has greater *Il6* and *Nos2* gene expression than lean ATM, and these genes are associated with inflammation. In contrast, CD11c negative cell populations were shown to express anti-inflammatory genes such as *Il10*.

The chemokine MCP-1 is a key instigator of macrophage recruitment. In murine models of

obesity, WAT and BAT *MCP-1* expression is increased (Kanda et al. 2006), and this is coincident with IR, macrophage infiltration of WAT and hepatic TAG accumulation (Kamei et al. 2006; Kanda et al. 2006). Such features are absent in HFD-fed *MCP-1*$^{-/-}$ mice. Overexpression of *MCP-1* increases WAT and plasma, TNF-α (alpha), and IL-6 levels, concomitant with reduced hepatic and skeletal muscle pPKB, suggesting a role for circulating MCP-1 in systemic IR (Kamei et al. 2006). Recently it has been demonstrated that TNF-α (alpha) treatment increased *MCP-1* expression in 3T3-L1 preadipocytes (Kabir et al. 2014), but this induction did not occur when mature 3T3-L1 cells were treated with TNF-α (alpha). Thus in experimental models, TNF-α (alpha) can halt preadipocyte maturation while increasing preadipocytes MCP-1 production. Genetic manipulation of the MCP-1 receptor has a positive impact on IS. MCP-1 signals via the C–C chemokine receptor (CCR)2 receptor and *Ccr2* expression are increased in HFD-fed WAT (Weisberg et al. 2006). High levels of CCR2 have been shown in macrophages that are located in regions of WAT where there are crown-like structures (CLS), a description given to a group of macrophages that surround dying adipocytes (Lumeng et al. 2008). The presence of CLS in WAT is associated with obesity.

The origin of ATM however is not certain. There is evidence to suggest that the obese environment draws monocytes from the circulation into WAT. The monocytes then differentiate into macrophages which express distinct cell surface markers, behavior, and secretory patterns from the resident ATM population (Lumeng et al. 2008). Lumeng et al. labeled ATM from lean and HFD-fed mice in order to determine if there were distinct localization patterns in the obese environment (Lumeng et al. 2008). This research showed that in obese WAT, ATM with pro-inflammatory characteristics preferentially localized in CLS clusters. This study also highlighted that resident ATM localization occurs independently of MCP-1 signaling. Importantly, despite the presence of these CLS, resident ATM populations remain in interstitial spaces between adipocytes, as is the case in lean WAT. Approximately 90 % of ATM in both obese mice and humans are localized to CLS (Cinti et al. 2005). The role of hematopoietic IL-1R has also been demonstrated to be involved in monocytosis. Nagareddy et al. performed bone marrow transplants and fat pad transplants on *ob/ob* and HFD-fed murine models to highlight a positive feedback loop between ATM and bone marrow myeloid progenitor cells in obesity (Nagareddy et al. 2014). The results of this study show that in inflamed WAT, an increase in inflammatory mediators is accompanied by increased cross talk with hematopoietic progenitor cells. The IL-1R plays an important role in this signaling which the researchers suggest, ultimately leads to an increase in circulating monocytes and increased WAT infiltration.

Alternatively, the obese environment may initiate a phenotypic change in resident ATM causing these cells to act in a pro-inflammatory manner. New research demonstrated that tissue resident macrophages originate during embryonic development rather than from infiltration of circulating monocytes (Epelman et al. 2014). Fate-mapping techniques track embryonic macrophage populations into adulthood and allow comparative functional relationships of resident macrophages and circulating monocytes (Epelman et al. 2014). Further, a separate study demonstrated that macrophage populations' resident in the WAT undergo local cell differentiation in response to MCP-1 treatment ex vivo, independently of monocyte recruitment (Amano et al. 2014). It is likely that a combination of events takes place in the obese environment, including the recruitment of monocytes into the WAT and a shift in the phenotype of the resident ATM when weight gain promotes aberrant cytokine and chemokine secretion in WAT.

Recently there have been discussions around the naming conventions of macrophages in obesity-induced inflammation (Murray et al. 2014). At present, the inflammatory macrophages that increase with obesity are considered M1 or classically activated ATM, while resident macrophages, with a regulatory or anti-inflammatory phenotype, are classified as M2 or alternatively activated macrophages. This M1–M2 split

has since been further subdivided as research demonstrates subpopulations of M1 and M2 cells, with unique characteristics. It is likely that in obese WAT, ATM phenotypes lie along a spectrum ranging from M1–M2 (Mosser and Edwards 2008).

Resident macrophages from different organs have been shown to be as distinct from each other as they are from circulating macrophages (Gautier et al. 2012). This suggests that tissue-specific factors drive macrophage differentiation. In the liver, resident macrophages called Kupffer cells play a role in tissue homeostasis. However with obesity, additional macrophages are present within the liver, recruited by MCP-1 signaling. Depletion of all macrophages from the liver is protective against HFD-induced IR. Recently, hepatic macrophage content was shown to decrease by 80 % when *Ccr2*$^{-/-}$ monocytes were injected into obese WT mice (Oh et al. 2012). Kupffer cells mediate the recruitment of hepatic macrophages in obesity (Morinaga et al. 2014). These recruited macrophages are six times more prevalent in obese vs. lean mice and demonstrate greater *Il6*, *Tnfa*, and *MCP-1* expression (Morinaga et al. 2014). The presence of hepatic macrophages impacts on hepatic IS rather than systemic IS (Cai et al. 2005).

4.3 Further Inflammatory Cells Types

Other immune cell types are also drawn into the chronic inflammatory tissue environment. These include cells of the innate and adaptive immune response. Dendritic cells (DC) are hematopoietic-derived cells, and function in antigen-presenting, an important process in initiating a T cell response (Sallusto and Lanzavecchia 1994). Murine models of DIO have demonstrated an increase in DC number in bone marrow, WAT, and liver (Chen et al. 2014; Reynolds et al. 2012; Stefanovic-Racic et al. 2012). A comparison of DC isolated from the SVF of lean and obese mice demonstrated a difference in population subsets (Bertola et al. 2012). Dendritic cells derived from obese SVF have a greater propensity to drive the differentiation of a T-helper (T_H)17 cell population, which in turn produce high levels of pro-inflammatory IL-17 (Bertola et al. 2012; Chen et al. 2014). The DC-derived pro-inflammatory cytokine IL-12 has been shown to be increased with obesity, and elevated serum levels of IL-12 have been noted in human T2D studies (Mishra et al. 2011; Nam et al. 2013; Wegner et al. 2008). This cytokine can drive T cells to differentiate to pro-inflammatory T_H1 cells.

T cells make up approximately 30 % of the SVF in HFD-fed mice (McNelis and Olefsky 2014). T cell infiltration of WAT occurs before ATM expansion (Nishimura et al. 2009; Winer et al. 2009). In addition to increased numbers of T_H17 cells, obesity results in a change in other T cell populations such as a reduction in regulatory T cell (T_{reg}) number (Feuerer et al. 2009; Winer et al. 2009). These T cells promote alternative activated macrophage responses to inflammation (Osborn and Olefsky 2012), and when depleted, there is reduced tyrosine phosphorylation of IRS-1 (Feuerer et al. 2009). With HFD feeding, there is an increase in WAT T_H1 cell number (Winer et al. 2009), and these cells activate pro-inflammatory macrophages and increase IL-1β (beta), IL-6, and TNF-α (alpha) secretion. Thus the secretory profile of T cell populations becomes skewed with obesity, further promoting the inflammatory environment. T cells are traditionally thought to be activated by antigen-presenting cells such as DC, via interaction with the major histocompatibility complex (MHC). Recent research suggests a new role for the MHC II in obesity. Deng et al. demonstrated that within 2 weeks of HFD feeding, murine subcutaneous and visceral adipocytes upregulate genes involved in MHC II presentation and processing (Deng et al. 2013). A similar set of genes was also upregulated in a cohort of obese female subjects (Deng et al. 2013). In HFD-fed MHC II$^{-/-}$ mice, there was reduced T_H cell number, reduced expression of *Nlrp3* and *Tnf*, and improved IS. However, Morris et al. and follow-up research by Cho et al. describe the ATM MHC II–T cell interactions as an important driver of WAT inflammation, through T cell proliferation and WAT

inflammation (Cho et al. 2014; Morris et al. 2013) but did not support the finding of MHC II protein expression in WAT (Cho et al. 2014). This research revealed that macrophage cell-specific deletion of *MHC II* improved IS in HFD-fed mice.

4.4 The NLRP3 Inflammasome

The pro-inflammatory cytokine IL-1β (beta) is secreted by macrophages (Lumeng et al. 2007), as immature pro-IL1β (beta). It is processed to an active mature state via an inflammasome complex. Inflammasomes are multicomponent structures that assemble in response to danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns, in order to activate an immune response (Strowig et al. 2012). Such DAMPs include obesity-related metabolic stressors (monosodium urate, FA, ceramides, cholesterol crystals). There has been a particular focus on the NLRP3 inflammasome in relation to IL-1β (beta) processing (Mills and Dunne 2009). This inflammasome is comprised of an NLRP3 NOD-like receptor (NLR), an apoptosis-associated speck-like protein, containing a CARD (ASC) adaptor protein and caspase-1. The complex functions to activate caspase-1, which in turn cleaves immature pro-IL-1 family members to their active form (Agostini et al. 2004; Dinarello 2009). Activation of the NLRP3 inflammasome itself is required for cytokine processing to proceed; in vitro, this can be achieved through a two-step process of priming followed by activation. Firstly, TLR4 is activated by a ligand such as LPS or SFA, and this initiates pro-IL-1β (beta) production (Reynolds et al. 2012; Wen et al. 2011) and is considered a first "hit." A second activation signal results in the assembly of the inflammasome complex. Exogenous adenosine triphosphate (ATP) may be used as a second activation stimulus in experimental models.

NLRP3 activation by FA is variable upon FA saturation (Finucane et al. 2015). Whereas SFA prime the NLRP3 inflammasome, monounsaturated fatty acids (MUFA) have a reduced ability to prime the complex. Consequently, in MUFA-HFD-fed mice, there is reduced WAT *Nlrp3*, *caspase-1*, and *Il1β* (beta) expression ex vivo relative to SFA-HFD. Research has shown a role for the metabolic sensor AMPK in NLRP3 activation (McGettrick and O'Neill 2013). This complex is involved in energy balance and FA metabolism, and it is activated by threonine phosphorylation (McGettrick and O'Neill 2013; Zeng et al. 2014). Treatment with the SFA, palmitate, reduces AMPK activation in bone marrow macrophages (BMM) and is coincident with increased IL-1β (beta) secretion (Wen et al. 2011). Finucane et al. demonstrated a significant reduction in SFA-HFD-fed WAT pAMPK levels relative to a chow and MUFA-HFD group. Oleic acid, a MUFA, induces BMM AMPK activity in vitro which in turn reduces the IL-1β (beta) response to ATP stimulation (Finucane et al. 2015). Ex vivo analysis of LPS-treated monocyte-derived macrophages (MDM) from T2D patients demonstrates increased expression in *Nlrp3* and *Asc* (Lee et al. 2013) and following stimulation with DAMPs increased IL-1β (beta) secretion. Metformin treatment of T2D patients prevented maturation of MDM-derived IL-1β (beta), through enhanced AMPK phosphorylation. Together these studies highlight a link between AMPK and NLRP3 inflammasome activity (Fig. 2) and point to AMPK activation as an attractive target to attenuate "metaflammation."

4.5 Linking Inflammatory and Insulin Signaling Pathways

Toll-like receptor-4 has a central role in inflammatory signaling in the context of obesity. This receptor is present on the cell surface of adipocytes and macrophages and can induce inflammation in response to diverse stimuli including LPS and SFA. Hematopoietic cell depletion of TLR4 protects mice from diet-induced IR and results in a reduction in *Tnfa* and *Il6* expression in WAT and liver (Orr et al. 2012). Signaling via the TLR4 receptor can activate either the MyD88-dependent pathway or the TRIF-dependent pathway, and these pathways converge at the protein kinase TAK-1. Activation of TAK-1 results in downstream activation of

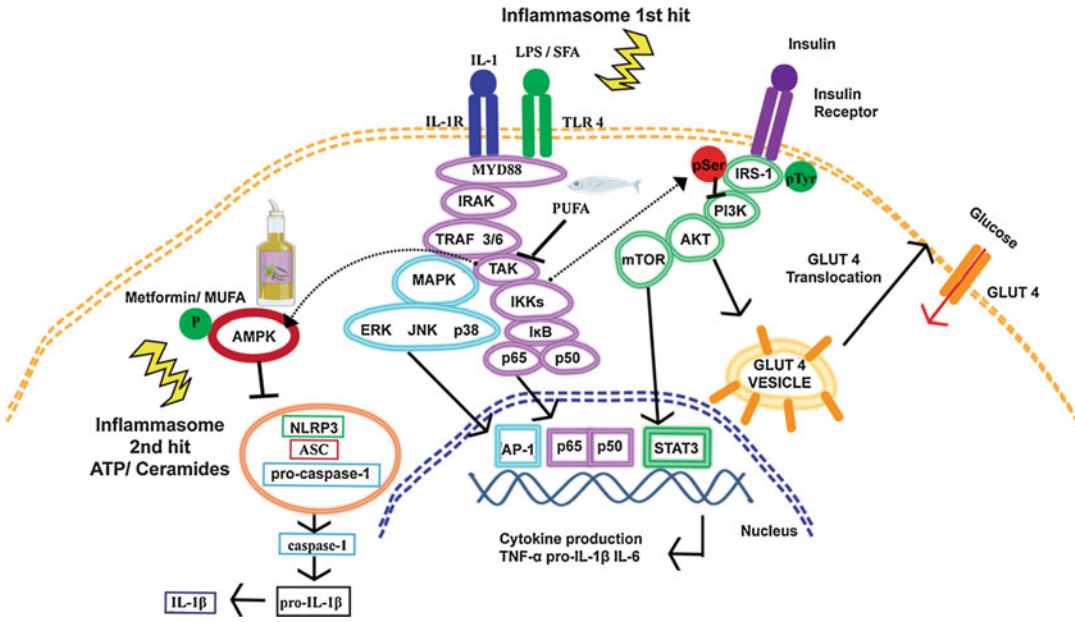

Fig. 2 Metaflammation – interaction between inflammatory and insulin signaling pathways. With obesity, the interaction between inflammatory signaling pathways and the insulin signaling pathway results in diminished insulin signaling and, if the inflammatory state persists, insulin resistance and reduced insulin-stimulated glucose uptake. Inflammatory signaling results in preferential serine/threonine phosphorylation of IRS-1, and this halts the signaling cascade and prevents GLUT4 trafficking to the cell surface. Research into the role of the NLRP3 inflammasome in pro-inflammatory IL-1β (beta) processing has emphasized the cross talk between inflammatory signaling and insulin resistance and highlighted this inflammasome complex as a therapeutic target. Metformin and oleic acid, a monounsaturated fatty acid, reduce NLRP3 inflammasome activity via activation of the metabolic sensor AMPK. Blocking of NF-κ (kappa) B signaling by the dietary fatty acids EPA and DHA has shown antiinflammatory potential in vitro models, but data on this effect is contentious in human studies

the NF-κ (kappa) B and mitogen-activated protein kinase (MAPK) signaling pathways (Könner and Brüning 2011).

The NF-κ (kappa) B pathway is downstream of receptors TLR4, TNFR, and IL1R. This pathway has a major role in a number of inflammatory conditions (Baltimore 2011; Ben-Neriah and Karin 2011). Activation of NF-κ (kappa) B signaling drives secretion of TNF-α (alpha), IL-1β (beta), and IL-6, thus propagating the inflammatory environment (Donath and Shoelson 2011). Upon receptor engagement, a signaling cascade is initiated, resulting in the phosphorylation and thus activation of the Iκ (kappa) B kinase (IKK) complex and subsequently phosphorylation of inhibitor of κ (kappa) B (Iκ (kappa) B), marking this molecule for degradation and releasing the NF-κ (kappa) B transcription factor. Once released, NF-κ (kappa) B translocates to the nucleus and initiates expression of cytokines.

With obesity, there is increased expression of suppressor of cytokine signaling (SOCS) proteins, and members of this family act to inhibit insulin signaling (Emanuelli et al. 2008; Emanuelli 2000; Ueki et al. 2004). The SOCS-1 and SOCS-3 proteins function to control cytokine action through feedback loops. These proteins also partially block tyrosine phosphorylation of the insulin receptor, and downstream from this, phosphorylation of IRS-1 and IRS-2 is almost entirely inhibited (Ueki et al. 2004). Preferential phosphorylation of serine/threonine residues on IRS-1 over tyrosine residues results in abrogation of the insulin receptor signaling cascade (Gual et al. 2005; Paz et al. 1997). Factors that promote aberrant serine/threonine IRS-1 phosphorylation

include SOCS-3 but also FFA and inflammatory mediators such as TNF-α (alpha), via NF-κ (kappa) B, JNK, and MAPK pathways (Gual et al. 2005; Tanti and Jager 2009). Tyrosine phosphorylation of IRS-1 allows for continuation of insulin signaling. Downstream of IRS-1 lie the molecules phosphoinositide-3-kinase (PI3K) and AKT, and these function in glucose uptake into the WAT, liver, and muscle. In normal physiological conditions, insulin-dependent signaling results in AKT-stimulating glucose transporter type (GLUT) 4 translocation to the cell surface via PKC phosphorylation of AS160 (Imamura et al. 2003; Ng et al. 2010); GLUT4 functions in the transport of glucose into the cell.

5 Therapeutic Approaches

There is sound evidence showing that an obesity-induced inflammatory state promotes the progression of IR. Therefore, therapeutic approaches which attenuate this state and/or promote the resolution of inflammation may impact favorably upon obesity-induced IR. Several pharmacological agents and lifestyle interventions have an impact on both metabolism and inflammation. In reviewing the concept of resolution of metabolic inflammation, it is clear that exact processes involved are not completely understood. Thus more research is required to identify and assess effective anti-inflammatory treatment strategies.

5.1 Drug Therapies

As IR can precede the development of T2D by decades, therapies that target inflammation associated with IR are central to halting the progression toward overt T2D. If IR progresses to T2D, there are a variety of treatments available. Some pharmacological approaches which show potential include metformin, TZDs, and anakinra. While these therapies have potential in terms of clinical efficacy, they are limited by their side effects. Anti-inflammatory therapies also have potential adverse effects, linked to long-term usage and immune suppression.

At present, guidelines recommend metformin as a first-line treatment for T2D (Centre for Clinical Practice at NICE 2009). The biomarker HbA1c gives a measure of average plasma glucose concentrations over the previous weeks and therefore indicates loss of glycemic control associated with T2D. Metformin leads to an initial drop in HbA1C, after which patients exhibit a loss of glycemic control and HbA1C levels increase (Turner et al. 1999). Metformin regulates lipid and glucose metabolism through increased phosphorylation and activation of AMPK (Zhou et al. 2001). This antidiabetic drug inhibits mitochondrial function, leading to elevated AMP and ADP levels, thus stimulating AMPK activation (McGettrick and O'Neill 2013). Given the role of metabolic stress on IL-1 β (beta) activation and IR, this has important implications with respect to attenuating the inflammatory response associated with obesity and T2D. Therapies which inhibit pro-inflammatory responses offer an opportunity to correct the metabolic consequences of obesity.

The insulin-sensitizing class of drugs, TZDs, are selective ligands of PPAR-γ (gamma) and target IR (Yki-Järvinen 2004). These PPAR-γ (gamma) ligands function by increasing both peripheral glucose disposal and adiponectin levels while also decreasing FFA and pro-inflammatory cytokine levels (Hotamisligil 2005). Insulin signaling is enhanced through increased IRS-1 expression and inhibition of the MAPK pathway (Miyazaki et al. 2003). Therapies that regulate PPAR-γ (gamma) activity by targeting post-translational modifications of its receptor have the potential to preserve the treatment effect of TZDs while minimizing the side effects associated with their use (Lefterova et al. 2014). Nevertheless the cross talk between PPARγ activation and inflammation requires further investigation.

In obese WAT, macrophage number correlates with the extent of tissue IR. Therefore, therapies which target macrophage accumulation are of particular interest. With obesity, pro-inflammatory macrophages are characterized by the expression of CD11c. Depletion of CD11c macrophages results in reduced WAT inflammation and improved IS in obese mice (Patsouris

et al. 2008). Clodronate liposomes that ablate macrophages in a tissue-specific manner offer another potential approach (Feng et al. 2011). In a murine model, macrophage ablation specific to WAT improved glucose homeostasis, increased adiponectin levels, reduced TAG levels, and significantly altered cytokine expression levels (Feng et al. 2011). While this type of therapy is not yet suitable for clinical use, it presents an interesting proof of concept.

Increased TNF-α (alpha) levels are well documented in obesity; however, inhibition of TNF-α (alpha) provided limited success in humans with T2D (Dali-Youcef et al. 2013). Certain TNF-α (alpha) inhibitors such as etanercept that have beneficial effects in other inflammatory conditions such as rheumatoid arthritis and psoriasis, are associated with a decreased risk of developing T2D but are not currently used in the treatment of T2D (McNelis and Olefsky 2014). Targeting another pro-inflammatory cytokine, IL-1β (beta) has shown some positive results. Anakinra is an IL-1 receptor antagonist (RA) that improves glycemic control, preserves β (beta)-cell function, and reduces markers of inflammation (Larsen et al. 2007). Use of the monoclonal antibody XOMA 052 also targets IL-1β (beta), resulting in improved glycemic management and β (beta)-cell function in a murine model of DIO (Owyang et al. 2010). As the IL-1 family is key to the inflammatory response in metabolic dysregulation, IL-1 antagonism has therapeutic potential (Donath and Shoelson 2011). However, global anti-inflammatory therapies such as TNF-α (alpha), IL-1 RA, and MAPK inhibitors are not without side effects (Kaminska 2005). The chronic nature of obesity-associated inflammation requires long-term treatment which raises concern for potential interference with inflammatory-mediated immune responses and key cellular processes (Dinarello 2010).

Co-stimulatory interactions have been implicated in obesity-associated inflammation. One such pair is the co-stimulatory protein CD40 and its ligand CD40L, members of the tumor necrosis factor receptor (TNFR) family. The positive correlations between increased body mass index (BMI) and CD40 and the implication of CD40 ligation in activation of pro-inflammatory pathways such as JNK, MAPK, and NF-κ (kappa) B make it an interesting therapeutic target (Seijkens et al. 2014). In HFD-fed mice, small molecule-mediated inhibition of the CD40-TRAF6 interaction improved glucose tolerance (van den Berg et al. 2014). However, immunosuppressive side effects prevent long-term use of antibody treatment against co-stimulatory molecules and cytokine inhibition. Therapies which inhibit the NLRP3 inflammasome offer a more targeted approach rather than global immunosuppressive agents. Recently, the small molecule inhibitor MCC950 was shown to inhibit the NLRP3 inflammasome activation and reduce serum IL-1β (beta) levels in a murine model of inflammatory disease (Coll et al. 2015). Existing therapies that decrease NLRP3 activation have shown clinical efficacy. The success of metformin (Lee et al. 2013), anakinra (Larsen et al. 2007), and the sulfonylurea glyburide (Masters et al. 2010) highlights the potential for NLRP3 inhibitors as targets for the treatment of metabolic disorders (McGettrick and O'Neill 2013).

5.2 Lifestyle Interventions

From the lifestyle perspective, weight loss is one strategy that reduces inflammation and halts the development of IR. Dietary and lifestyle modifications that attain significant weight loss attenuate inflammation and improve IS by lowering metabolic stress and reducing ATM number (Kovacikova et al. 2011). However, achieving and maintaining weight loss is challenging (Finucane et al. 2015; Gage 2012). Exercise improves insulin IS, and it increases IL-6 and diacylglycerol acyltransferase (DGAT) 1 expression in skeletal muscle (Schenk and Horowitz 2007). Skeletal muscle-derived-IL-6 induces the production of IL-1 RA and IL-10, inhibits TNF-α (alpha) secretion, and functions to promote glucose uptake (Petersen and Pedersen 2005). DGAT induces TAG formation from DAG, thereby reducing DAG concentrations, which otherwise impede insulin signaling (Corcoran et al. 2007). Even a single bout of exercise can reduce the lipotoxic and potentially

pro-inflammatory effect of elevated DAG levels to improve IS. Presently, there is lack of firm evidence as to whether anti-inflammatory strategies are the most efficacious therapy within the context of obesity. Further work is needed in this area to understand fully their mechanism of action.

5.3 Nutrient-Based Approaches: Reducing Inflammation

Inflammatory signaling through several kinases, namely, MAPK, PKC, and NF-κ (kappa) B, drives obesity-induced inflammation (Hotamisligil 2005). Therapies which target NF-κ (kappa) B, TLR4, and PPAR-γ (gamma) are of clinical importance.

Long-chain n-3 polyunsaturated fatty acids (LC n-3 PUFA), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), exert anti-inflammatory effects (Calder 2006). Animal studies provide convincing mechanistic evidence that LC n-3 PUFA stimulate G protein-coupled receptor 120 (GPR120) (Oh et al. 2010; Yan et al. 2013), resulting in inhibition of TAK phosphorylation, and this halts further signaling (Oh et al. 2010). Additionally, a role for EPA and DHA has been proposed in ameliorating the pro-inflammatory effects of SFA which activate TLR4 and increase NF-κ (kappa) B transcriptional activity (Reynolds et al. 2012). LC n-3 PUFA also inhibit the production of pro-inflammatory eicosanoids (Calder 2006), due to a combination of reduced arachidonic acid, the precursor of pro-inflammatory eicosanoids (Caughey et al. 1996), and enhanced DHA-derived resolvin and protectin synthesis (Calder 2006).

Despite consistent in vitro data demonstrating the benefits of LC n-3 PUFA on metabolic health, these effects have translated to only a modest effect in vivo (Kabir et al. 2007; Tierney et al. 2011). Long-term LC n-3 supplementation did not show the positive effects on IS observed in short-term high-dose studies or in in vitro models (Tierney et al. 2011). Some cross-sectional and epidemiological data suggests that high LC n-3 PUFA status is associated with a reduced risk of obesity-associated inflammation and IR (Lopez-Garcia et al. 2004). Human LC n-3 PUFA interventions provide conflicting evidence on the efficacy of n-3 PUFA supplementation, and these show little or no effect on inflammatory markers or IR (McMorrow et al. 2015) and only modestly alter lipoprotein risk factor profile; TAG levels are significantly altered, while there was no significant impact on LDL or HDL levels (Dyerberg et al. 2004; Finnegan et al. 2003). It is possible that LC n-3 PUFA may be ineffective when the metabolic stress associated with obesity goes beyond a certain level, after which the potential efficacy-associated LC n-3 PUFA are negated by the adverse metabolic phenotype. Alternatively, an individual's responsiveness to LC n-3 PUFA interventions may be due to age, gender, genetic variability, variations in treatment duration, dose, or the populations studied (Calder et al. 2011). For example, in the case of gender-specific effects, LIPGENE demonstrated that LC n-3 PUFA were only effective in men but not in women with MetS (Tierney et al. 2011). A similar gender effect was also observed in the FINGEN study (Caslake et al. 2008).

A number of additional nutrients impact on the NF-κ (kappa) B pathway, including the polyphenols epigallocatechin gallate, found in green tea, which also suppresses ERK phosphorylation, and resveratrol present in red wine (Bakker et al. 2010; Liu et al. 2006; Yang et al. 2001). Curcumin is a known anti-inflammatory and anticarcinogenic agent that has also been shown to inhibit NF-κ (kappa) B activation (Singh and Aggarwal 1995).

Combinations of anti-inflammatory nutritional therapies may offer a more robust effect, capable of targeting multiple inflammatory signaling pathways. A dietary intervention which included resveratrol, lycopene, epigallocatechin gallate, α (alpha)-tocopherol, vitamin C, EPA, and DHA given over 5 weeks elicited anti-inflammatory effects on healthy overweight subjects (Bakker et al. 2010). This anti-inflammatory dietary mix increased adiponectin levels; however, C-reactive protein and pro-inflammatory cytokines remained

largely unchanged (Bakker et al. 2010). A similar anti-inflammatory dietary mix in mice reduced plasma cholesterol, TAG, and serum amyloid A and improved inflammatory risk factors of cardiovascular disease such as intercellular adhesion molecule-1 (ICAM-1) and E-selectin (Verschuren et al. 2011). Despite the potential of an anti-inflammatory dietary mix for disease prevention, their impact to date has resulted in only subtle improvements in inflammatory biomarkers, and future work in this area is required to maximize this potential.

Pharmacological therapies such as co-stimulatory molecule and cytokine inhibitors, clodronate liposomes, PPAR-γ (gamma) ligands, and therapies which stimulate AMPK activation have been shown to effectively reduce obesity-associated inflammation thus providing treatment opportunities for conditions such as IR and T2D. However, from a nutritional perspective, although some prospective and cross-sectional data is potentially promising, results from interventions are mixed. Perhaps nutritional status can prevent development but not treat inflammation or IR once established. Certain individuals may respond more favorably to interventions based on age, gender, and genetics.

6 Conclusion

The past two decades have seen a drastic increase in obesity levels; however, our understanding of the underlying mechanism of action has also greatly increased. Greater knowledge of the underlying pathology of obesity-induced inflammation and IR may reveal new treatment options. A good lifestyle and metabolic phenotype can attenuate the risk of developing IR (Phillips et al. 2013; Rhee et al. 2014). Nevertheless, there is lack of clarity in relation to dietary/lifestyle/pharmaceutical intervention strategy efficacy. Therefore, greater knowledge in relation to potential therapies which target the chronic low-grade inflammation associated with obesity and metabolic disorders such as IR and T2D is vitally important.

7 Cross-References

- ▶ Adipokines and Metabolism
- ▶ Adipose Structure (White, Brown, Beige)
- ▶ Brain Regulation of Feeding and Energy Homeostasis
- ▶ Carbohydrate, Fat, and Protein Metabolism in Obesity
- ▶ Childhood Environment and Obesity
- ▶ Diet and Obesity (Macronutrients, Micronutrients, Nutritional Biochemistry)
- ▶ Diet, Exercise, and Behavior Therapy in the Treatment of Obesity and Metabolic Syndrome
- ▶ Dyslipidemia in Obesity
- ▶ Gut Microbiome, Obesity, and Metabolic Syndrome
- ▶ Insulin Resistance in Obesity
- ▶ Linking Obesity, Metabolism, and Cancer
- ▶ Myokines and Metabolism
- ▶ Obesity and Cardiac Disease
- ▶ Overview of Metabolic Syndrome
- ▶ Pharmacotherapy of Obesity and Metabolic Syndrome
- ▶ Type 2 Diabetes: Etiology, Epidemiology, Pathogenesis, Treatment

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Dyslipidemia in Obesity

28

Dick C. Chan, Jing Pang, and Gerald F. Watts

Contents

Abstract

Obesity is associated with an increased risk of atherosclerosis and coronary artery disease, in part due to its strong association with atherogenic dyslipidemia. The latter is characterized by elevated plasma triglycerides, low plasma high-density lipoprotein (HDL) cholesterol, and high plasma concentrations of apolipoprotein (apo) B-containing lipoproteins. Dysregulation of lipoprotein metabolism in obese subjects may be due to a combination of overproduction of very-low-density lipoprotein, decreased catabolism of apoB-containing particles, and increased catabolism of HDL particles. These abnormalities may be consequent on a global metabolic effect of insulin resistance and an excess of visceral fat. Lifestyle modifications (dietary restriction and increased physical activity) are first-line therapies to improve lipid abnormalities in obesity. Pharmacological treatments, such as statins, fibrates, ezetimibe, and fish oils, could also be employed alone or in combination with other agents to optimize the benefit of lifestyle modifications on atherogenic dyslipidemia. Kinetic studies show that improvements in lipid and lipoprotein profiles in obesity can be collectively achieved by several mechanisms of action including decreased secretion and increased catabolism of apoB, as well as increased secretion and decreased catabolism of apoA-I. There are several pipeline therapies for correcting atherogenic abnormalities in

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lipoprotein metabolism. However, their clinical efficacy, safety, and cost-effectiveness remain to be demonstrated.

Keywords
Visceral Obesity • Lipoprotein Metabolism • Insulin Resistance • Metabolic Syndrome • Cardiovascular Disease • Lipid Management

1 Introduction

Obesity, particularly the visceral type, increases the risk of atherosclerosis and coronary artery disease principally owing to the effects of coexistent insulin resistance, atherogenic dyslipidemia (elevated triglyceride, low HDL cholesterol, and elevated small, dense LDL particles), hypertension, and pro-inflammatory/thrombotic state (Poirier et al. 2006; Yusuf et al. 2005; Després et al. 1990; Tchernof and Després 2013). This constellation of metabolic disorders is known collectively as the metabolic syndrome (MetS) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001; Alberti and Zimmet 1998). Dyslipidemia is the most common and consistent abnormality in obese subjects. This review focuses on the dysregulation and therapeutic regulation of lipoprotein transport in obese subjects from studies chiefly carried out in vivo with stable isotope tracers. We also examine the kinetic effects of lifestyle modification and pharmacotherapy for correcting the lipid and lipoprotein abnormalities in visceral obesity.

1.1 Dyslipidemia: A Cardiovascular Risk Factor in Obesity

Visceral obesity is strongly associated with dyslipidemia. High plasma triglycerides, low HDL cholesterol, and high concentrations of apolipoprotein (apo) B-containing lipoproteins are arguably the major mediators of atherogenicity (Després et al. 1990; Tchernof and Després 2013). In the INTERHEART study, the ratio of apoB to apoA-I was found to be the strongest risk factor followed by diabetes and hypertension in predicting myocardial infarction (Yusuf et al. 2004). In the European Prospective Investigation into Cancer Study-Norfolk (EPIC-Norfolk), both men and women with metabolic dyslipidemia had increased coronary artery disease (CAD) risk (HR 1.61, 95 % CI 1.40–1.86 and HR 1.78, 95 % CI 1.47–2.15) compared with subjects with normal triglyceride and HDL cholesterol levels (Rana et al. 2009).

1.1.1 Hypertriglyceridemia

The epidemiological evidence that hypertriglyceridemia is an independent risk factor for CVD has been demonstrated by two *Mendelian* randomization studies showing the causal association between genetic variation in the apoA5, apoC-III, and LPL genes with myocardial infarction (Miller et al. 2011; Jorgensen et al. 2012; Varbo et al. 2013). The atherogeneity of hypertriglyceridemia relates to small triglyceride-rich lipoprotein (TRL) remnant particles which induce endothelial dysfunction, inhibit fibrinolysis, and enhance coagulation and vascular inflammation. Readily traversing the arterial wall, smaller TRL remnants (that are rich in cholesterol and apoE) are trapped by connective tissue matrix and after phagocytosis transform arterial wall macrophages to atherogenic "foam cells." TRL lipolysis also releases toxic products, such as oxidized free fatty acids (FFAs) and lysolecithin, that further induce endothelial cell inflammation and coagulation (Nordestgaard and Nielsen 1994; Tabas et al. 2007; Goldstein et al. 1980; Zheng and Liu 2007).

1.1.2 Low HDL Cholesterol

Population studies have shown that plasma HDL levels correlate inversely with cardiovascular disease risk (Singh et al. 2007). Evidence suggests that the cardiovascular effect of the HDL system may relate chiefly to apoA-I content of HDL particles. The IDEAL and EPIC-Norfolk studies indicated that higher apoA-I is an independent, negative predictor of cardiovascular risk (van der Steeg et al. 2008). The anti-atherogenic effect of HDL is attributed to its role in reverse cholesterol transport (RCT) in which HDLs remove cholesterol from cells (such as macrophages in the artery wall) directly back to the liver or indirectly via intermediate-density lipoprotein (IDL) and

low-density lipoprotein (LDL) particles (Lewis and Rader 2005). HDLs also inhibit LDL oxidation, promote endothelial repair, improve endothelial function, have antithrombotic and anti-inflammatory properties, and inhibit the binding of monocytes to the endothelium (Kontush and Chapman 2006).

1.1.3 Elevated ApoB-100 and Small, Dense LDL

ApoB-100 is the major constituent protein of very-low-density lipoprotein (VLDL), IDL, and LDL particles. Hence, plasma concentration of apoB-100 reflects the total numbers of atherogenic particles (Young 1990). Prospective epidemiological studies and lipid-lowering trials clearly demonstrate that apoB-100 is at least as good as and often better than LDL cholesterol in estimating CVD risk (Chan and Watts 2006). Emerging evidence also suggests that subclasses of LDL are also important indicating that accumulation of small, dense LDL particles in plasma is associated with increased risk of cardiovascular disease (CVD) (Berneis and Krauss 2002). The atherogenicity of these particles involves several mechanisms, including greater susceptibility to oxidative modification, decreased affinity for LDL receptor, increased binding to heparan sulfate proteoglycans in the matrix of arterial wall, and impairment of endothelial function due to depression in expression and activity of nitric oxide synthase (Krauss 2010).

1.2 Pathogenesis of Atherogenic Dyslipidemia in Obesity

Integral to atherogenic dyslipidemia in obesity is dysregulation of VLDL metabolism. This results from hepatic insulin resistance which is related to ectopic fat accumulation in visceral adipose tissue and liver (Ginsberg and Huang 2000; Taskinen 2003; Adiels et al. 2008).

Increased FFA released from adipose tissue suppresses insulin-mediated glucose uptake by the skeletal muscle. To compensate for the decreased insulin sensitivity in the muscle, the pancreas increases insulin secretion to maintain normal glucose tolerance. Chronic hyperinsulinemia may further exaggerate insulin resistance by downregulating insulin receptors and desensitizing post-receptor pathways. Moreover, the diminished fatty acid oxidation capacity in the skeletal muscle cells also increases the intramyocellular lipid (fatty acyl-CoA and triglycerides) concentration. This effect in turn further impairs skeletal muscle glucose uptake and whole-body insulin sensitivity.

The production of apoB-100 is mainly regulated by the availability of triglyceride and cholesterol in the liver (Sniderman and Cianflone 1993; Thompson et al. 1996). Increased visceral fat accumulation in obesity markedly increases the flux of FFA in the portal vein to the liver. The increased flux of FFAs to the liver stimulates hepatic secretion of apoB-100 by increasing synthesis of cholesterol and triglycerides (Tchernof and Després 2013). Insulin resistance is also a major determinant of VLDL apoB-100 metabolism in obesity. Forkhead box protein O1 (FOXO1) is a transcription factor that activates gluconeogenesis (Matsumoto et al. 2006; Brown and Goldstein 2008). In the insulin-resistant state, insulin fails to inactivate FOXO1, thereby enhancing gluconeogenesis and de novo lipogenesis (DNL). Chronic hyperinsulinemia also induces DNL by enhancing sterol regulatory element binding protein 1-c (SREBP-1c) and delays the intrahepatic degradation of apoB (Uyeda and Repa 2006; Horton et al. 2002). In the skeletal muscle and adipose tissue, insulin resistance also impairs TRL catabolism by decreasing lipoprotein lipase (LPL) activity (Tchernof and Després 2013). Insulin resistance impairs LDL receptor expression and activity necessary for normal LDL apoB-100 clearance. ApoC-III, an inhibitor of LPL and of TRL remnant uptake by hepatic lipoprotein receptors, is strongly associated with insulin resistance. A loss of insulin-mediated suppression of apoC-III via the FOXO1 pathway (Altomonte et al. 2004), coupled with glucose-stimulated apoC-III expression, further delays the apoB-100 catabolism by inhibiting LPL and receptor-mediated uptake by the liver. Increased competition between VLDLs, chylomicrons, and their remnants for lipolytic and receptor-mediated clearance further exacerbates hypertriglyceridemia in the fasted and postprandial states

(Taskinen et al. 2011). Moreover, experimental studies have demonstrated that insulin resistance stimulates de novo lipogenesis, increases microsomal triglyceride transfer protein, and enhances intracellular apoB-48 stability in the intestine (Duez et al. 2008). Increased FFA load delivered to the enterocyte, especially during the postprandial period, may further impair insulin signaling. Collectively, these effects would increase enterocytic secretion of apoB-48.

Consistent with the aforementioned mechanisms, we have demonstrated that insulin-resistant, obese individuals have elevated hepatic secretion of apoB-100, apoC-III, and triglycerides in VLDL compared with nonobese individuals (Chan et al. 2006a). This abnormality is associated with the delayed clearance of IDL and LDL apoB-100 (Chan et al. 2002a). We have found that high liver and visceral fat contents are strong predictors of VLDL apoB-100 oversecretion in subjects with visceral obesity (Chan et al. 2010a; Watts et al. 2003a). Recently, we also demonstrate that postprandial hypertriglyceridemia in visceral obesity relates to an overproduction and impaired catabolism of apoB-48-containing lipoproteins (Wong et al. 2014a).

The increased hepatic secretion of large triglyceride-rich VLDL has a major qualitative and quantitative impact on the metabolism of LDL and HDL (Adiels et al. 2008; Rashid et al. 2003). Briefly, a high hepatic triglyceride content expands the plasma pool of triglyceride-rich VLDL and results in increased cholesteryl ester transfer protein (CETP)-mediated heteroexchange of neutral lipid with LDL. Under the action of hepatic lipase (HL), which is overactive in insulin resistance, the triglyceride-rich LDL particles are hydrolyzed into small, dense LDL, which are less efficiently cleared from the circulation. The same metabolic process is also involved in the remodeling of HDL particles. Hydrolysis of triglyceride-rich HDL particles by HL decreases the size of HDL particles, which are then cleared rapidly from plasma.

In summary, a critical, selective effect of insulin resistance and visceral fat accumulation increases the secretion of VLDL apoB-100 and chylomicron apoB-48; delays the hepatic clearance of chylomicron remnants, VLDL and LDL apoB-100; and enhances the catabolism of HDL apoA-I (Fig. 1). These can be therapeutically modulated with lifestyle and drug therapy.

1.3 Management of Dyslipidemia

Prevention and treatment of dyslipidemias is an integral part of CVD prevention. LDL cholesterol remains the primary target of therapy in most strategies of dyslipidemia management (Reiner et al. 2011; Stone et al. 2014). The consensus statement from the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) on the prevention of CVD in clinical practice recommends the assessment of total CAD or CV risk. Patients with known clinical CVD and those who do not have clinical CVD but who have chronic kidney disease (as defined by a GFR <60 mL/mim/1.73 m^2), type 2 diabetes, or type 1 diabetes with microalbuminuria or those with a 10-year risk of a first fatal atherosclerotic CV event (Systematic Coronary Risk Evaluation, SCORE) of >10 % are considered at very high risk; they should be treated to an LDL cholesterol goal of <70 mg/dL (1.8 mmol/L) or a ≥ 50 % reduction from baseline LDL cholesterol, a non-HDL cholesterol goal of <100 mg/dL (2.6 mmol/L), and an apoB-100 goal of <80 mg/dL. For subjects at high (with a SCORE risk 5–10 % or familial dyslipidemia) and moderate (with a SCORE risk 1–5 %) risks, an LDL cholesterol target of <2.5 mmol/L and <3 mmol/L should be considered, respectively (Reiner et al. 2011). The ESC/EAS guidelines also recognize other factors, such as elevated triglycerides, social deprivation, central obesity, elevated lipoprotein, subclinical atherosclerosis, or family history of premature CVD, may further modify absolute risk.

The recent guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA) on the control of blood cholesterol to reduce atherosclerotic cardiovascular disease (ASCVD) in adults do not specify LDL cholesterol targets (Stone et al. 2014). Patients with known clinical ASCVD and those who do not

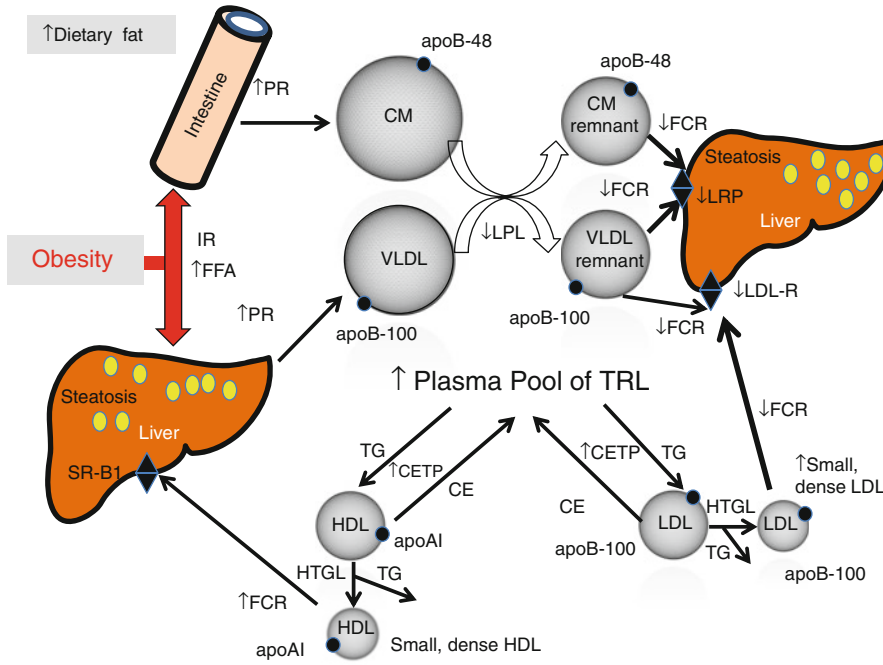

Fig. 1 Pathogenesis of atherogenic dyslipidemia in the setting of hypertriglyceridemia, insulin resistance, and obesity

have clinical ASCVD but who have primary elevation of LDL cholesterol (>4.9 mmol/L) or diabetes (type I or type II) with LDL cholesterol between 1.8 and 4.9 mmol/L and a 10-year ASCVD risk of >7.5 % are considered at high risk; they should be treated with high-intensity statin achieving >50 % reduction of LDL cholesterol. The guidelines recommend that those with a predicted ASCVD risk of >7.5 % should be considered for moderate- to high-intensity statin. Those who have a predicted ASCVD risk of 5–7.5 % or diabetes with low risk should consider moderate-intensity statin therapy to achieve 30–50 % reduction of LDL cholesterol. However, both the ESC/EAS and ACC/AHA guidelines do not specify targets for triglyceride and HDL cholesterol levels.

Treatment should initially focus on lifestyle modifications including weight loss, dietary modification, and exercise. Lipid-regulating agents may be used as second-line strategy to optimize the regulation of dyslipoproteinemia (Third report of the National Cholesterol Education Program (NCEP) 2002). The commonly used lipid-regulating agents include statins, fibrates, cholesterol absorption inhibitors, and n-3 polyunsaturated fatty acid (n-3 PUFA) supplementation. Details of the use of each treatment are discussed below with specific reference to mechanisms of action (Table 1).

1.3.1 Dietary and Lifestyle Modification

Weight loss Studies of weight loss have shown that weight reduction is associated with a reduction in CVD and diabetes mortality, probably owing to improvements in a number of cardiovascular risk factors including insulin resistance, dyslipidemia, glycemic control, hypertension, and hemostatic factors (Van Gaal et al. 1997). Dietary intervention is the most commonly used weight loss strategy. Weight reduction can result in a 10 % decrease in total cholesterol, a 15 % decrease in LDL cholesterol, a 30 % decrease in triglycerides, and an 8 % increase in HDL cholesterol for every 10 kg loss (Dattilo and Kris-Etherton 1992). A low-calorie diet of about 1,000–1,500 kcal per day is the preferred method of dietary intervention. Reduced intakes of saturated fats (<7 % of total calories) and cholesterol (<200 mg/day) produce the most desirable

Table 1 Effect of therapeutic interventions on plasma lipid and lipoprotein concentrations in obesity

Plasma lipid and lipoprotein concentrations					
Interventions	LDL cholesterol (%)	Non-HDL cholesterol (%)	ApoB (%)	Triglyceride (%)	HDL cholesterol (%)
Weight loss	↓10–20	↓10–20	↓10–20	↓10–30	↑5–10
Exercise	↓5–15	↓5–15	↓10–20	↓10–25	↑5–10
Statins	↓20–55	↓15–55	↓15–50	↓5–30	↑5–10
Ezetimibe	↓10–20	↓5–15	↓10–20	↓5–10	↑0–5
Fibrates	↓5–20	↓5–25	↓5–20	↓20–50	↑10–20
n-3 PUFAs	↑5–10	↓0–20	↓5–20	↓25–30	↑0–5
PCSK9 inhibitor	↑40–60	↓35–55	↓35–50	↓15–25	↑4–10
PPAR-α/δ agonists	↓0–15	↓0–15	↓5–15	↓15–25	↑8–10
CETP inhibitors	↓10–40	↓30–35	↓5–20	↓0–10	↑80–150
MTP inhibitors	↓30–50	↓30–50	↓25–50	↓10–50	↑5–10
ApoB ASO	↓35–50	↓35–50	↓35–45	↓35–45	↑5–15
ApoC-III ASO	↓0–5	NA	NA	↓20–50	↑0–20
GLP-1 agonist	↓10–20	↓5–20	↓5–15	↓10–30	↑0–10
5-HT2C receptor agonist	↓0–2	NA	↓2–5	↓5–8	↑1–3
Phentermine + topiramate	↓5–10	↓5–10	NA	↓5–15	↑5–10

ApoA-I apolipoprotein A-I, *apoB* apolipoprotein, *ASO* antisense oligonucleotides, *CETP* cholesteryl ester transfer protein, *GLP-1* glucagon-like peptide-1 receptor, *HDL* high-density lipoprotein, *MTP* microsomal triglyceride transfer protein, *NA* data not available, *PCSK9* proprotein convertase subtilisin/kexin type 9, *PPAR* peroxisome proliferator-activated receptors, *PUFAs* polyunsaturated fatty acids, *LDL* low-density lipoprotein, *5-HT2C* Serotonin 2C, *TG* triglyceride, ↑ increase, ↓ decrease

lipoprotein responses. Mediterranean-style diets can achieve sustained reductions in plasma triglycerides (10–15 %), insulin resistance, systolic blood pressure, and risk of type 2 diabetes (Shai et al. 2008; Esposito et al. 2010). Such diets have recently been shown to decrease the incidence of major CVD events in a primary prevention setting in people with dyslipidemia, metabolic syndrome, and type 2 diabetes (Estruch et al. 2013). Our tracer kinetic data suggest that weight loss using a standard low-fat, low-caloric diet decreases the hepatic secretion of VLDL apoB-100 and reciprocally upregulates apoB-100 catabolism (Riches et al. 1999). These mechanisms could also explain improvements in plasma markers for TRL metabolism (apoC-III, apoB-48, remnant-like particle cholesterol) (Chan et al. 2008a). These events were chiefly related to the reduction in visceral adipose tissue and intrahepatic fat content, as well as improvements in insulin sensitivity (Estruch et al. 2013). The increase in LDL apoB-100 clearance following weight loss could be due to increased LDL receptor activity related to reduction in both de novo cholesterol synthesis and hepatic insulin resistance (James et al. 2003). The improvement in LDL metabolism with weight loss is also associated with an increase in LDL particle size. We also found that weight loss decreased both the catabolism and production of HDL apoA-I, thereby not altering plasma HDL apoA-I nor HDL cholesterol concentrations (Ng et al. 2007). As indicated earlier, the catabolic changes in HDL with weight loss could be a consequence of reduction in the plasma VLDL-triglyceride pool available for exchange with HDL (Adiels et al. 2008; Rashid et al. 2003).

Physical activity A sedentary lifestyle in obese individuals may partly increase risk of CVD by exacerbating insulin resistance and dyslipidemia (Knowler et al. 2002). Several studies have reported that increased physical activity corrects dyslipidemia in patients with obesity and type 2 diabetes (Wing et al. 2011; Bassuk and Manson 2003). However, the type of exercise differentially affects lipoprotein metabolism (Kraus and Houmard 2002). Endurance exercise training

reduces plasma triglyceride and raises HDL cholesterol, particularly in patients with coexisting hypertriglyceridemia and low HDL cholesterol. Resistance training has a minimal impact on plasma triglyceride and TRLs. Previous kinetic studies suggested that endurance exercise training decreases plasma triglyceride by decreasing VLDL-triglyceride secretion and augmenting VLDL-triglyceride clearance (Tsekouras et al. 2009; Magkos et al. 2006). In people with type 2 diabetes who were overweight/obese, a 6-month supervised exercise program decreases plasma triglyceride levels chiefly by decreasing VLDL apoB-100 secretion and pool size, with no effect on LDL apoB metabolism (Alam et al. 2004; Stolinski et al. 2008). These favorable effects of exercise on lipoprotein metabolism may be mediated by favorable changes in body weight and composition, as well as by enhancements in hepatic insulin sensitivity and blood flow, and increase in peripheral LPL activity (Westheim and Os 1992). Few studies have examined the effect of exercise on HDL metabolism. Using radiolabeled autologous HDL, exercise was shown to increase plasma HDL cholesterol by a mechanism involving both decreased HDL apoA-I catabolism and increased HDL apoA-I secretion in overweight men whose weight remained stable (Thompson et al. 1997).

1.3.2 Pharmacotherapy

Although treatment of dyslipidemia with diet and other lifestyle measures can improve dyslipidemia in obesity, their efficacy is generally disappointing owing to poor adherence (Euroaspire and Group 2001). Effective management of dyslipidemia therefore requires lipid-regulating pharmacotherapy. The treatment and target of LDL cholesterol reduction in obese individuals should follow the recommendations of the ESC/EAS and ACC/AHA guidelines as discussed earlier.

HMG-CoA reductase inhibitors Clinical trials have demonstrated consistently that cholesterol-lowering effect with statin therapy is associated with a reduction in the incidence of myocardial infarction and other coronary events in both primary and secondary prevention settings (Ray et al. 2010). Statins are potent LDL cholesterol-lowering agents (up to 60 %) with lesser but significant effects on triglyceride (up to 30 %) and increases in HDL cholesterol (up to 10 %). The efficacy of statins in decreasing plasma triglyceride concentrations depends on the baseline plasma triglyceride level and is proportional to their LDL-lowering effect (Stein et al. 1998). Statins also reduces small LDL particles but with variations between the different statins (Asztalos et al. 2002).

Inhibition of the enzyme HMG-CoA reductase (a rate-limiting enzyme in hepatic cholesterol synthesis) by statin results in a reduction in intracellular cholesterol content that induces an increase in LDL receptor synthesis and thus an increase in LDL and chylomicron remnant clearance (Ginsberg 2006). This mechanism is consistent with kinetic studies in humans, demonstrating that statin treatment accelerates the catabolism of apoB-100-containing lipoprotein and chylomicron remnants (Chan et al. 2002b, c). However, treatment of viscerally obese subjects with atorvastatin or rosuvastatin failed to lower VLDL apoB-100 secretion (Chan et al. 2002b; Ooi et al. 2008a). The lack of effect of these potent statins on VLDL apoB-100 secretion may be partly attributable to uncorrected and persistent insulin resistance. Increased intestinal absorption of dietary cholesterol with statin potentially increases lipid substrate availability to the liver (Watts et al. 2003b); this may stimulate apoB secretion, thereby diminishing the effect of statins on apoB secretion. These two mechanisms could also account for the lack of efficacy of statins in lowering plasma triglyceride levels in some studies.

Statins do not generally significantly raise HDL cholesterol, any increase in obese subjects probably being consequent to a triglyceride-lowering effect. Recent in vitro data suggested that inhibition of cholesterol biosynthesis with statins increases the production of apoA-I by decreasing the Rho signaling pathway and activating peroxisome proliferator-activator receptor-α (PPAR-α) (Geneieve et al. 2001). However, divergent results have also been reported on the effects of statins on HDL apoA-I metabolism. We found that atorvastatin (40 mg/day) did not alter HDL apoA-I

kinetics in subjects with visceral obesity (Chan et al. 2006b). In another study, we showed that rosuvastatin concomitantly increased the production and catabolism of HDL apoA-I, with no change in plasma HDL apoA-I concentration in MetS patients who were overweight/obese (Ooi et al. 2008b). These findings suggest a specific effect on HDL apoA-I metabolism. Whether the effects of these changes in HDL metabolism contribute to the CV benefits of statin requires further investigation.

Fibric-acid derivatives Several trials show that fibrates decrease CVD events, particularly in patients with atherogenic dyslipidemia and type 2 diabetes (Scott et al. 2009; The ACCORD Study Group 2010). Data from a meta-analysis of five randomized trials of fibrates also suggest that these agents reduce CVD events among patients with a high triglyceride and low HDL cholesterol phenotype (Sacks et al. 2010). Fibrates can decrease plasma triglyceride concentrations by up to 50 % and LDL cholesterol up to 20 %, increase HDL cholesterol by up to 20 %, and favor the formation of large, less dense LDL particles (Katsiki et al. 2013). The benefit of fibrates in clinical endpoint trials may be partly related to correction of lipid and lipoprotein metabolism, in particular TRL and HDL metabolism.

Fibrates are PPAR-α agonists that may reduce triglyceride substrate availability to the liver by stimulation of peroxisomal and mitochondrial β-oxidation thereby decreasing hepatic VLDL secretion. Fibrates promote VLDL lipolysis by activating LPL and reducing apoC-III gene expression (Staels et al. 1998; Forcheron et al. 2002; Berge and Moller 2002) Fibrates also increase the expression of apoA-I and ABCA1 transporters by activating the liver X receptor alpha (LXR-α) pathway, thereby promoting cholesterol transport from the periphery to the liver via HDL (Liang et al. 2000). Recent evidence suggests that fibrates also stimulate the hepatic receptor-mediated uptake of LDL by inhibition of hepatic cholesterol synthesis via its effect on SREBPs (Liang et al. 2000). Consistent with this, we found that in MetS subjects who were overweight/obese, fenofibrate significantly increased the catabolism of VLDL, IDL, and LDL apoB-100, and this may partly relate to reduction in apoC-III production (Watts et al. 2003c; Chan et al. 2008b). Fenofibrate does not appear to decrease hepatic secretion of VLDL apoB-100, and this could relate to uncorrected insulin resistance. Fenofibrate increased plasma concentration of apoA-I by enhancing the production of HDL apoA-I (Watts et al. 2003c).

Cholesterol absorption inhibitors Hepatic availability of cholesterol, a regulator of plasma apoB transport, is in part determined by intestinal absorption. Ezetimibe, a cholesterol absorption inhibitor, has been shown to reduce LDL cholesterol by about 20 % (Pandor et al. 2009). Although its effect on plasma triglyceride is modest, ezetimibe may have a more pronounced postprandial effect in lowering TRL remnants against background statin therapy (Bozzetto et al. 2011). Ezetimibe also significantly decreases LDL particle number but has an inconsistent effect on LDL particle size (Rizzo et al. 2009). The effect of ezetimibe on CVD outcomes is unclear (Fleg et al. 2008; Kastelein et al. 2008; Baigent et al. 2011), with some studies reporting no benefit effect while others showing atherosclerosis regression and reduction in CVD events following in combination with statins. The recent outcome of IMPROVE-IT study (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) supports the use of ezetimibe in high-risk subjects on optimal statin therapy (Cannon 2014). In a subgroup analysis, patients with type 2 diabetes seemed to show a greater benefit with ezetimibe/simvastatin than nondiabetic individuals.

Inhibition of intestinal cholesterol absorption by ezetimibe results in a reduction in intracellular cholesterol content that induces an increase in LDL receptor synthesis and thus an increase in LDL and chylomicron remnant clearance (Phan et al. 2012). Ezetimibe decreases plasma concentrations of apoB-100 and LDL cholesterol chiefly by increasing the fractional catabolism of LDL apoB-100 in subjects with hypercholesterolemia (Tremblay et al. 2006). We also found that addition of ezetimibe to a moderate weight loss diet in obese subjects can significantly lower plasma concentrations of apoB-100 and LDL cholesterol

chiefly by increasing LDL apoB-100 FCR (Chan et al. 2010b). Another important finding from this study was that adding ezetimibe to weight loss diet further decreased intrahepatic triglyceride content independent of body weight, visceral fat, and insulin sensitivity (Chan et al. 2010b). The precise mechanism remains unclear but may relate to its inhibitory effect on hepatic SREBP-1c mRNA expression, which in turn inactivates the hepatic expression of genes involved for lipogenesis (Naples et al. 2012). Whether the improvement in hepatic steatosis contributes to the CV benefits of ezetimibe remains to be investigated.

n-3 PUFAs Fish oils are a rich source of n-3 PUFAs, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) (Jump 2002). n-3 PUFAs also have a wide range of anti-atherosclerotic effects including improvement in blood pressure, cardiac and vascular function, prostanoids, coagulation, and immunological and inflammatory events (Angerer and von Schacky 2000). However, the role of n-3 PUFAs in reducing CVD events and mortality has not yet been established. Two clinical outcome trials with n-3 PUFAs, however, failed to show significant CVD benefit in high-risk patients treated with a statin (ORIGIN Trial Investigators 2012; Risk and Prevention Study Collaborative Group 2013). The apparent lack of benefits in these trials could be attributed to the lower doses of n-3 PUFA employed.

Nevertheless, the modification of lipid and lipoprotein metabolism by higher doses of n-3 PUFAs could have significant anti-atherogenic effects. Human studies show that n-3 PUFA supplementation decreases plasma triglyceride concentrations by up to 40 % but no consistent effects on plasma concentrations of HDL cholesterol and apoA-I (Harris 1997). The mechanism of action of n-3 PUFAs on plasma triglyceride level could result in a decrease in hepatic triglyceride synthesis as a consequence of inhibition of diacylglycerol acyltransferase (DGAT), fatty acid synthase, and acetyl-CoA carboxylase enzyme activities (Price et al. 2000). n-3 PUFAs also enhance fatty acid ß-oxidation by stimulating PPAR-α activity and decrease the hepatic pool of triglyceride by suppressing the expression of SREBP-1c gene via inhibition of de novo synthesis of both fatty acids and triglycerides (Xu et al. 1999).

Consistent with the above mechanisms, we found that in obese men n-3 PUFA ethyl esters (4 g/day) diminished the hepatic secretion of VLDL apoB-100 with no effect on the catabolisms of VLDL, IDL, and LDL apoB-100 (Chan et al. 2002d). The 6-week treatment of n-3 PUFAs also decreased the catabolic and production rates of HDL apoA-I, accounting for the lack of demonstrable effect on plasma apoA-I concentrations (Chan et al. 2006b). Reduction in HDL apoA-I catabolism may relate to the decrease in plasma triglyceride and greater stability of HDL particles (Rashid et al. 2003). Furthermore, our recent data also suggest that addition of n-3 PUFA supplementation to a moderate weight loss diet in obese subjects can significantly improve chylomicron metabolism by independently decreasing the secretion of apoB-48 (Wong et al. 2014b). The precise mechanism of action of n-3 PUFAs on chylomicron TRL metabolism is also not fully understood but may relate to decreased enterocyte secretion of apoB-48.

Niacin Pharmacological doses of niacin decrease plasma triglyceride, LDL cholesterol, and lipoprotein(a) by up to 35 %, 15 %, and 30 %, respectively, and increase HDL cholesterol by 25 % (Chapman et al. 2010). The mechanism of action involves decreased adipose tissue lipolysis and flux of FFAs to the liver, which, together with direct inhibition of hepatic triglyceride synthesis, decreases VLDL secretion and LDL production (Kamanna and Kashyap 2000). Niacin also raises HDL cholesterol and apoA-I by decreasing the FCR of apoA-I (Lamon-Fava et al. 2008). Data from cellular studies show that niacin selectively decreases the hepatic catabolism of apoA-I via the "HDL holoparticle catabolism receptor" pathway (van der Hoorn et al. 2008), thereby increasing the recycling of HDL particles and theoretically augmenting RCT. While early trials suggested that niacin could decrease CVD events and mortality in patients with coronary disease (Carlson and Rosenhamer 1988; The Coronory Drug Project Group 1975; Canner et al. 1986; Brown et al. 2001), two recent

clinical trials have failed to show significant benefits of niacin on CVD events (The AIM-HIGH Investigators 2011; Landray et al. 2014). The HPS2-THRIVE (Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events), the largest trial employing niacin, examined the effect of Tredaptive (ER niacin combined with laropiprant, a prostaglandin D2 inhibitor) in CVD patients with well-controlled LDL cholesterol on simvastatin receiving or not receiving ezetimibe (Landray et al. 2014). This trial found no significant benefit on the primary CV but serious adverse events including excess absolute diabetic complications, new onset type 2 diabetics, hemorrhagic stroke, infections, gastrointestinal intracranial bleeding, and gastrointestinal complications. The unfavorable risk-to-benefit ratio has resulted in withdrawal of niacin-laropiprant from the market.

1.3.3 Combination Therapy

In many obese patients with atherogenic dyslipidemia, more aggressive treatment strategies involving the use of more than one lipid-regulating agent may be required (Jacobson 2001). This approach harnesses the complementary mechanistic effects of the different agents on lipid and lipoprotein metabolism. However, the ACC/AHA guidelines recommend that adherence to lifestyle and to statin therapy should be emphasized before the addition of a nonstatin drug is considered because there is no convincing data to support the routine use of nonstatin drugs combined with statin therapy to reduce CVD events (Stone et al. 2014).

Several possible combinations include statin-fibrate, statin-ezetimibe, and statin-n-3 PUFA regimens. In patients who are statin intolerant or are not able to tolerate higher statin doses, other combinations such as ezetimibe with bile acid sequestrants may be considered. We have reported that in insulin-resistant obese men, combination treatment with atorvastatin and fish oils resulted in additive effects on plasma triglyceride (−40 %) and HDL cholesterol (+15 %) than either of atorvastatin or fish oil alone (Chan et al. 2002e). Kinetic data revealed that atorvastatin plus fish oils decreased VLDL apoB-100 secretion and increased the FCRs of VLDL, IDL, and LDL apoB (Chan et al. 2002d). These improvements were not achieved by either of atorvastatin or fish oil monotherapy.

Hence, combination lipid-regulating therapy may be clinically important to manage dyslipidemia in obesity. As reviewed earlier, their mechanisms of action of all these agents on lipoprotein kinetics are different. Therefore, addition of any of these agents to a statin should theoretically correct mixed lipid disorders in obesity. The beneficial effects of combination therapy (such as statin-fibrate or statin-ezetimibe regimens) on CVD reduction have been demonstrated. However, the use of lipid-regulating drugs in combination (such as statin-fibrate regimens) may have the potential for interactions that increases the risks of adverse effects, such as myositis and hepatotoxicity (Bays and Dujovne 1998). Therefore, clinicians should carefully understand the mechanism of potential therapeutic drug interactions prior to combining two or more lipid-regulating drugs.

Agents in pipeline or development There are several novel approaches for regulating lipoprotein metabolism that are relevant to the future management of atherogenic dyslipidemia, and these warrant investigation. These include selective PPAR-α modulators; PPAR-α/δ agonists; inhibitors of diacylglycerol acyltransferase, proprotein convertase subtilisin/kexin type 9 (PCSK9), CETP, and microsomal triglyceride transfer protein (MTP); antisense oligonucleotides (ASO) of apoB-100 and apoC-III; and reconstituted and recombinant HDL (Watts et al. 2013; Stein and Raal 2014). Although these newer agents appear to be promising approaches for use in the treatment of atherogenic dyslipidemia, safety issues, in particular increased risk of hepatic steatosis with apoB-100 ASO and MTP inhibitors, require caution (Thomas et al. 2013; Cuchel et al. 2007). Nevertheless, PCSK9 inhibition appears to be a safe and promising therapeutic approach for regulating lipoprotein metabolism (Dadu and Ballantyne 2014). Several clinical trials with monoclonal antibodies to PCSK9

(alirocumab and evolocumab) consistently demonstrate significant reductions in plasma concentrations of LDL and TRLs (Raal et al. 2015; McKenney et al. 2012). The clinical benefit of PCSK9 inhibition to lower LDL cholesterol levels has been recently demonstrated in two long-term studies of patients at high risk of CVD or with FH reporting approximately 50 % reductions in composite cardiovascular events at 12–18 months with anti-PCSK9 therapy (Robinson et al. 2015; Sabatine et al. 2015). Whether these drugs will be endorsed by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for wider use in other patient groups, including obese and type 2 diabetes with dyslipidemia, remains questionable. This will depend on the outcome of ongoing, large-scale clinical trials and demonstrated cost-effectiveness.

There are several recently approved agents for obesity in combination with lifestyle modification that may improve lipoprotein metabolism. These include liraglutide (a glucagon-like peptide-1 receptor agonist) (Drucker et al. 2010), lorcaserin (a serotonin 5-HT2C receptor agonist), and Qsymia (an extended-release combination of phentermine and topiramate) (Fidler et al. 2011; Garvey et al. 2012). Moreover, bariatric surgery has also gained importance for the treatment of obesity, showing significant improvement in body weight maintenance and glycemic control (Poirier et al. 2011). However, the precise mechanism of action of these agents on lipoprotein metabolism remains to be demonstrated.

2 Conclusion

Obesity is an escalating problem worldwide and is frequently associated with insulin resistance and dyslipidemia, which in turn is causally related to an increased risk of type 2 diabetes and CVD. Dyslipidemia in visceral obesity is characterized by elevated plasma triglycerides, reduced HDL cholesterol, elevated apoB concentrations, and a predominance of small, dense LDL particles. These abnormalities arise from kinetic defects in lipoprotein metabolism, including overproduction of VLDL apoB-100, VLDL apoC-III, and chylomicrons; decreased catabolism of chylomicron remnants, VLDL and LDL apoB-100; and an increased catabolism of HDL apoA-I particles. The management of obesity, including weight loss and increased exercise, should be initially implemented in treating obesity-related dyslipidemia. The use of anti-obesity drugs or bariatric surgery may further improve the lipid-lowering effect in combination with lifestyle modification. Correction of elevated LDL cholesterol and apoB-100 with statins should be employed at high absolute risk of CVD concurrently with lifestyle modification in obese subjects. However, statins only contribute to modest improvements in atherogenic dyslipidemia but are not as effective as other lipid-regulating agents, such as fibrate and n-3 PUFAs. Intensive treatment could involve additional therapy with fibrates or n-3 PUFA supplementation. However, there is limited clinical evidence to support the routine use of combination therapy to reduce CVD events in obese individuals or people at high risk of CVD.

At present, the use of statin-fibrate combination in insulin-resistant patients with atherogenic dyslipidemia is supported by subgroup analysis from clinical outcome studies. However, safety and tolerability must be considered carefully. The recent results from the IMPROVE-IT trial demonstrate incremental clinical benefit when adding ezetimibe to statin therapy reducing cardiovascular events. There is no convincing clinical trial evidence that the safer combination of statins with n-3 PUFA improves CVD outcomes despite decreases in plasma triglyceride and increases in HDL cholesterol. New therapies, such as dual PPAR-α/PPAR-δ agonists, DAG, inhibitors of DGAT-1, MTP and PCSK9, ASOs for apoB-100 and apoC-III, and reconstituted and recombinant HDL therapies, could also be employed alone or in combination with conventional therapies to optimize treatment. However, the clinical efficacy, mechanism of action, safety, and tolerability of these newer agents require testing in clinical trials.

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Myokines and Metabolism

29

Bente Klarlund Pedersen

Contents

Abstract

Skeletal muscle has been defined as an endocrine organ. Cytokines and other peptides that are produced, expressed, and released by muscle fibers and exert either autocrine, paracrine, or endocrine actions have been defined as "myokines." The finding that the muscle secretome appears to consist of several hundred secreted factors provides a conceptual basis and a new paradigm for understanding how muscles communicate with other organs such as adipose tissue, liver, and pancreas and how physical activity mediates its numerous effects against the metabolic syndrome.

Keywords

Exercise • Physical training • Inflammation • Myokines

1 Introduction

Regular physical activity is known to have multiple health benefits (Booth et al. 2012), and it is reasonable to suggest that skeletal muscle might mediate some of the well-established protective effects of exercise via secretion of proteins that could counteract the harmful effects of the proinflammatory adipokines secreted by adipose tissue in the obese state (Pedersen 2013).

It is well established that physical inactivity increases, e.g., the risk of type 2 diabetes (Tuomilehto et al. 2001), cardiovascular diseases

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(CVD) (Nocon et al. 2008), colon cancer (Wolin et al. 2009), postmenopausal breast cancer (Monninkhof et al. 2007), and osteoporosis (Borer 2005). Moreover, even short periods of physical inactivity are associated with metabolic changes including decreased insulin sensitivity, attenuation of postprandial lipid metabolism, loss of muscle mass, and accumulation of visceral fat (Olsen et al. 2008; Krogh-Madsen et al. 2010). Such abnormalities are likely to represent a link between reduced exercise and the risks that have been associated with the progression of chronic disorders and premature mortality (Booth et al. 2002).

It has been well recognized that muscles release large amounts of metabolites, such as lactate, during anaerobic, physical exercise. Lactate and other secretory low molecular weight molecules are important, e.g., in training adaptation. However, the recent focus on the secretory capacity of skeletal muscle has been on protein factors. In 2003, we suggested that cytokines or other peptides that are produced, expressed, and released by muscle fibers and exert endocrine effects should be classified as "myokines" (Pedersen et al. 2003). Recently, it was suggested that exercise factors were defined as a subgroup of myokines (Catoire and Kersten 2015).

The recent identification of skeletal muscle as a secretory organ has created a new paradigm: Muscles produce and release myokines, which work in a hormone-like fashion, exerting specific endocrine effects on distant organs. Other proteins produced by skeletal muscle may not be released into the circulation but may rather work via autocrine or paracrine mechanisms, exerting their effects on signaling pathways within the muscle itself (Long et al. 2004; Pedersen 2006, 2009; Walsh 2009; Pedersen and Febbraio 2008; Pedersen et al. 2007). Thereby, myokines may be involved in mediating the multiple health benefits of exercise.

The idea that muscle cells might produce and release a humoral factor dates back many years before the identification of adipose tissue as an endocrine organ (Cook et al. 1987). For nearly half a century, researchers had hypothesized that skeletal muscle cells possessed a "humoral" factor that was released in response to increased glucose demand during contraction (Goldstein 1961). Due to lack of more precise knowledge, the unidentified contraction-induced factor has been named "the work stimulus" or "the work factor" (Pedersen et al. 2003).

It was obvious that the plural form "exercise factors" would be more applicable given the fact that multiple metabolic and physiologic changes are induced by exercise. The early view on the exercise factor concept was predicated on the fact that contracting skeletal muscle mediates metabolic and physiologic responses in other organs, which are not mediated via the nervous system.

This idea was supported by the fact that electrical stimulation of paralyzed muscles in spinal cord injured patients with no afferent or efferent impulses induces many of the same physiological changes as in intact human beings (Kjaer et al. 1996; Mohr et al. 1997). Therefore, it was clear that contracting skeletal muscles were able to communicate to other organs via humoral factors, which are released into the circulation during physical activity. Such factors might directly or indirectly influence the function of other organs such as the adipose tissue, the liver, the cardiovascular system, and the brain.

During the past decade, myocytes have been identified as cells with a high secretory capacity in parallel with the concept of adipocytes being major endocrine cells. It appears that muscle cells, here defined as myoblasts or myocytes, have the capacity to produce several hundred secreted factors (Bortoluzzi et al. 2006; Yoon et al. 2009; Henningsen et al. 2010; Pal et al. 2014; Eckardt et al. 2014; Raschke and Eckel 2013; Catoire and Kersten 2015; Benatti and Pedersen 2015; Pedersen 2012, 2013; Munoz-Canoves et al. 2013; Henriksen et al. 2012; Pedersen and Febbraio 2012; Catoire et al. 2014).

The term "myokine" refers to a protein that is secreted from myocytes. Muscles are able to produce and release proteins that are able to communicate with cells locally within the muscles (autocrine/paracrine) or to other distant tissues (endocrine). This chapter provides an update on some of the muscle-derived cytokines that may be involved in mediating the effects of exercise on components of the metabolic syndrome.

2 Myokines and Adipokines in a Yin-Yang Concept

Adipose tissue was initially considered an inert storage compartment for triglycerides, not the least due to pioneering work from the Spiegelman and Flier (Cook et al. 1987) laboratories in the mid-1980s, who demonstrated that adipocytes are capable of releasing a specific secretory protein called adipsin or complement factor D. Friedman and colleagues later identified leptin as a fat cell-specific secretory factor, deficient in the ob/ob mouse, and responsible for mediating a hormonal signal between fat and the brain (Zhang et al. 1994). Since then, adiponectin, resistin, acylation-stimulating protein, visfatin, and retinol-binding protein 4 have been added to the growing list of adipokines (for review see Scherer 2006). Notwithstanding the role of adiponectin (Shetty et al. 2009), most of the factors that are produced by adipocytes are, however, considered to be proinflammatory, e.g., tumor necrosis factor-alpha (TNF-α), monocyte chemoattractant protein-1, and plasminogen activator inhibitor type 1, and potentially harmful with regard to the development of obesity-induced metabolic and cardiovascular diseases (Pedersen and Febbraio 2012). In order to neutralize the effect of the proinflammatory adipokines, it is obvious that another organ or tissue might offer protection and contribute to produce antiinflammatory components that could provide a counterbalance to the proinflammatory factors that are produced by adipocytes. Given that exercise offers multiple health benefits, it was reasonable to suggest that skeletal muscle might secrete proteins that could counteract the harmful effects of the proinflammatory adipokines secreted by adipose tissue in the obese state (Fig. 1).

The word "myokine" is derived from the Greek words for "muscle" and "motion," and in 2003, we suggested this term should be used as a classification for cytokines or other peptides that are produced, expressed, and released by muscle fibers and exert endocrine effects (Pedersen et al. 2003).

While the word adipokine refers to factors secreted from adipose tissue, the term "myokine" refers to a protein that is secreted from myocytes. Characterization of a number of myokines reveals that skeletal muscles are capable of producing and releasing proteins that can both communicate with cells locally within the muscles (autocrine/paracrine) or to other distant tissues (endocrine).

3 The Myokines

We have previously suggested that physical inactivity and muscle disuse lead to accumulation of visceral fat and consequently to the activation of a network of inflammatory pathways, which promote development of insulin resistance, atherosclerosis, neurodegeneration, and tumor growth and thereby the development of a cluster of chronic

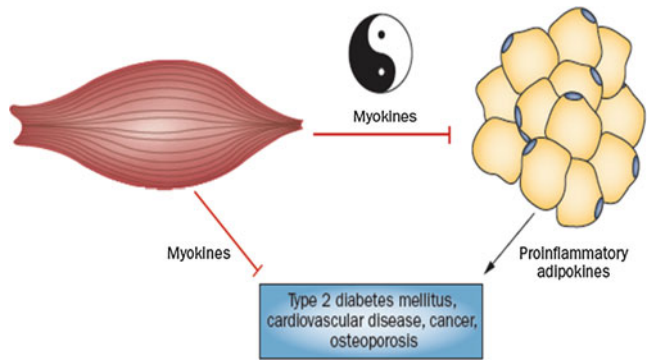

Fig. 1 The interplay between adipokines and myokines represents a yin-yang-balance. Especially under conditions of obesity, adipose tissue secretes adipokines, which contribute to establish a chronic inflammatory environment, which promotes pathological processes such as atherosclerosis and insulin resistance. Skeletal muscles are capable of producing myokines that confer some of the health benefits of exercise. Such myokines may counteract the harmful effects of proinflammatory adipokines (Adapted from Pedersen and Febbraio 2012)

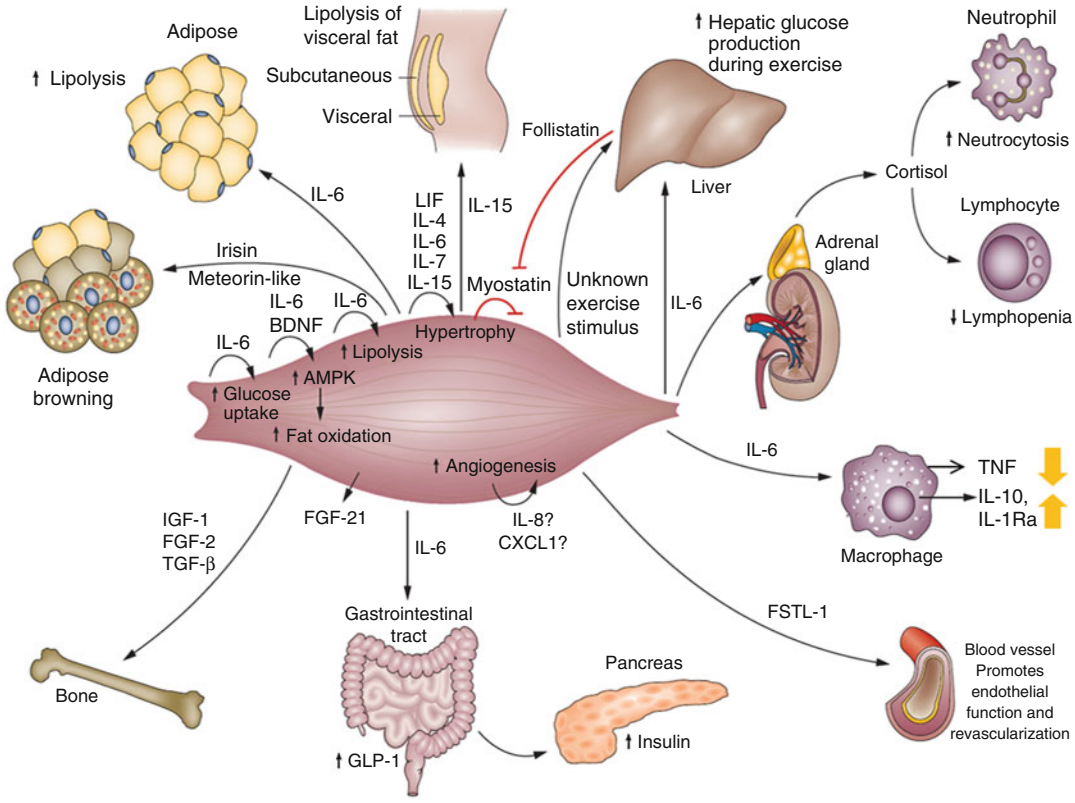

Fig. 2 Skeletal muscle is a secretory organ. LIF, IL-4, IL-6, IL-7, and IL-15 promote muscle hypertrophy. Myostatin inhibits muscle hypertrophy and exercise provokes the release of a myostatin inhibitor, follistatin, from the liver. BDNF and IL-6 are involved in AMPK-mediated fat oxidation; IL-6 stimulates lipolysis and IL-15 stimulates lipolysis of visceral fat. IL-6 enhances insulin-stimulated glucose uptake and stimulates glucose output from the liver, but only during exercise. IL-6 increases insulin secretion via upregulation of GLP-1 in the L cells of the intestine. IL-6 has antiinflammatory effects as it inhibits TNF production, but stimulates the occurrence of the antiinflammatory cytokines IL-1ra and IL-10. Furthermore, IL-6 stimulates cortisol production and hence neutrocytosis and lymphopenia. IL-8 and CXCL-1 may promote angiogenesis. IGF 1, FGF 2, and TGF-β are involved in bone formation, and follistatin-related protein 1 improves endothelial function and revascularization of ischemic vessels. Irisin and meteorin-like have a role in "browning" of white adipose tissue (Adapted from Benatti and Pedersen 2015)

diseases (Pedersen 2009). The finding that muscles produce and release myokines provides a conceptual basis for understanding some of the molecular mechanisms, whereby physical activity stimulates interorgan communication and may protect against features of the metabolic syndrome and ultimately premature mortality (Fig. 2).

3.1 Interleukin-6

It is well known that increased plasma concentration of interleukin-6 (IL-6) is found in obese people and in patients with the metabolic syndrome. In an attempt to clarify the role of IL-6, several studies implicated IL-6 as a co-inducer of the development of obesity-associated insulin resistance. However, the identification of IL-6 as a myokine and the demonstrating of its multiple metabolic roles provided a contrasting identity of IL-6 (Pal et al. 2014).

Myostatin appears to be the first muscle-derived peptide to fulfill the criteria for a myokine (Pedersen and Febbraio 2012). However, the gp130 receptor cytokine interleukin-6 (IL-6) was the first myokine that was found to be secreted into the bloodstream in response to muscle contractions (Pedersen and Febbraio 2008). IL-6 was

shown to increase in an exponential fashion proportional to the length of exercise and the amount of muscle mass engaged in the exercise. Thus, plasma IL-6 may increase up to 100-fold, although less dramatic increases are more frequent (for review, see Fischer 2006).

Of note, the increase of IL-6 in the circulation occurs during exercise without any sign of muscle damage (Fischer 2006). Until the beginning of this millennium, it was commonly thought that the increase in IL-6 during exercise was a consequence of an immune response due to local damage in the working muscles (Nieman et al. 1998) and it was hypothesized that macrophages were responsible for this increase (Nehlsen Cannarella et al. 1997). An early study by the our group (Ullum et al. 1994) demonstrated, however, that IL-6 mRNA in monocytes did not increase as a result of exercise. Further work from our group confirmed this finding at the protein level (Starkie et al. 2000, 2001).

Several pieces of work confirmed that skeletal muscle was the source of IL-6 during exercise. It was demonstrated that the nuclear transcription rate for IL-6 and the IL-6 mRNA levels increases rapidly and markedly after the onset of exercise (Keller et al. 2001; Steensberg et al. 2002), suggesting that a factor associated with contraction increases IL-6 transcriptional rate within the nuclei from myocytes. Further evidence that contracting muscle fibers themselves are a source of IL-6 mRNA and protein has been achieved by analysis of biopsies from the human vastus lateralis using in situ hybridization and immunohistochemistry techniques (Hiscock et al. 2004).

It has, however, been the simultaneous measurement of arteriovenous IL-6 concentrations and blood flow across the leg that has demonstrated that large amounts of IL-6 are released into the circulation from the exercising leg (Steensberg et al. 2000). IL-6 has been shown to be expressed by human myoblasts (De Rossi et al. 2000; Bartoccioni et al. 1994) and by human cultured myotubes (Keller et al. 2006). Moreover, IL-6 is locally and transiently produced by growing murine myofibers and associated muscle stem cells (satellite cells) (Serrano et al. 2008). In addition, IL-6 is released from human primary muscle cell cultures from healthy individuals (Haugen et al. 2010; Green et al. 2011) and from patients with type 2 diabetes (Green et al. 2011).

Muscle-derived IL-6 works as an exercise sensor (Pedersen 2012; Ruderman et al. 2006; Pedersen et al. 2004; Hoene and Weigert 2008). Thus, enhanced glucose availability and training adaptation attenuate the exercise-sensitive increase in IL-6 plasma concentration (Pedersen 2012; Fischer et al. 2004).

It appeared that human skeletal muscle is unique, in that it can produce IL-6 during contraction in a strictly TNF-independent fashion (Keller et al. 2006). This finding led us to suggest that muscular IL-6 has a role in metabolism rather than in inflammation. In continuation, we found that both intramuscular IL-6 mRNA expression (Keller et al. 2005) and protein release (Steensberg et al. 2001) are markedly enhanced when intramuscular glycogen is low, suggesting that IL-6 works as an energy sensor. This idea has been supported by numerous studies showing that glucose ingestion during exercise attenuates the exercise-induced increase in plasma IL-6 (Pedersen and Febbraio 2008) and inhibits the IL-6 release from contracting skeletal muscle in humans (Febbraio et al. 2003; Pedersen and Febbraio 2008).

Training adaptation increases preexercise skeletal muscle glycogen content, enhances activity of key enzymes involved in the β-oxidation, increases sensitivity of adipose tissue to epinephrine-stimulated lipolysis, and increases oxidation of intramuscular triglycerides, whereby the capacity to oxidize fat is increased. As a consequence, the trained skeletal muscle is less dependent on plasma glucose and muscle glycogen as substrates during exercise (Pedersen and Febbraio 2008; Phillips et al. 1996). Several epidemiological studies have reported a negative association between the amount of regular physical activity and the resting plasma IL-6 levels: the more fit, the lower basal plasma IL-6 (Fischer 2006). High plasma levels of IL-6 are closely associated with physical inactivity and the metabolic syndrome (Sattar et al. 2003; Freeman et al. 2002).

Moreover, basal levels of IL-6 are reduced after training (Fischer 2006). In addition, it

appears that the exercise-induced increase in plasma IL-6 and muscular IL-6 mRNA is diminished by training (Fischer et al. 2004). It is worth noting that while plasma IL-6 appears to be downregulated by training, the muscular expression of the IL-6 receptor (IL-6R) appears to be upregulated. In response to exercise training, the basal IL-6R mRNA content in trained skeletal muscle is increased by ~100 % (Keller et al. 2005). It, therefore, appears that with exercise training, the downregulation of IL-6 is partially counteracted by an enhanced expression of IL-6R, whereby the sensitivity to IL-6 is increased. Our hypothesis is that muscle disuse may also lead to IL-6 resistance and elevated circulating levels of IL-6 in parallel with the well-known facts that insulin resistance is accompanied by hyperinsulinemia and that chronic high circulating levels of leptin reflect leptin resistance.

Acute treatment of muscle cells with IL-6 increased both basal glucose uptake and the translocation of the glucose transporter GLUT4 from intracellular compartments to the plasma membrane (Carey et al. 2006). Moreover, IL-6 increased insulin-stimulated glucose uptake in vitro, while infusion of recombinant human IL-6 into healthy humans during a hyperinsulinemic, euglycemic clamp increased glucose infusion rate without affecting the total suppression of endogenous glucose production (Carey et al. 2006). The effects of IL-6 on glucose uptake in vitro appeared to be mediated by activation of AMP-activated protein kinase (AMPK), since the results were abolished in cells infected with an AMPK dominant-negative adenovirus (Carey et al. 2006). Apart from the effects of IL-6 on glucose metabolism, several studies have reported that IL-6 may increase intramyocellular (Bruce and Dyck 2004; Petersen et al. 2005; Carey et al. 2006) or whole body (van Hall et al. 2003) fatty acid oxidation. This effect may also be mediated by AMPK (Kahn et al. 2005; Carey et al. 2006). A recent study suggests that IL-6 activates AMPK in skeletal muscle by increasing the concentration of cAMP and, secondarily, the AMP-ATP ratio (Kelly et al. 2009). It appears that IL-6 acutely mediates signaling through the gp130 receptor and exhibits many "leptin-like" actions such as activating AMPK (Minokoshi et al. 2002; Watt et al. 2006a; Steinberg et al. 2003) and insulin signaling (Steinberg et al. 2009). It is quite clear that in healthy skeletal muscle, and not least in humans, the IL-6-induced activation of AMPK overrides the IL-6-induced activation of suppressor of cytokine signaling (SOCS)-3. Of note, IL-6 knockout mice develop mature onset obesity and glucose intolerance (Wallenius et al. 2002), supporting the notion that IL-6 may exert beneficial effects on metabolism.

IL-6 has been shown to contribute to hepatic glucose production during exercise (Febbraio et al. 2004). The mechanisms that mediate the tightly controlled production and clearance of glucose during muscular work are unclear. It has been suggested that an unidentified "work factor" exists that influences the contraction-induced increase in endogenous glucose production (EGP). We have performed studies in which we have infused recombinant human IL-6 (rhIL-6) at physiological concentrations into resting human subjects. Acute administration of rhIL-6 has no effect on whole-body glucose disposal, glucose uptake, or EGP (Steensberg et al. 2003b; Lyngso et al. 2002; Petersen et al. 2005). In contrast, we found that IL-6 contributes to the contraction-induced increase in EGP. Human subjects performed bicycle exercise at high or low intensity with or without an infusion of recombinant IL-6. Interestingly, the group performing exercise at a low intensity and concomitant IL-6 infusion showed a higher glucose turnover than the group at low exercise intensity without IL-6 infusion. It was therefore suggested that the primary role of IL-6 during exercise is to support glucose disposal. In support of this notion, in human lean, healthy subjects undergoing a hyperinsulinemic, euglycemic clamp, the gold standard method to assess insulin sensitivity, IL-6 infusion resulted in an increase in glucose infusion rate (Carey et al. 2006). The study demonstrated a direct muscle-liver "cross talk." It was clear that IL-6 appeared to play a role in EGP during exercise in humans; however, its action on the liver was dependent on a yet unidentified muscle contraction-induced factor (Febbraio et al. 2004).

Moreover, infusion of rhIL-6 into healthy humans caused an increase in lipolysis in the absence of hypertriglyceridemia or changes in catecholamines, glucagon, insulin, or any adverse effects in healthy individuals (van Hall et al. 2003; Petersen et al. 2005; Lyngso et al. 2002). These findings combined with cell culture experiments showed that IL-6 had direct effects on both lipolysis and fat oxidation and identify IL-6 as a lipolytic factor (Petersen et al. 2005).

In a recent human study, we were able to distinguish between lipolysis in muscle and adipose tissue. The findings from the latter study suggested that an acute increase in IL-6 at a normophysiological level primarily stimulates lipolysis in skeletal muscle, whereas adipose tissue is unaffected (Wolsk et al. 2010).

Interestingly, patients with insulin resistance appear to demonstrate an abnormal response to IL-6. Myocytes from patients with diabetes appeared resistant to IL-6-induced AMPKα2 activation (Scheele et al. 2012). A similar deficiency has been reported for leptin signaling in myocytes derived from obese subjects in comparison to lean (Steinberg et al. 2006). The finding of possible IL-6 resistance was further supported in a recent study (Harder-Lauridsen et al. 2014).

Ellingsgaard et al. (2011) demonstrated that the exercise-induced release of IL-6 from skeletal muscle triggers the secretion of GLP-1 from pancreatic α cells and L cells from the intestine. This increase in GLP-1 led to enhanced insulin secretion and to improved glycemia and glucose tolerance, and the effects were completely abolished in GLP1-R KO mice, although the levels of IL-6 were still increased. It was further shown that injections of IL-6 improved glucose tolerance, an effect that was abolished in GLP-1 KO animals. The latter study therefore describes a major pathway by which exercise-induced IL-6 leads to enhanced levels of GLP-1, which in turn results in increased insulin secretion post exercise.

Finally, IL-6 appears also to mediate some of the antiinflammatory and immunoregulatory effects of exercise (Nielsen and Pedersen 2008; Petersen and Pedersen 2005). IL-6 inhibits LPS-induced TNF production in cultured human monocytes (Schindler et al. 1990), and levels of TNF-α are markedly elevated in anti-IL-6-treated mice and in IL-6-deficient knockout mice (Mizuhara et al. 1994), suggesting that circulating IL-6 is involved in the regulation of TNF levels. In addition, both rhIL-6 infusion and exercise inhibit the endotoxin-induced increase in circulating levels of TNF-α in healthy humans (Starkie et al. 2003). The antiinflammatory effects of IL-6 are also demonstrated by IL-6 stimulating the production of the classic antiinflammatory cytokines IL-1ra and IL-10 (Steensberg et al. 2003a). Taken together, it appears that an acute increase in IL-6 can mediate antiinflammatory effects.

The myokine field is new and so far most of the human studies have focused on the biological role of IL-6. The finding that muscle-derived IL-6 appears to have several beneficial metabolic effects makes it a possible candidate in chronic diseases associated with a physically inactive lifestyle. White and colleagues have demonstrated that human IL-6 transgenic mice with sustained elevated circulating IL-6 display enhanced central leptin action and improved nutrient homeostasis leading to protection from diet-induced obesity (Sadagurski et al. 2010). In addition, Wunderlich et al. (2010) have shown that IL-6 signaling is required for normal liver metabolism in mice. Of note, ciliary neurotrophic factor (CNTF) is a member of the IL-6 family of cytokines and also improves metabolic homeostasis in both high fat diet-induced (Watt et al. 2006a) and lipid infusion-induced (Watt et al. 2006b) insulin resistance. It should be noted that a CNTF variant, Axokine, was in clinical trials for type 2 diabetes, but failed due to antibody development (Ettinger et al. 2003). Nonetheless, given that exercise induces transient insulin sensitivity, many clues can be gained from the study of myokines in relation to novel drug targets for the treatment of metabolic diseases.

3.2 IL-15

IL-15 belongs to the IL-2 superfamily and is expressed in human skeletal muscle. In addition to its anabolic effects on skeletal muscle, IL-15 may play a role in lipid metabolism (Nielsen and

Pedersen 2007). IL-15 decreases lipid deposition in preadipocytes and decreases the mass of white adipose tissue (Carbo et al. 2001; Quinn et al. 2005). In support, a negative association has been found in humans between plasma IL-15 on the one hand and total fat mass, trunk fat mass, and percent fat mass on the other (Nielsen et al. 2008).

IL-15 mRNA levels increased in human skeletal muscle biopsies following a bout of strength training, suggesting that IL-15 may accumulate within the muscle as a consequence of regular training (Nielsen et al. 2007).

Physical inactivity leads to loss of muscle mass and accumulation of visceral fat (Olsen et al. 2008), and there are some pieces of evidence pointing at IL-15 somehow being involved in the regulation of abdominal adiposity. In humans, we found a negative association between plasma IL-15 concentration and trunk fat mass, but not limb fat mass. In support, we demonstrated a decrease in visceral fat mass, but not subcutaneous fat mass, when IL-15 was overexpressed in murine muscle (Nielsen et al. 2008).

3.3 BDNF

Neurotrophins are a family of structurally related growth factors, including brain-derived neurotrophic factor (BDNF), which exert many of their effects on neurons primarily through Trk receptor tyrosine kinases. Among these, BDNF and its receptor TrkB are the ones most widely and abundantly expressed in the brain (Huang and Reichardt 2001). However, several studies verify that skeletal muscle is also capable of expressing BDNF (Pedersen 2009, 2011; Pedersen et al. 2009).

Studies in rodents demonstrate that both exercise and electrical stimulation (and contraction) of skeletal muscle lead to an induction of BDNF expression in muscle (Copray et al. 2000; Gomez-Pinilla et al. 2002; Seidl et al. 1998; Matthews et al. 2009).

Several studies have also reported that exercise induces an expression of BDNF in skeletal muscle. For example, Copray et al. (2000) found that intense contraction of the soleus muscle in both normal and diabetic rats caused an increase in the expression of BDNF. In addition, ultrastructural studies from these same authors found that BDNF expression was localized within muscle fibers and activated satellite cells. Importantly, no expression of BDNF was observed in Schwann cells or fibroblasts, suggesting that the localization of BDNF was defined within the muscle fibers.

In other studies, Gomez-Pinilla et al. (2002) found that BDNF mRNA and protein levels in rodents increased in the soleus muscle after 3 and 7 days of exercise. Interestingly, following paralysis of the soleus muscle, BDNF mRNA levels were reduced, demonstrating that active muscle contraction is important in modulating BDNF levels in muscle.

We studied whether human skeletal muscle would produce BDNF in response to exercise (Matthews et al. 2009) and found that BDNF mRNA and protein expression were modestly increased in human skeletal muscle after exercise. However, muscle-derived BDNF appeared not to be released into the blood. Interestingly, however, Raschke et al. reported BDNF in the supernatant fraction of human myotubes (Raschke et al. 2013).

While in patients with type 2 diabetes circulating levels of BDNF are decreased independently of obesity (Krabbe et al. 2007), it has been shown in humans that 70–80 % of circulating BDNF originates from the brain during both rest and after exercise, suggesting the brain as a major source of this factor (Rasmussen et al. 2009).

BDNF mRNA and protein expression were clearly increased in muscle cells that were electrically stimulated. Interestingly, BDNF increased phosphorylation of AMPK and ACC and enhanced fat oxidation both in vitro and ex vivo. Thus, we were able to identify BDNF as a novel contraction-induced muscle cell-derived protein that may increase fat oxidation in skeletal muscle in an AMPK-dependent fashion (Pedersen 2009, 2011; Pedersen et al. 2009). Other studies consistently demonstrate that muscle-derived BDNF and other neurotrophins serve as important regulators of the maintenance, function, and regeneration of skeletal muscle fibers. Thus, BDNF is an injury-related factor that is involved in the survival and function of innervating motor neurons (reviewed in Sakuma and Yamaguchi 2011). In

addition, BDNF appears to play a role in the development and differentiation of myoblasts and muscle fibers (Mousavi and Jasmin 2006; Miura et al. 2012).

Taken together, BDNF is a protein produced in skeletal muscle cells, which is increased by contraction to enhance fat oxidation in an AMPK-dependent fashion, most probably by acting in an autocrine and/or paracrine manner within skeletal muscle. In addition, muscle-derived BDNF plays a role in muscle repair, regeneration, and differentiation. Thus, in addition to its well-known role in neurobiology, BDNF can be identified as a myokine that plays a role in peripheral metabolism, myogenesis, and muscle regeneration.

4 Other Myokines

Several research groups have contributed to the identification of the muscle cell secretome (Bortoluzzi et al. 2006; Yoon et al. 2009; Henningsen et al. 2010; Raschke et al. 2013; Hartwig et al. 2014; Norheim et al. 2011). Several of the exercise-regulated factors have the potency to mediate an interorgan cross talk. In addition, the autocrine or paracrine functions of the secreted peptides and proteins may have consequences for whole-body metabolism. Recent advantages in metabolomics and lipidomics may add metabolites and lipids with autocrine, paracrine, or endocrine function to the contraction-induced secretome of the skeletal muscle as recently outlined (Weigert et al. 2014). In addition, we found that the muscle-specific miRNA signatures of human plasma are regulated by exercise and training, suggesting that miRNAs may be involved in interorgan communication (Nielsen et al. 2014).

As previously reviewed (Pedersen 2013; Benatti and Pedersen 2015; Eckardt et al. 2014), the myokines, myostatin, leukemia inhibitory factor (LIF), IL-4, IL-6, ,IL-7, and IL-15 may be involved in muscle hypertrophy and myogenesis. Recently, decorin was identified as a new myokine involved in muscle hypertrophy (Kanzleiter et al. 2014). As already mentioned, BDNF and IL-6 have been implicated in AMPK-mediated fat oxidation, and both IL-6 and IL-15 have lipolytic effects. IL-6 also appears to have systemic effects on the liver, adipose tissue, and the immune system and may mediate the cross talk between intestinal L cells and pancreatic islets. Insulin-like growth factor 1 (IGF-1), fibroblast growth factor-2 (FGF-2), and transforming growth factor-β (TGF-β) have been identified as osteogenic factors; follistatin-related protein 1 (FSTL-1) may improve the endothelial function of the vascular system and the proliferator-activated receptor-gamma coactivator-1 (PGC-1)-α-dependent myokine irisin has been shown to drive brown-fat-like development. Recently, meteorin-like has been identified as a myokine that regulates immune-adipose interactions to increase beige fat thermogenesis (Rao et al. 2014). Moreover, other studies suggest the existence of yet unidentified factors, secreted from muscle cells, which may influence cancer cell growth (Pedersen and Hojman 2012) and pancreas function (Plomgaard et al. 2012). A study in humans supports the notion that FGF-21 is a myokine, which is upregulated by insulin (Hojman et al. 2009b). Other muscle cell-derived proteins include calprotectin (Mortensen et al. 2008) and erythropoietin (Hojman et al. 2009a), and IL-4 has been shown to enhance muscle regeneration by stimulating the fusion of myoblasts with myotubes (Horsley et al. 2003).

ANGPTL4 is a secreted protein that regulates the influx of plasma triglyceride-derived fatty acids into tissues by inhibiting the enzyme lipoprotein lipase (Catoire and Kersten 2015). It has been shown that acute exercise increased ANGPTL4 levels in plasma but only when the exercise was performed in the fasted condition. Coingestion of glucose, which blocks the elevation in plasma-free fatty acids during exercise, prevented the exercise-induced increase in plasma ANGPTL4, suggesting that induction of plasma ANGPTL4 by exercise is mediated by elevated free fatty acids (Kersten et al. 2009).

SPARC was identified as a myokine in a screening study in mice using microarrays. The study revealed that SPARC gene expression levels are increased after acute exercise and exercise training. Acute exercise also significantly increased plasma levels of SPARC, and this result

was reproduced in humans, suggesting a potential systemic role of SPARC during exercise. Furthermore, it was suggested that SPARC has an inhibitory effect on tumorigenesis in the colon during exercise (Aoi et al. 2013). Yet another study suggested that myokines may also be involved in the fight against breast cancer. In fact, we found that oncostatin M (OSM), a member of the IL-6 superfamily, may be classified as a myokine and may be mediating inhibitory effects on mammary cell growth (Hojman et al. 2011).

Apart from the effects of myokines on peripheral insulin sensitivity via the activation of AMPK, evidence is emerging that myokines may also play a major role in pancreatic β-cell metabolism. In a study by Halban and coworkers, human skeletal muscle cells were cultured with tumor necrosis factor (TNF)-α to induce insulin resistance. Conditioned media were collected and candidate cytokines were measured by antibody array. Human and rat primary β-cells were used to explore the impact of exposure to conditioned media for apoptosis, proliferation, short-term insulin secretion, and key signaling protein phosphorylation and expression. The study showed that human myotubes express and release a different panel of myokines depending on their insulin sensitivity, with each panel exerting differential effects on β-cells. Conditioned medium from control myotubes increased proliferation and glucose-stimulated insulin secretion (GSIS) from primary β-cells, whereas conditioned medium from TNF-α-treated insulin-resistant myotubes exerted detrimental effects. Taken together, the data clearly suggest a new route of communication between skeletal muscle and β-cells that is modulated by insulin resistance and could contribute to normal β-cell functional mass in healthy subjects, as well as to the decrease seen in type 2 diabetes (Bouzakri et al. 2011).

5 Conclusion

Given that muscle is the largest organ in the body, the identification of the muscle secretome may set a new agenda for the scientific community. To view skeletal muscle as a secretory organ provides a conceptual basis and a whole new paradigm for understanding how muscles communicate with other organs such as the adipose tissue, liver, and pancreas.

Box 1 Characteristics of Myokines

- Myokines are cytokines or other peptides that are produced, expressed, and released by muscle fibers.
- Myokines may exert autocrine, paracrine, or endocrine effects.
- Myokines may balance and counteract the detrimental effects of adipokines produced in the obese state.
- Myokines may exert antiinflammatory effects.
- Myokines may have effect on visceral fat mass.
- The muscle cell secretome consists of several hundred secreted products.
- Myokines may mediate protective effects of muscular exercise with regard to diseases associated with a physically inactive lifestyle.

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6 Cross-References

- ▶ Adipokines and Metabolism
- ▶ Body Composition Assessment
- ▶ Diet, Exercise, and Behavior Therapy in the Treatment of Obesity and Metabolic Syndrome
- ▶ Insulin Resistance in Obesity
- ▶ Linking Inflammation, Obesity, and Diabetes
- ▶ Overview of Metabolic Syndrome

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Circadian Rhythms and Metabolism

30

Edith Grosbellet and Etienne Challet

Contents

Abstract

The circadian system relies on a master clock in the suprachiasmatic nucleus of the hypothalamus (SCN), synchronizing a multitude of brain and peripheral oscillators that set physiological and metabolic functions in phase with the light–dark cycle. The SCN functions as a relay integrating environmental signals before sending appropriate neuronal and hormonal cues to the brain and peripheral tissues to control, among others, sleep/wake and feeding/fasting cycles. Many evidences show that metabolism and circadian system are tightly interconnected. Peripheral oscillators, such as the liver and adipose tissue, can be shifted by mealtime. By contrast, feeding signals do not affect the master clock under light–dark conditions, although nutritional cues affect its functioning under metabolic challenges, such as calorie restriction and high-fat diet. Circadian desynchronization, such as shift work and chronic jet lag, is now recognized as a determinant of metabolic disturbances. Therefore, chronotherapeutic approaches of daily dieting to avoid circadian misalignment are advisable for the management of obesity and type 2 diabetes.

Keywords

Circadian rhythm • Clock gene • Feeding time • Desynchronization • Metabolic disturbances • Obesity • Diabetes

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1 Introduction

Every day we experience rhythms of our physiological functions and behaviors, which follow the 24-h light–dark cycle due to the rotation of Earth around its axis. For instance, we are awake and eat during daytime, while we sleep during the night. Our body temperature drops every night and most of our hormones are secreted at particular times of day, like melatonin released from the pineal gland only during the night. As detailed in this chapter, these daily rhythms are not passive responses to the changing outside world, but are controlled by a network of endogenous circadian clocks and oscillators. Here, we will particularly focus on the relationships between circadian system and metabolism. After presenting the organization of the circadian system and its involvement in metabolism, we will detail the nature of signals synchronizing peripheral oscillators, thus ensuring the circadian control of metabolism. The last part presents pathological situations in which circadian disruptions lead to metabolic troubles, and vice versa.

2 A Network of Clocks and Oscillators Ensuring the Circadian Control of Metabolism

2.1 The Master Clock in the Suprachiasmatic Nucleus

In mammals, the daily variations of physiological functions and behaviors are controlled by a multi-oscillatory network that generates internal daily oscillations and adjusts their timing to external temporal cues, such as the 24-h variations in ambient light. At the top of this circadian network, a master clock located in the suprachiasmatic nucleus of the hypothalamus (SCN) adjusts the timing of secondary clocks and oscillators in most other brain regions and peripheral tissues, via nervous and hormonal signals (Dibner et al. 2010).

The clock mechanism in the SCN involves 24-h oscillations of core clock components, called clock genes and defined as genes whose protein products are necessary for the generation and regulation of circadian rhythms within individual cells (Ko and Takahashi 2006). The heterodimer CLOCK/BMAL1 stimulates expression of essential clock components PERs and CRYs which, after a delay, repress the transcriptional activity of the CLOCK/BMAL1 heterodimer by inhibiting its binding to their own promoters. This main loop is responsible for oscillations of PER and CRY proteins. CLOCK/BMAL1 also stimulates expression of other clock-related proteins, such as REV-ERBα (alpha) and RORα (alpha), which create auxiliary loops that help stabilizing the main loop (Fig. 1). The circadian transcription factors control the temporal transcription of numerous downstream, clock-controlled genes, which constitute outputs of the molecular clock and are involved in a large variety of biological processes. Many levels of regulation are important for the proper functioning of the circadian clock, including epigenetic, transcriptional, post-transcriptional, and posttranslational mechanisms. All together, these regulations provide robust oscillations, resilient to large fluctuations in temperature (the so-called temperature compensation) and overall transcription rates (Dibner et al. 2010).

In absence of environmental inputs, the master clock "free-runs" with a period close to, but not exactly, 24 h. Therefore, biological rhythms need to be synchronized to the day–night cycle, which represents the most important environmental cue for most organisms. The resetting effects of light on circadian rhythms depend on the time of light exposure. For a nocturnal rodent, light in early and late night produces phase delays and advances, respectively, while light during most of day has no effect on the phase of the SCN clock.

Light is perceived in the retina by classical photoreceptors and a subset of ganglion cells that are photosensitive because they express a photopigment called the melanopsin, highly responsive to blue light stimulation (Hattar et al. 2006). These ganglion cells project via the retinohypothalamic tract to the ventral SCN, where they release mainly glutamate and

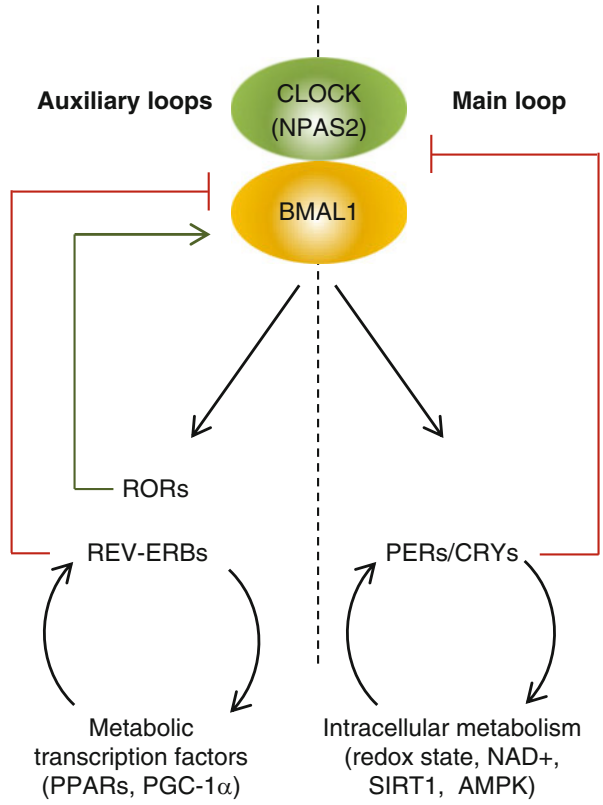

Fig. 1 Molecular clockwork and its interactions with cellular metabolism. The mammalian molecular clockwork consists of a set of clock genes and their protein products that generate 24-h feedback loops of transcription and translation. Main loop: The heterodimer CLOCK/BMAL1 stimulates the expression of core clock components *Pers* and *Crys*, which in turn repress the transcriptional activity of the CLOCK/BMAL1 heterodimer by inhibiting its binding to the E-box response elements located in their own promoters, through formation of a complex with the casein kinase 1ε and δ. Auxiliary loop: CLOCK/BMAL1 also stimulates expression of other clock-related proteins, such as REV-ERBs and RORs, which create an auxiliary loop that helps stabilize the main regulatory loop. Outputs of the clock: These circadian transcription factors control numerous clock-controlled genes to influence a variety of biological activities. The molecular clockwork interacts with intracellular metabolism via redox changes, PPARs, SIRT1, and AMPK. *AMPK* 5′ adenosine monophosphate-activated protein kinase, *BMAL1* brain and muscle arnt-like protein 1, *CLOCK* circadian locomotor output cycles kaput, *CRY* cryptochrome, *NAD+* nicotinamide adenine dinucleotide, *NPAS2* neuronal PAS domain protein 2, *PER* period, PGC-1α (*alpha*): PPARγ (*gamma*): coactivator-1α (*alpha*), *PPAR* peroxisome proliferator-activated receptor, *ROR* retinoic acid receptor-related orphan nuclear receptor, *REV-ERB* reverse viral erythroblastosis oncogene product, *SIRT1* sirtuin 1 (Data from Rutter et al. (2001), Ko and Takahashi (2006), Asher et al. (2008), Nakahata et al. (2008), Teboul et al. (2008))

the neuropeptide pituitary adenylate cyclase-activating protein (PACAP) (Golombek and Rosenstein 2010). The downstream signaling pathway in ventral SCN cells induces acute expression of clock genes *Per1* and *Per2*, together with several immediate early genes such as *c-fos* (Golombek and Rosenstein 2010).

The retinohypothalamic tract also projects to the thalamic intergeniculate leaflets (IGLs). From the IGL, the geniculohypothalamic tract projects to the SCN and can thus indirectly convey light information by releasing neuropeptide Y (NPY), γ-aminobutyric acid (GABA), and enkephalin (Harrington 1997). Other structures can also convey indirect light information to the SCN.

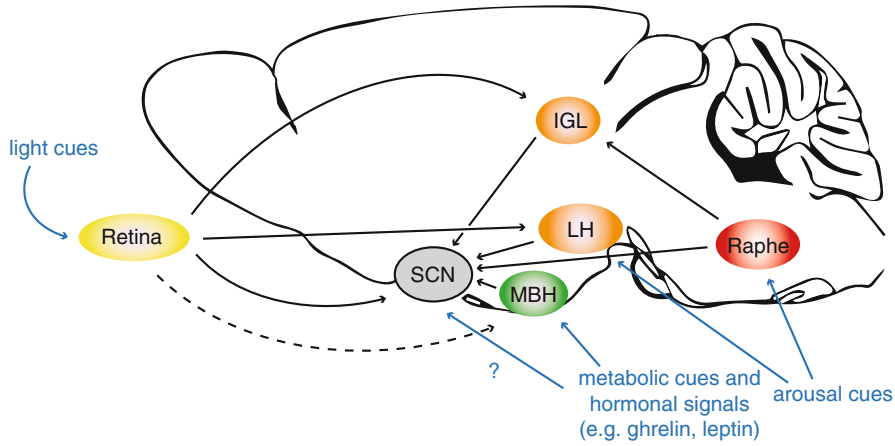

Fig. 2 Main afferent pathways to the master clock in rodents. Structures conveying directly or indirectly light information to the SCN are in *yellow* (retina) and *orange* (IGL and LH). The raphe nuclei (*red*) convey non-photic information to the master clock, while the IGL receives both photic and non-photic cues. The MBH (*green*) integrates metabolic signals and possibly photic cues. *IGL* intergeniculate leaflet of the thalamus, *LH* lateral hypothalamic area, *SCN* suprachiasmatic nucleus, *MBH* mediobasal hypothalamus (i.e., arcuate and ventromedial hypothalamic nuclei) (Data from Morin (1999), Hattar et al. (2006), Yi et al. (2006), Challet (2010))

Arousal-promoting orexigenic neurons of the lateral hypothalamic area (LH), for instance, are a target of retinal projections (Hattar et al. 2006) and project in turn to the immediate vicinity of the SCN (Brown et al. 2008).

Even if the light is the most important time-giver (also called *zeitgeber* in chronobiology), other temporal cycling cues called "non-photic," such as food availability, temperature, or stimulated locomotor activity, are putative synchronizers. Two major input pathways convey non-photic messages to the SCN: the NPYergic projection from the IGL, also transmitting photic information, and the serotonergic input from the midbrain raphe nuclei (Harrington 1997; Morin 1999). Besides a possible direct action of metabolic cues on SCN cells, the pathways conveying feeding and metabolic cues to the SCN may involve nuclei of the mediobasal hypothalamus, such as arcuate nucleus (ARC) and ventromedial hypothalamic nucleus (VMH), which could integrate metabolic information and energy status before projecting to the SCN (Challet 2010) (Fig. 2).

To sum up, the SCN is a robust clock, whose self-sustained rhythmicity, relying on molecular transcriptional–translational feedback loops, is synchronized by photic and non-photic synchronizers and distributed to the whole organism.

2.2 Central Clocks and Oscillators

2.2.1 Presentation

Many brain areas exhibit daily oscillations of clock genes (Feillet et al. 2008; Dibner et al. 2010). Retina and olfactory bulb are extra-SCN oscillators fulfilling all the criteria to be considered as circadian clocks (Guilding and Piggins 2007): self-sustained oscillations compensated for temperature and reset by environmental inputs and outputs distributed out of the structure. Some other brain areas have been classified as semiautonomous, such as ARC and dorsomedial hypothalamic nuclei (DMH), both structures of the medial hypothalamus involved in feeding and energy metabolism (Guilding and Piggins 2007). Cells of these oscillators exhibit independent circadian rhythms, but appear less coupled in vitro than SCN cells. Moreover, their timing of clock gene oscillations differs from SCN. For instance, in rat, the peak of *Per1* mRNA in ARC occurs at dusk, i.e., 6 h later than in SCN, while *Per2* mRNA is delayed by 4 h (Shieh et al. 2005).

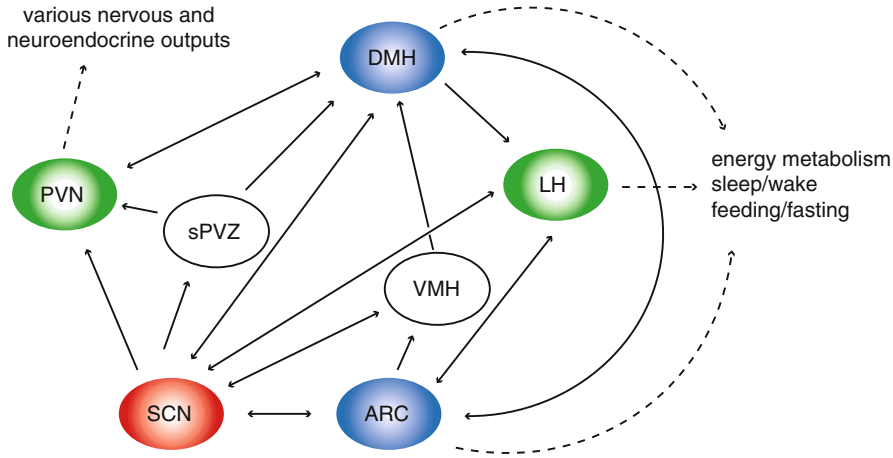

Fig. 3 Intra-hypothalamic network connecting the master clock and nuclei involved in the regulation of energy metabolism and feeding rhythm. Nuclei of metabolic hypothalamus are interconnected and share reciprocal connections with the SCN. This network of hypothalamic oscillators is supposed to be involved in circadian control of feeding and energy metabolism. The SCN clock is in *red*; semiautonomous oscillators are in *blue* and slave oscillators in *green*. *Solid arrows* represent direct neuronal connections, while *dashed arrows* represent indirect outputs. *SCN* suprachiasmatic nucleus, *ARC* arcuate nucleus, *VMH* ventromedial hypothalamic nucleus, *DMH* dorsomedial hypothalamic nucleus, *sPVZ* subparaventricular zone, *PVN* paraventricular hypothalamic nucleus, *LH* lateral hypothalamic area (Data from Chou et al. (2003), Yi et al. (2006), Challet (2010), Bechtold and Loudon (2013))

The slave oscillators are independently arrhythmic but can provide a circadian output totally dependent on inputs from clocks or semiautonomous oscillators (Guilding and Piggins 2007). For instance, LH and hypothalamic paraventricular nucleus (PVN) display a rapid dampening of rhythmicity of *Per1-luc* expression in vitro (Abe et al. 2002). Of note, the core clock mechanism in brain oscillators is similar to the one in SCN. However, NPAS2, a paralog of CLOCK that dimerizes with BMAL1, may replace CLOCK in the mammalian forebrain (Reick et al. 2001).

2.2.2 Entrainment of Brain Oscillators by Inputs from SCN

The SCN efferents terminate in relatively few brain sites, mainly limited to the hypothalamus and thalamus. Within the hypothalamus, the SCN projects most densely to the subparaventricular region. Of interest for the present topic are the projections of the SCN on hypothalamic nuclei involved in energy balance, referred as "metabolic hypothalamus," receiving SCN input directly or via polysynaptic relays (principally via the subparaventricular region). Pre-autonomic neurons in PVN and arousal-promoting orexin neurons in the LH are controlled by a daily balance between glutamatergic and GABAergic inputs from the SCN (Kalsbeek et al. 2006). Neurosecretory corticotrophin-releasing factor neurons in PVN, involved in hypothalamic–pituitary–adrenal axis, are inhibited by vasopressinergic SCN inputs. GABAergic and vasopressinergic SCN neurons project also on DMH, a key site for integration of circadian timing into numerous physiological processes (Kalsbeek et al. 2006) (Fig. 3). Moreover, dopaminergic neurons of the semiautonomous oscillator ARC, which express rhythmic clock genes, are directly regulated by SCN neurons containing vasoactive intestinal peptide (Gerhold et al. 2001; Sellix et al. 2006). Finally, it is also noteworthy that nervous outputs from the SCN are not required for the establishment of locomotor activity rhythms (Silver et al. 1996), suggesting the presence of paracrine factors diffusing from SCN cells and controlling rhythmic activity. At least three diffusible circadian factors have been identified, namely, transforming growth factor alpha (α), prokineticin 2, and cardiotrophin-like cytokine (Li et al. 2012b).

2.2.3 Outputs of Brain Oscillators: The Case of Feeding/Fasting Cycle

Circadian oscillations in the hypothalamus influence a multitude of physiological processes and behaviors such as reproductive cycle, thermoregulation, sexual and maternal behavior, stress-related responses, and food intake. Circadian oscillations in hypothalamic nuclei may ensure the expression of appropriate behaviors at appropriate times of the day, thus avoiding the disadvantageous expression of multiple and incompatible behaviors at the same time, like sleep and food intake (Guilding and Piggins 2007).

Lesions in SCN abolish rhythmic behaviors, including feeding rhythm (Nagai et al. 1978). However, feeding/fasting cycle is likely not a passive consequence of the sleep/wake cycle and could involve the circadian timing of nuclei in the mediobasal hypothalamus. The direct projections from SCN to these nuclei may provide a first gating of feeding responses. We will further focus on ARC and DMH, key structures for regulation of energy balance and food intake (Williams and Elmquist 2012). ARC contains neurons sensitive to circulating nutrients (e.g., glucose-sensing neurons) (Burdakov et al. 2005) and to feeding-related hormones, like leptin, secreted from adipose tissue (Ahima and Lazar 2008). This integration of peripheral energetic information constitutes a homeostatic feedback loop. Moreover, both ARC and DMH are robust oscillators, likely implicated in feeding rhythm (Fig. 3).

Two populations of ARC neurons express neuropeptides oppositely involved in food intake regulation. Neuropeptide Y (NPY) and agouti-related peptide (AgRP) are orexigenic, while pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) are anorexigenic. These neuropeptides are rhythmically synthesized in the ARC (Akabayashi et al. 1994; Steiner et al. 1994; Xu et al. 1999). Feeding rhythm is profoundly disrupted by targeted destruction of either leptin-responsive or NPY-responsive neurons in ARC (Wiater et al. 2011; Li et al. 2012a).

The DMH is important for the integration of circadian rhythms into various physiological functions and behaviors, due to its wide afferent and efferent connections to hypothalamic (e.g., PVN, ARC, and LH) and extra-hypothalamic sites (Bechtold and Loudon 2013). Excitotoxic lesions of the DMH disrupt circadian rhythms of wakefulness, feeding, locomotor activity, and serum corticosterone (Chou et al. 2003). By its circadian oscillations, sensitivity to feeding-related cues, and involvement in homeostatic regulation of food intake, the DMH could thus be a key structure in the hypothalamic network controlling rhythms in feeding behavior. Hypothalamic oscillators seem to play a salient role in timing of feeding and energy metabolism (Fig. 3). Moreover, food intake can entrain specific circadian rhythms in anticipation of fixed mealtimes. These feeding-entrainable rhythms will be detailed below in the section describing the effects of feeding time on extra-SCN brain clocks.

Because peripheral tissues involved in metabolism harbor circadian oscillators, it is essential for the circadian regulation of energy balance to consider their oscillatory characteristics and their cross talk with the central actors aforementioned.

2.3 Peripheral Oscillators

The vast majority of cells in peripheral tissues contain the molecular clock machinery (Balsalobre et al. 1998; Yagita et al. 2001). Bioluminescent constructs allowed the real-time visualization of clock genes oscillations, both in vitro (Yoo et al. 2004) and in vivo (Tahara et al. 2012). Some peripheral tissues can exhibit self-sustained oscillations for several days, but the coupling is weaker than in SCN clock. Moreover, as in SCN clock, the period of peripheral oscillators is resilient to large fluctuations in temperature and overall transcription rates, as shown in cultured fibroblasts (Dibner et al. 2009). They also exhibit circadian outputs, as exemplified below. Circadian transcriptome profiling studies reveal that around 10 % of a tissue's transcriptome has a circadian pattern of expression (Panda

et al. 2002). Finally, peripheral oscillators are entrained by neuronal and endocrine signals emanating from the SCN or indirectly by SCN-controlled behavioral rhythms (feeding/fasting and sleep/wake cycles).

2.3.1 Outputs of Peripheral Oscillators

Rhythmically expressed genes control a multitude of physiological functions. For instance, they encode key enzymes involved in hepatic metabolism of fatty acids, cholesterol, bile acids, amino acids, and xenobiotics (Gachon et al. 2006) and control adipogenesis and lipid metabolism in adipose tissue (Gimble et al. 2011). The rhythmic physiological outputs of peripheral tissues result from signals emanating from the SCN and/or from local peripheral oscillators. Specific inactivation of the clock gene *Bmal1* in the liver of mice (L-*Bmal1*$^{-/-}$) disrupts rhythmic expression of genes involved in glucose metabolism, as well as rhythmic circulating glucose levels. During their resting phase, L-*Bmal1*$^{-/-}$ mice display mild hypoglycemia, suggesting that the daily rhythm of hepatic glucose export driven by the liver clock counterbalances the brain-driven feeding/fasting cycle (Lamia et al. 2008).

The adipose tissue also exhibits robust oscillations of core clock components, controlling the circadian expression of many transcription factors (Ando et al. 2005; Zvonic et al. 2006). Moreover, the adipose tissue secretes several hormones termed adipokines, including leptin and adiponectin, involved in the regulation of energy balance (Ahima and Lazar 2008). Ando and colleagues (2005) showed a rhythmic expression of several adipokine genes. Circulating levels of leptin display clear diurnal variations in both rodents and humans (Sinha et al. 1996; Kalsbeek et al. 2001; Cuesta et al. 2009). Moreover, leptin secretion is rhythmic in cultured adipocytes (Otway et al. 2009). These results strongly suggest that rhythmic expression of adipokines is under control of the adipose clock, although the underlying mechanisms are still unclear.

Another example is the pancreas in which specific inactivation of the clock gene *Bmal1* leads to glucose intolerance and hyposecretion of insulin, highlighting the importance of the pancreatic clock in glucose homeostasis (Marcheva et al. 2010).

2.3.2 Circadian Control of Metabolism at Molecular Level

The link between molecular clock and metabolism may be provided either by metabolic functions of clock genes (i.e., pleiotropy of clock genes) or by the involvement of clock-controlled genes. Both mechanisms seem to exist, involving many nuclear receptors, such as REV-ERBs and RORs (components of the molecular clockwork) and peroxisome proliferator-activated receptors (PPARs, clock-controlled proteins) (Teboul et al. 2008). RORα (alpha) directly regulates genes involved in the fatty acid metabolism of skeletal muscles (Lau et al. 2004). Moreover, REV-ERBα (alpha) is important for the daily variations of fuel utilization (Delezie et al. 2012) and plays a pivotal role in the interface between liver clock and lipid metabolism. PPARs are members of the steroid/nuclear receptor superfamily, acting as ligand-activated transcription factors. *Pparα* (alpha), a clock-controlled gene whose activation requires CLOCK, is rhythmically expressed in tissues with a high rate of fatty acid catabolism (e.g., the muscles, heart, or liver) and is involved in lipoprotein and lipid metabolism (Oishi et al. 2005b; Yoon 2009). *Pparα* (alpha) is therefore recognized as a strong link between circadian clocks and lipid metabolism in peripheral tissues (Teboul et al. 2008). Furthermore, as demonstrated by lipidomic profiling in adipose tissue, PER2 is important for normal lipid metabolism. This effect is mediated by PPARγ (gamma), a master regulator of adipogenesis and lipid metabolism in adipose tissue, whose transcriptional activity is directly inhibited by PER2 (Grimaldi et al. 2010) (Fig. 1). To ensure a proper control of circadian metabolism, central and peripheral clocks need to be phase adjusted. The next paragraph investigates the nature of signals synchronizing peripheral oscillators. First, we consider nervous and hormonal signals emanating from the SCN, acting as a relay between environmental synchronizers and peripheral tissues. Then, we present the resetting effects of nutritional cues.

3 Nature of Signals Synchronizing Peripheral Oscillators

3.1 Entrainment by Nervous Outputs from the SCN

3.1.1 SCN Controls Glucose Metabolism

The daily rhythmicity of plasma glucose, peaking before the onset of activity in rats, is not a passive response to the feeding/fasting cycle (La Fleur et al. 1999). The liver plays a pivotal role in glycemic regulation, as a site of glucose uptake and a major source of glucose production (Kalsbeek et al. 2010). Glucose homeostasis requires both functional hepatic and SCN clocks (La Fleur et al. 1999; Lamia et al. 2008). Besides SCN lesion, glucose rhythm can also be disturbed by inactivation of either sympathetic or parasympathetic inputs (Cailotto et al. 2008), underlying the importance of balanced inputs from the SCN via the autonomous nervous system (ANS). The actual model is that rhythmic GABAergic input from the SCN inhibits the sympathetic and parasympathetic pre-autonomic neurons of the PVN, predominantly during the day. By contrast, glutamatergic projections from the SCN stimulate sympathetic pre-autonomic neurons of the PVN (Kalsbeek et al. 2010). Thus, the entrainment of circadian glucose rhythm is controlled by the SCN, fine-tuning the balance between both branches of the ANS innervating the liver clock (Fig. 4).

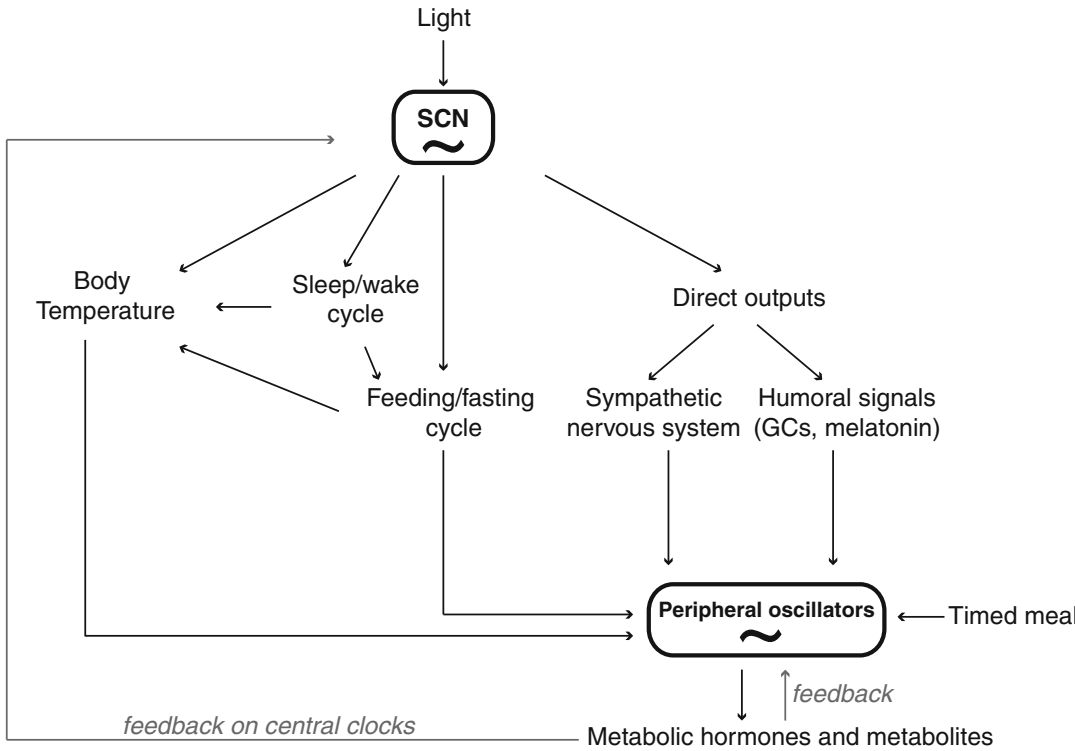

Fig. 4 Functional organization of the circadian timing system. The master clock in the SCN is mostly reset by ambient light. Extra-SCN oscillators in the brain (not shown) and in peripheral tissues are phase controlled by cues from the SCN and by timed feeding. The SCN clock transmits temporal cues to peripheral oscillators via "direct" outputs using nervous and hormonal pathways and indirectly via behavioral (i.e., feeding/fasting and sleep/wake cycles) and physiological (i.e., body temperature cycle) rhythmic signals. In turn, peripheral oscillators release rhythmically metabolic hormones and metabolites that feedback to central and peripheral oscillatory structures. *SCN* suprachiasmatic nucleus, *GCs* glucocorticoids (Based on Challet (2010), Dibner et al. (2010))

Moreover, hypothalamic orexin is a key regulator of plasma glucose, being particularly the main effector of the peak occurring before the activity phase. Sympathetic denervation of the liver prevented the stimulatory effect of orexin on glucose levels, suggesting that orexin translates SCN-derived GABAergic rhythms into glucose rhythm via the sympathetic nervous system (Yi et al. 2009).

3.1.2 SCN and the Adipose Tissue

The adipose tissue is densely innervated by sympathetic fibers, whose activation stimulates lipolysis. Parasympathetic innervation of adipose tissue has been shown more recently (Kreier et al. 2002). As for the liver, the SCN controls both branches of ANS innervating adipose tissues, modulating the rhythmic outputs of the adipose clock. For instance, the activity of hormone-sensitive lipase, exhibiting a daily rhythmicity, is increased by 50 % in adipose tissue selectively denervated for the parasympathetic input (Kreier et al. 2002). Moreover, leptin rhythm is under the control of both local adipose clock (Otway et al. 2009) and the master SCN clock since SCN lesions suppress the daily rhythm of plasma leptin in rats (Kalsbeek et al. 2001).

By modulating the autonomous innervations of liver and adipose clocks, the SCN thus controls the circadian rhythmicity of metabolites (carbohydrates and lipids) and metabolic hormones (e.g., leptin). However, some peripheral clocks do not respond directly or only to nervous cues. Glucocorticoid (GC) and melatonin, whose rhythmic release is driven by the SCN via nervous pathways, can in turn entrain many peripheral oscillators.

3.2 Entrainment by Hormonal Outputs: Glucocorticoids and Melatonin

Glucocorticoids (GCs) show a strong circadian rhythm, their secretion from the adrenal glands peaking around wake-up time (morning in humans and evening in nocturnal rodents). Different actors are involved in the circadian rhythmicity of GCs' secretion. The SCN drives GCs' rhythm via the hypothalamic–pituitary–adrenal axis and modulates the daily sensitivity of adrenal gland to ACTH via splanchnic fibers (Ulrich-Lai et al. 2006). Furthermore, the local adrenal clock gates the sensitivity of the adrenal gland to ACTH, therefore modulating the secretion of GCs throughout the day (Oster et al. 2006). The GC nuclear receptor is expressed in virtually all cell types in periphery and the brain, except in adult SCN cells (Rosenfeld et al. 1988). Activated GC receptors act as transcription factors, via direct activation or repression of various target genes (Surjit et al. 2011). Around 60 % of rhythmic transcriptome in mouse liver, mostly genes involved in metabolism, lose their rhythmicity after adrenalectomy, while expression of clock genes is hardly affected (Oishi et al. 2005a). Dexamethasone, a glucocorticoid receptor agonist, activates *Per1* expression and synchronizes rat fibroblasts in vitro (Balsalobre et al. 2000a). In the same study, dexamethasone was shown to phase shift peripheral clocks (liver, kidney, and heart), but not SCN clock, in vivo. Thus, glucocorticoids possess clock-resetting properties and represent a robust phase-entrainment signal from the SCN (Fig. 4).

Melatonin is derived from the amino acid tryptophan and secreted from the pineal gland always during the dark phase, either in nocturnal or diurnal mammals. The rhythmic release of melatonin is driven by SCN clock and acts an internal daily time-giver (Pevet and Challet 2011) (Fig. 4). Of interest for the circadian control of metabolism, MT1 and MT2 melatonin receptors are present in pancreatic islets (Mulder et al. 2009). Simple and double knockout mice for MT1 and MT1/MT2 exhibit an upregulation of insulin secretion, highlighting a negative action of melatonin signaling on insulin secretion (Mühlbauer et al. 2009). Moreover, melatonin applied on isolated islets, for 2 h at the maximum of the circadian insulin rhythm, induces a 9-h phase advance of the insulin rhythm (Peschke and Peschke 1998). Genetic studies in humans have correlated the presence of an allele variant of the melatonin receptor in the pancreatic islets, hyperglycemia, and impaired early-phase insulin secretion

(Bouatia-Naji et al. 2009). Thus, the homeostatic and circadian effects of melatonin on insulin secretion pave the road for further investigations in type 2 diabetes.

3.3 Coupling the SCN to Peripheral Clocks in Diurnal and Nocturnal Species

At the cellular level in peripheral clocks involved in metabolism, anticipation of metabolic pathways optimizes food processing. Peripheral clocks also sequester chemically incompatible reactions (e.g., gluconeogenesis and glycolysis in liver) to different time windows and limit metabolic processes with adverse side effects to times when they are needed. At physiological level, the subtle differences in how peripheral clocks are phased by the master clock allow different organs to synchronize their functions. At behavioral level, circadian rhythms allow organisms to anticipate and thus adapt to daily environmental variations. Of interest, phases of clock genes oscillations and their photic entrainment in the SCN are similar between nocturnal and diurnal species (Mrosovsky et al. 2001; Caldelas et al. 2003), while their respective phase of circadian gene expression in peripheral tissues is opposite, in the liver, for instance (Lambert and Weaver 2006). Therefore, the signals emanating from the SCN are differentially interpreted at downstream targets. One possible mechanism would be differences in polysynaptic relays conveying SCN outputs to peripheral targets. For instance, SCN releases vasopressin on interneurons of PVN during daytime. The targeted interneurons are excitatory in nocturnal rodents, while inhibitory in diurnal rodents (such as Sudanian grass rat, *Arvicanthis ansorgei*), leading to an opposite phase release of GCs between nocturnal and diurnal species (Kalsbeek et al. 2008). Furthermore, several species can even switch between nocturnal and diurnal patterns of behaviors. These switches might rely on modifications of polysynaptic relays from SCN to periphery, highlighting the adaptive value of the multistage organization of circadian timing.

3.4 Adjusting Clocks with Metabolism

3.4.1 Extra-SCN Clocks Are Entrained by Feeding Time

Among the different ways used by the SCN to synchronize peripheral clocks, the daily rhythm in spontaneous food intake is a strong *zeitgeber* for many tissues. In normal conditions, food ingestion is in phase with activity period. Restricted feeding in nocturnal rodents (i.e., when food is available few hours during the day, corresponding to the usual resting period) inverts the phase of gene expression in peripheral organs within about a week, thereby uncoupling peripheral clocks from the SCN (Damiola et al. 2000; Stokkan et al. 2001) (Fig. 4).

In the brain, food restriction entrains the activity of numerous oscillating structures. For example, the multineuronal activity in LH and VMH of rats under restricted feeding shows a peak entrained to the time of feeding (Kurumiya and Kawamura 1991). Moreover, daily oscillations of clock genes and proteins in various brain areas, such as the cerebral cortex or the striatum, from mice entrained to daytime-restricted feeding also show phase shifts with peaks around mealtime, different from the nocturnal peaks of expression in animals fed ad libitum (Wakamatsu et al. 2001; Feillet et al. 2008). All these data suggest that clocks within and outside of the brain are affected by restricted feeding schedules.

The effects of food on the circadian system involve a specific clock mechanism, the food-entrainable oscillator (FEO). Under restricted feeding, several components of physiological and metabolic functions become entrained to the availability of food (e.g., anticipatory bouts of locomotor activity and rises in body temperature and GC release), and some of them, such as the food-anticipatory activity, are still evident in SCN-lesioned animals. This implies the existence of the FEO, located outside of the SCN. The location and mechanisms of the FEO have been the subject of much controversy. Most evidences support the fact that FEO is a network of neural sites in the hypothalamus and brainstem, which interact to provide timing and behavioral entrainment of feeding (Mistlberger 2011).

3.4.2 Mechanisms of Entrainment of Extra-SCN Clocks by Food

The nature of signals that arise from feeding and entrain peripheral clocks has been an area of intense research. It is now established that feeding cues include food itself, the increase of postprandial temperature, food-derived metabolites, metabolic hormones, and energetic status of cells.

Temperature Fluctuations

While variations in temperature can entrain behavioral rhythms in ectothermic organisms such as flies, temperature fluctuations mimicking body temperature rhythms sustain previously induced oscillations in cultured rat fibroblasts. In vivo, inverted environmental temperature cycles reverse circadian rhythms of clock genes (*Per2* and *Cry1*) in the liver without affecting the SCN (Brown et al. 2002). Thus, postprandial temperature elevation could be an entrainment pathway from feeding/fasting cycle in homeothermic organisms. Hepatic heat-shock factor 1 (HSF1), which exhibits a highly rhythmic activity that drives the expression of heat-shock proteins in liver, could be a key component linking temperature fluctuations to the phase of molecular clocks (Buhr et al. 2010; Saini et al. 2012) (Fig. 4).

Food-Related Hormones

Anorexigenic (e.g., insulin, leptin) and orexigenic hormones (e.g., ghrelin) may participate to the entrainment of peripheral clocks by food intake. For example, insulin causes an acute induction of *Per1* mRNA levels in cultured rat fibroblasts (Balsalobre et al. 2000b) and phase shifts of *Per2* expression rhythm in liver explants (Tahara et al. 2011; Sato et al. 2014). *Ob/ob* mice, genetically obese mice lacking functional leptin, display alterations in clock gene oscillations of peripheral clocks but not in SCN. Of interest, impairments of peripheral clocks appear in young 3-week-old *ob/ob* mice, before appearance of metabolic disorders, and are partially improved by leptin treatment (Ando et al. 2011). The mechanisms by which leptin would modulate peripheral clocks need further investigations. It could involve a direct action of leptin on peripheral oscillators or a central action of leptin affecting in turn peripheral tissues. For instance, leptin is known to modulate various physiological processes in peripheral tissues via activation of sympathetic innervations (Haynes et al. 1997; Takeda et al. 2002).

Other hormones which could participate in meal entrainment in rodents are GCs. Restricted feeding in rats triggers an anticipatory rise of corticosterone in addition to the nocturnal rise controlled by the SCN (Honma et al. 1984), and corticosterone is known to entrain peripheral clocks as aforementioned. However, corticosterone injections fail to mimic the phase-shifting effects of feeding in rats (Stokkan et al. 2001). Gene expression rhythm in the liver of adrenalectomized or GC receptor-deficient mice is still entrained under food restriction, the phase shifts being even faster in absence of GCs (Le Minh et al. 2001). Hence, the role played by GCs in meal entrainment is still unclear.

Metabolites (Lipids and Glucose)

In addition to their role of mediators of metabolism (see first part), nuclear receptors can regulate clock components, therefore participating in the pathway by which food intake entrains peripheral oscillators. The transcription factor PPARα (alpha) is essential for lipid metabolism. After activation by fatty acids, PPARα (alpha) directly binds to a response element in *Bmal1* promoter (Canaple et al. 2006). PPARα (alpha) can also directly activate *Rev-erbα* expression, and PER2 is able to recruit PPARα (alpha) and REV-ERBα (alpha) to modulate *Bmal1* expression, highlighting the intimate reciprocal interactions between clock components and metabolism (Gervois et al. 1999; Schmutz et al. 2010). Additionally, PGC-1α (alpha), a coactivator of PPAR (PPARγ (gamma) coactivator-1α (alpha)), stimulates *Bmal1* expression through coactivation of ROR proteins. Since PGC-1α (alpha) is sensitive to various signals including nutritional status, activity, and temperature and regulates energy metabolism in peripheral tissues, it could be a key component in the coupling of metabolism and clocks (Liu et al. 2007) (Fig. 1).

Noteworthy, *Per1* and *Per2* mRNA levels are downregulated after the addition of glucose in the

culture medium of rat fibroblasts, while the expression of many other genes, including transcription factors, is upregulated. The glucose-induced decrease of *Per* mRNA levels seems mediated by glucose metabolism (involving transcriptional regulators) rather than glucose itself (Hirota et al. 2002). Thus, both lipids and glucose, major food metabolites, can reset peripheral clocks, constituting an important pathway of entrainment of peripheral clocks by feeding time.

Intracellular Redox State

CLOCK (or its paralog NPAS2), BMAL1, and/or PERs may directly sense energy-related signals through their PAS domain, by detecting the reduced or oxidized environment within the cell. Redox signals, closely tied to the energy status, are transduced by PAS domains which modulate the functional state of the protein (Gu et al. 2000). In vitro, the DNA-binding activity of the dimers CLOCK/BMAL1 and NPAS2–BMAL1 is altered by cellular redox status (Rutter et al. 2001). The reduced forms of the nicotinamide adenine dinucleotide, NADH and NADPH, activate DNA binding of CLOCK (or NPAS2)–BMAL1, whereas their oxidized forms inhibit it. NAD(P)H/NAD(P)$^+$ ratio reflects mitochondrial activity and the switch between activation and inhibition of DNA binding is very sensitive, providing a rapid mechanism which could convey changes in feeding to the cellular clocks (Rutter et al. 2001). Sirtuin 1 (SIRT1), another energy sensor, links metabolism to circadian physiology. SIRT1 catalyzes the deacetylation of various substrates in NAD$^+$-dependent manner. By deacetylating histones, SIRT1 participates to epigenetic silencing by chromatin condensation. By deacetylating metabolic enzymes and transcription factors, SIRT1 contributes to multiple metabolic pathways, including gluconeogenesis, lipid metabolism, insulin secretion, and thermogenesis. Besides being a critical component of the longevity response to calorie restriction (Yu and Auwerx 2009), SIRT1 is circadianly regulated. A specific deletion of SIRT1 in liver of mice shows its participation to circadian control in vivo (Nakahata et al. 2008). SIRT1 influences the transcription of a number of clock genes and promotes deacetylation of PER2, thus modulating the phase of the clockwork (Asher et al. 2008). In addition to NAD and SIRT1, 5′ adenosine monophosphate-activated protein kinase (AMPK) is another important metabolic fuel gauge, sensing changes in the AMP/ATP ratio. AMPK detects nutritional and hormonal signals in peripheral tissues and the hypothalamus (Kahn et al. 2005). As SIRT1, AMPK can directly impact the clockwork, thus phase shifting peripheral oscillators (Um et al. 2007; Lamia et al. 2009) (Fig. 1).

Coupling of cellular metabolism to the molecular clockwork in peripheral tissues has been intensely investigated, while less is known in central extra-SCN oscillators. Many mechanisms could be similar, including aforementioned sensors of energy and redox states. In particular, AMPK is a potent regulator of energy balance within the hypothalamus. For example, leptin inhibits specifically AMPK in ARC and PVN, and this inhibition is required to mediate anorexigenic and weight loss effects of leptin (Kahn et al. 2005). AMPK signaling is thus a likely route through which circadian and feeding signals are integrated in the hypothalamus (Bechtold and Loudon 2013).

3.5 Nutritional Cues and the Master Clock

3.5.1 Effects of Metabolic Signals on the Master Clock

While peripheral clocks are entrained by feeding time with great efficiency, the SCN clock seems impervious to the synchronizing effects of mealtime, provided that animals are exposed to a light–dark cycle and ingest enough daily energy (Damiola et al. 2000; Stokkan et al. 2001). However, SCN can respond to feeding cues under specific calorie conditions. In particular, rats exposed to a light–dark cycle and entrained to restricted feeding coupled with a hypocaloric diet display phase advances for circadian rhythms of locomotor activity, body temperature, and melatonin in comparison to animals fed ad libitum (Challet et al. 1997). Entrainment to light–dark cycle is

also altered in mice submitted to a timed hypocaloric feeding and their SCN clockwork is phase advanced (Mendoza et al. 2005). Conditions of low glucose availability can alter the circadian responses to light (Challet et al. 1999). In the absence of photic cues (i.e., constant darkness), the mouse SCN can also entrain to regular scheduled feeding (Castillo et al. 2004). Under constant light conditions, leading to behavioral arrhythmicity in albino rats, scheduled feeding rescues both locomotor activity rhythm and clock gene oscillation in the SCN (Lamont et al. 2005). Free access to high-fat diet also impacts on the master clock, as evidenced by lengthened free-running period in mice housed under constant darkness (Kohsaka et al. 2007; Mendoza et al. 2008). In mice with free access to chow diet, a palatable food (chocolate) given every day at the same time entrains the SCN clock in constant darkness and reduces its circadian responses to light (Mendoza et al. 2010). Taken together, these results highlight that the SCN function can be changed by various nutritional cues.

The pathways conveying metabolic signals to the SCN are not well identified. It is possible that timed calorie changes the redox status of SCN cells. Of note, redox signals in SCN exhibit circadian rhythm, which modulates the excitability of SCN neurons (Wang et al. 2012). This result demonstrates the close connection between cellular metabolism and dynamic regulation of SCN functioning. Another possibility would involve relays from brain structures sensitive to nutrients. Lesion experiments suggest an involvement of IGL in the transmission of metabolic information to the SCN (Challet et al. 1996; Saderi et al. 2013). Moreover, orexigenic and anorexigenic neurons in the hypothalamus controlling feeding behavior respond to fluctuations in circulating nutrient (e.g., glucose, fatty acids, amino acids) levels that reflect nutritional status (Williams and Elmquist 2012). Since SCN receives numerous projections from hypothalamic nuclei, the metabolic hypothalamus could integrate and transmit information from circulating nutrients to the SCN. For example, VMH has been involved to some extent in mediating the behavioral phase advance produced by timed caloric restriction (Challet 2010).

3.5.2 Feedback of Metabolic Hormones

Since receptors of ghrelin, insulin, and leptin are present on SCN cells, these hormones are good candidates to provide metabolic information to the SCN (Unger et al. 1991; Guan et al. 1997; Zigman et al. 2006). These receptors are also present on several hypothalamic structures which project on the SCN, such as ARC (Yi et al. 2006), raising the possibility of either a direct or indirect effect on the master clock.

Ghrelin is predominantly synthesized by stomach. Ghrelin receptors are present in the hypothalamus, including SCN and mediobasal hypothalamic nuclei involved in food intake (Zigman et al. 2006). Ghrelin levels exhibit a circadian rhythm and closely follow feeding schedules, making this peptide a putative candidate for food-related entraining signals. In vitro, ghrelin phase advanced the electrical rhythm of SCN slices and the *PER2::LUC* expression in cultured SCN explants (Yannielli et al. 2007), suggesting a direct action of ghrelin on the SCN. In vivo experiment shows that besides increasing food intake, ghrelin treatment only causes phase shifts in fasted mice, but not in mice fed ad libitum (Yannielli et al. 2007). The shifting effects of ghrelin on the SCN and its reducing effects of photic responses in the SCN could be mediated by the ARC (Yi et al. 2006, 2008).

Insulin, mostly synthesized by β-cells of pancreas, can cross the blood–brain barrier. Insulin receptors are present on SCN cells (Unger et al. 1991), and insulin applied during the subjective day inhibits firing rate of the SCN neurons (Shibata et al. 1986). Little is known, however, about the possible phase-shifting effects of insulin on free-running activity rhythms of rodents in constant darkness. Thus, the possible feedback role of insulin on the SCN deserves further investigation.

Leptin, encoded by the gene *ob*, is produced and secreted by the white adipose tissue, and consequently, its circulating levels are closely related to body fat mass. Among all its targets, leptin signals to the hypothalamus, where it promotes satiety and stimulates energy expenditure (Ahima and Lazar 2008). The mediobasal hypothalamus lies within close proximity to the median eminence, a circumventricular structure

containing specialized hypothalamic glial cells called tanycytes. It has recently been shown that circulating leptin enters the brain via the median eminence, through internalization by tanycytes, which release leptin in the mediobasal hypothalamus (Balland et al. 2014). In addition to its effects on energy balance, leptin can affect the circadian system. Indeed, expression of leptin receptors has been detected in the SCN (Guan et al. 1997). Leptin in vitro can phase advance the SCN oscillations (Prosser and Bergeron 2003) and modulate firing rates of SCN neurons (Inyushkin et al. 2009). In vivo injections of leptin modulate the photic synchronization of the master clock in mice (Mendoza et al. 2011), this effect being likely mediated by the mediobasal hypothalamus (Grosbellet et al. 2015).

3.5.3 Feedback of Other Hormones: Glucocorticoids and Melatonin

While the GC agonist dexamethasone can phase shift circadian gene expression in peripheral clocks, it does not affect clock gene expression in the SCN (Balsalobre et al. 2000a). However, mice with genetic ablation of adrenal clock, as well as adrenalectomized rats, reentrain faster to a new light–dark cycle than control animals, suggesting that the adrenal clock feeds back to the SCN, probably via indirect effect of GCs (Sage et al. 2004; Kiessling et al. 2010). At least midbrain raphe nuclei are identified relays mediating feedback effects of GCs on the SCN via the serotonergic system. Indeed, daily variations of circulating GCs trigger the daily rhythm of *tryptophan hydroxylase* mRNA, a limiting enzyme for serotonin synthesis (Malek et al. 2007).

Melatonin is known for its sedative (i.e., sleep-promoting) effect in humans (Sack et al. 1997). Beyond its effect on sleep, melatonin has been shown to directly influence the SCN, where melatonin receptors MT1 and MT2 are present. Daily perfusions of supraphysiological doses of melatonin can entrain the free-running activity of rats. Melatonin also accelerates the reentrainment of circadian rhythms after a shift in the light–dark cycle (Pevet and Challet 2011). Thus, together, melatonin and glucocorticoid rhythms appear to stabilize the functioning of the circadian system.

The above sections showed the cross talk between circadian system and metabolism, leading to a finely tuned regulation of circadian and energy physiology. The other side of the coin, developed below, is that disruptions in the circadian system disturb metabolism, and vice versa.

4 Circadian Disruptions and Metabolic Disturbances

4.1 Circadian Disruptions Affect Metabolism

Since clock genes and clock-controlled genes determine the circadian organization of metabolism, genetic clock disruptions affect metabolism in rodents. For example, *Bmal1* deletion in mice impairs glucose metabolism and triglyceride rhythms in addition to increased body fat (Lamia et al. 2008). Moreover, *Clock* mutant mice are hyperphagic, with increased food intake during the resting period and decreased energy expenditure at night, leading to fat excess. *Clock* mutant mice show severe metabolic alterations, including disruptions in lipid (e.g., hypercholesterolemia and hypertriglyceridemia) and glucose (hyperglycemia) homeostasis (Turek et al. 2005).

The circadian rhythmicity can also be altered by environmental factors, such as chronic changes in timing of light–dark cycles (chronic jet lag) or work occurring during the usual resting period (shift work). Numerous epidemiological studies in different countries link the circadian desynchronization induced by shift work with increased risks for the metabolic syndrome. These observations lead to the concept of "chronobesity," defined as obesity induced or aggravated by circadian desynchronization. The metabolic disturbances resulting from shift work include impairments in lipid and glucose metabolism and hypertension (Karlsson et al. 2003; Dochi et al. 2009). Moreover, recurrent sleep debt is also a risk factor for obesity and diabetes (Spiegel et al. 2009), indicating that it is likely an aggravating factor for metabolic disturbances in shift workers.

In rats, repeated weekly light–dark shifts increase food intake and reduce activity, resulting in higher body weight gain (Tsai et al. 2005) or impaired insulin regulation (Bartol-Munier et al. 2006). Moreover, rats forced to work during daytime show no alteration in clock protein oscillations in the SCN, which remain in phase with the light–dark cycle, while temporal patterns of activity and food intake are altered. These rats also exhibit a loss of glucose rhythmicity and a reversed rhythm of triglycerides. These results reveal an internal desynchronization, in which activity combined with feeding uncouples metabolic functions from the master clock (Salgado-Delgado et al. 2008).

4.2 Metabolic Disruptions Induce Circadian Disturbances

4.2.1 Diet-Induced Obesity

Obesity in rodents can be induced by a high-fat regimen, in which more than 50 % of energy derives from fat. In mice, high-fat diet attenuates the daily pattern of locomotor activity, concomitantly with a hypoactivity, due to a reduction of activity during the dark phase. The daily pattern of food intake is also dampened, with increased feeding during the light phase and a relative decrease at night (Kohsaka et al. 2007). As aforementioned, high-fat feeding lengthens the free-running period of mice under dark conditions (Kohsaka et al. 2007). High-fat feeding also slows the resynchronization after shifts of the light–dark cycle and decreases light-induced phase shifts (Mendoza et al. 2008). All together, these results indicate that high-fat feeding affects the SCN clock. Moreover, high-fat feeding is accompanied by changes in neuropeptide expression in the mediobasal hypothalamus, despite no major modification in clock gene oscillations in that region (Kohsaka et al. 2007). In the brainstem, more precisely in the nucleus of the solitary tract, high-fat feeding alters the daily patterns of clock gene expression, including downregulated *Rev-erbα* (alpha), and upregulated *Bmal1* and *Clock* mRNA levels (Kaneko et al. 2009). These results suggest that central dysfunctions may contribute to the development of obesity in high-fat-fed mice.

Short-term high-fat feeding reduces circadian variations of leptin levels in rats (Cha et al. 2000). High-fat feeding also alters the daily variation in glucose tolerance and insulin sensitivity in mice (Delezie et al. 2012). Since metabolites, food-related hormones, and feeding rhythms are potent synchronizers for peripheral clocks, it would not be surprising that peripheral clocks are altered in high-fat-fed mice. High-fat feeding can attenuate the amplitude of clock gene expression and alters the rhythmic patterns of nuclear receptors, such as PPARγ (gamma) and RORα (alpha), in the adipose tissue and liver of mice (Kohsaka et al. 2007), while other studies found that high-fat diet fails to markedly alter peripheral clock gene oscillations (Yanagihara et al. 2006; Delezie et al. 2012; Eckel-Mahan et al. 2013). Several hepatic transcripts were even shown to gain rhythmicity in mice fed with high-fat diet (Eckel-Mahan et al. 2013). In humans, oscillations of clock genes in adipose tissue do not differ between lean, obese, and diabetic patients (Otway et al. 2011), suggesting that fat overload does not always impact peripheral clocks.

4.2.2 Genetic Obesity

Genetic obesity and diabetes in rodents provide experimental models suitable to study the impact of metabolic disturbances on circadian system. For instance, obese Zucker rats (*fa/fa* rats) that carry a mutation in the leptin receptor gene display phase advance in feeding (Fukagawa et al. 1992) and locomotor activity rhythms (Mistlberger et al. 1998). The amplitude of the activity–rest cycle is dampened in genetically obese rats and mice, due to increased activity during the resting light phase and decreased activity during nighttime (Mistlberger et al. 1998; Kudo et al. 2004; Sans-Fuentes et al. 2010). Obese *ob/ob* mice carry a mutation in the leptin (*ob*) gene and thus lack functional leptin, while *db/db* mice, obese and diabetic, carry a mutation in the leptin receptor. *Ob/ob* mice show altered photic resetting of the master clock (Sans-Fuentes et al. 2010; Grosbellet et al. 2015), albeit neither *ob/ob* nor *db/db* mice exhibit major alterations of

molecular clockwork in the SCN (Kudo et al. 2004; Ando et al. 2011).

In sharp contrast, the daily variations of clock gene expression are clearly reduced in liver and adipose tissue of obese *ob/ob* mice and in liver of *db/db* mice (Kudo et al. 2004; Ando et al. 2011). Of interest, impairments of peripheral clocks in *ob/ob* mice precede the appearance of metabolic disorders, suggesting that the circadian disturbances are due to the lack of leptin and not to a passive consequence of obesity. Accordingly, leptin injection partially restores clock gene oscillations in peripheral clocks (Ando et al. 2011). The relationship between obesity and circadian disturbances appears often to be a chicken-and-egg problem, since, in most cases, it is difficult to determine which problem appears first and disturbs the other system. Notwithstanding, circadian desynchrony could be an aggravating factor for the development of obesity and/or diabetes and as such deserves careful examination.

4.3 Preventive Treatments for Internal Desynchronization and Its Metabolic Consequences

One possibility to improve circadian alignment in individuals submitted to shift work or jet lag is timed exposure to light since light is able to reset circadian rhythms, and in addition, it directly improves alertness in humans (Chellappa et al. 2011).

Because feeding time is a potent synchronizer of peripheral oscillators, it is also a possible resynchronizer in case of altered circadian rhythmicity. Obese Zucker rats (*fa/fa*) ingest a larger proportion of food during the light phase (i.e., the resting phase) than wild-type rats (Mistlberger et al. 1998). In this study, Zucker rats fed ad libitum gained 23 % more weight than animals with access to food limited to nighttime (i.e., the normal period of feeding in nocturnal rats), despite similar amounts of daily food intake. This suggests that excessive diurnal feeding may contribute to body weight gain. Moreover, the negative effects of unbalanced high-fat diet are limited if high-fat feeding is restricted to the dark phase in mice (Hatori et al. 2012).

In humans, eating during late evening is associated with higher daily energy intake, a major risk factor for weight gain (Reid et al. 2014). Furthermore, nocturnal feeding is correlated with an increased risk of overweight in some, but not all, epidemiological studies (Colles et al. 2007; Striegel-Moore et al. 2010). Although shift workers often report normal total energy intake, there is commonly an altered temporal distribution of feeding characterized by more irregular eating times, more snacking, and fewer substantial meals (Lowden et al. 2010).

All together, these results show that studies on obesity should not focus exclusively on food intake and energy expenditure. The timing of food intake itself plays a significant role in weight gain. Feeding at the right time might attenuate weight gain by normalizing the phase relation between circadian rhythms of food intake and metabolic processes involved in utilization and storage of ingested fuels.

In conclusion, this chapter shows that energy metabolism and circadian rhythmicity interact at multiple (i.e., molecular, cellular, and systemic) levels. The daily temporal regulation of energy metabolism is controlled by a multi-oscillatory network comprising a master clock in the SCN and numerous secondary clocks and oscillators in the brain and peripheral tissues. Furthermore, core clock components interact closely with molecular regulators of intracellular metabolism. While the ambient light detected by the retina is the most powerful synchronizer of the master clock, the SCN is also sensitive to metabolic signals associated with metabolic challenges. Mealtime can adjust the phase of many brain and peripheral oscillators outside the SCN. From a pathophysiological point of view, metabolic diseases are associated with circadian alterations. Conversely, induction of circadian disturbances by genetic alterations in the clockwork or by desynchronizing conditions (e.g., shift work, chronic jet lag) affects metabolism. Because altered circadian timing is recognized as a determinant of metabolic troubles, chronotherapeutic approaches of daily dieting should be taken into consideration for the management of metabolic health.

5 Cross-References

- Adipokines and Metabolism
- Brain Regulation of Feeding and Energy Homeostasis
- Diet, Exercise, and Behavior Therapy in the Treatment of Obesity and Metabolic Syndrome
- Overview of Metabolic Syndrome
- The Built Environment and Obesity

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Part V

Diseases Associated with Obesity

Body Composition Assessment

31

David R. Weber and Babette S. Zemel

Contents

Abstract

The recent and dramatic increases in worldwide obesity rates have resulted in a tremendous number of people at risk for the development of cardiometabolic diseases such as type 2 diabetes, hypertension, coronary artery disease, and stroke. Against this background, there is a pressing need to improve our understanding of the mechanisms underlying the contribution of obesity to the development of cardiometabolic disease. The expectation is that this knowledge will lead to better screening practices for the identification of those individuals at greatest cardiometabolic risk and the development of targeted prevention strategies and novel therapeutic agents. The use of body composition analysis is an essential tool to researchers and clinicians working in this field. The objectives of this chapter are to review the basic principles underlying body composition analysis, discuss existing models for applying body composition analysis to the study of cardiometabolic disease, and highlight new functional body composition models that seek to integrate established approaches with emerging techniques such as advanced medical imaging to provide a more complete understanding of the complex relationships between body compartments and disease states.

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1 Introduction

It is well recognized that obesity and obesity-related complications are a tremendous burden on both the public health system and the private lives of patients. According to the World Health Organization (WHO), in 2014 more than 1.9 billion adults were overweight or obese worldwide (WHO 2015). A global effort is underway to better understand the origins of obesity, to develop screening programs to accurately identify individuals at the greatest risk for the development of obesity-related disease, and to develop treatments for those already suffering from the complications of obesity. Body composition analysis is an important tool in this effort. The goal of this chapter is to review the basic principles underlying the study of human body composition and to discuss the different techniques available for the assessment of body composition in the clinical and research setting. The concept of functional body composition will be discussed, which aims to integrate traditional methods of body composition analysis with modern imaging and metabolomics techniques. Special focus will be paid to the relationships between body composition and cardiometabolic disease, including the metabolic syndrome.

1.1 Basic Principles of Body Composition Analysis

The assessment of body composition involves the measurement, quantification, and comparison of the amounts of different body tissues and in some cases their cellular, molecular, and atomic components. A fundamental concept underlying the approach to body composition analysis is that the human body can be partitioned into different *body compartments* for analysis. Conceptual models that describe the composition of different body compartments and define the relationships between compartments have been developed. These models provide an organizational framework for clinicians and researchers interested in body composition analysis.

1.2 The Five-Level Model

The human body can be organized according to compartments as described in the *five-level model* (Wang et al. 1992). This model describes the human body as a series of five interrelated and increasingly complex levels to describe the composition of the human body. It begins at the atomic level (Level I) and progresses in complexity through the molecular (Level II), cellular (Level III), and tissue levels (Level IV) and culminates at the level of the whole body (Level V). Each level has clearly defined components that necessarily sum to equal total body weight. Body composition can be assessed individually at a given level or in relation to other levels. Perturbations in body composition that affect one level necessarily affect all other levels.

For example, a patient successfully completing a weight loss program will demonstrate an absolute loss in total body weight (Level V). This will include losses of both fat and lean body mass (Level IV) as well as losses in cellular, molecular, and atomic components (Levels I–III) in proportion to the tissue losses (Pownall et al. 2015). The ability to assess tissue-specific losses may be clinically relevant in this example, as the respective losses of lean and fat mass may vary by weight loss intervention. For example, surgically induced weight loss as through bariatric surgery may result in, respectively, greater losses of lean body and bone mass compared to lifestyle interventions that include an exercise component (Chaston et al. 2007). The differences in weight loss between these two interventions would not be identified if only assessing body composition at Level V but rather would require a technique that assesses at Level IV or below.

The techniques required to assess body composition vary by level and generally increase in

complexity, cost, and risk to the patient/participant as the granularity of the information sought increases from Level V to Level I. Below is a brief summary of the information that can be attained at each level, as well as the primary techniques used to assess body composition at a given level. A more detailed discussion of the techniques commonly used in the study and management of cardiometabolic disease follows later in the chapter.

1.2.1 Level I: Atomic Level

The most fundamental level, Level I, provides information regarding the elemental composition of the body. Oxygen, carbon, hydrogen, nitrogen, and calcium are the most common elements present in the human body and account for >95 % of total body weight (Snyder et al. 1984). Elemental composition can be assessed in vivo using specialized techniques such as neutron activation and total body potassium counting (Heymsfield et al. 1997).

1.2.2 Level II: Molecular Level

Chemical elements combine to form molecules. The human body is composed of a large number of these chemical compounds. For the purposes of molecular body composition analysis, these chemical compounds are typically grouped into the following categories: water, lipid, protein, carbohydrates (mostly in the form of glycogen), mineral, and others. In the typical human body, water is the most abundant component (~60 % of total body weight), followed by lipid (~19 %), protein (~15 %), mineral (~5 %), and finally carbohydrates and other molecules which account for the remaining 1 % (Wang et al. 1992).

Many of the techniques used in the study and clinical evaluation of obesity and its associated complications are based on assessment of body composition at the molecular level. Techniques used at this level include isotope dilution and magnetic spectroscopy (Hwang and Choi 2015). These techniques can be combined with atomic level techniques including neutron activation and total body potassium counting to improve estimates of molecular components.

1.2.3 Level III: Cellular Level

Molecules in the human body are distributed into cellular and extracellular spaces. The extracellular compartment is often further divided into its fluid and solid components. Extracellular fluid is comprised mostly of water. It is found in the form of plasma in the intravascular space, and also as interstitial fluid between cells in various tissues or in cavities such as the peritoneum. Extracellular solids include organic compounds such as collagen and elastin and inorganic compounds such as hydroxyapatite. Hydroxyapatite is comprised primarily of calcium and phosphate and is an important contributor to bone strength. Several stable relationships between elements or molecules and cellular components have been identified and form the basis of techniques used to quantify body composition at Level III. Specific techniques include assessment of intracellular and extracellular body water using deuterium dilution or sodium bromide dilution and the use of total body potassium counting to estimate intracellular fluid or body cell mass (Silva et al. 2008).

1.2.4 Level IV: Tissue Level

Much of the clinical and research interest in the relationships between body composition and cardiometabolic disease is focused on Level IV. The cellular components of the body are organized into functional tissues. Common models at the tissue level partition the body into adipose tissue, skeletal muscle, organs, and bone. There is growing interest in further partitioning adipose tissue into subcutaneous, visceral, bone marrow, intermuscular, and intramuscular components as these different adipose depots appear to function differently and may be independent contributors to the development of cardiometabolic disease. A wide variety of techniques provide tissue-level information and include DXA, BIA, hydrodensitometry (also known as underwater weighing), air displacement plethysmography, computed tomography (CT), and magnetic resonance imaging (MRI).

1.2.5 Level V: Whole-Body Level

The most biologically complex level, Level V, provides information regarding the size and

shape of the human body. Weight, height, body segment lengths, circumferences, and skinfold thickness can all be obtained via anthropometry. The data obtained from anthropometry can be applied directly (e.g., waist circumference as an assessment of abdominal adiposity), combined into indices [e.g., body mass index (BMI), which is calculated as weight (kg)/height $(m)^2$], or, in the case of skinfold thicknesses, used to estimate percentage body fat (a Level IV component).

1.3 Compartment Models

A second and related approach to body composition analysis is to characterize body composition based upon the *number of compartments* described. Similar to the five-level model described above, the sum of the compartments always must be equal to total body weight. The accuracy of body composition improves with the number of compartments assessed, but so do the complexity, cost, and potential risk to the patient or participant.

1.3.1 One-Compartment Models

Similar to Level V, the body is considered as a whole. These models provide no information regarding the relative contribution of tissues, cells, molecules, or elements to total body weight within an individual. The use of one-compartment models to identify individuals with excess adiposity or low muscle mass is based on assumptions that the relative contributions of tissues to body weight are constant across different ages, maturational stages, racial/ethnic groups, and states of health and disease. Weight and BMI are examples of one-compartment models.

1.3.2 Multi-compartment Models

Many of the techniques used to derive *multi-compartment models* of body composition rely on the relationships between mass, volume, and density. Density is defined as body mass/body volume. Total body mass is easily attained via weighing, and total body volume can be measured via either water or air displacement. Total body density is assumed to be the sum of the densities of each of the body compartments being assessed. For a two-compartment model, for example, this is related by the equation

$$1/(\text{total body density}) = \text{FM}/(\text{FM density}) + \text{FFM}/(\text{FFM density})$$

FM density is commonly assumed to be 0.9007 kg/L (Brozek et al. 1963) and is relatively constant among individuals. FFM density, by contrast, is variable across the life-span, and age-specific values are typically used (Lohman 1986; Fomon et al. 1982). A discussion of the commonly used multi-compartment models is presented below.

1.3.3 Two-Compartment Models

Two-compartment models partition the body into *fat mass* (FM) and *fat-free mass* (FFM) components and are represented by the equation

$$\text{Total body mass} = \text{fat mass} + \text{fat free mass}$$

Conceptually, two-compartment models are based upon the assessments of body composition at the molecular/cellular level such that FM represents the extractable lipid component of the body and FFM represents everything else (Forbes 1987). Practically they are used to estimate tissue-level information whereby FM represents the body adipose tissue and FFM represents the remainder of the body including the muscle, organs, bone, and other supportive tissues.

These models improve upon one-compartment models by allowing for the assessment of the relative contribution of the adipose tissue to total body weight. *Percentage fat mass* [(fat mass/total body mass) * 100; also referred to as percentage body fat] is a commonly used measure to assess adiposity and cardiometabolic risk that is based upon a two-compartment model. Two-compartment models assume constant densities of the FM and FFM components. This is a reasonable assumption for FM but is problematic for FFM. The density of FFM is affected by hydration, which is known to vary according to age (Hewitt et al. 1993; Wells et al. 2010), body weight (Mingrone et al. 2001), and disease status

(Warner et al. 2004). Furthermore, the contribution of bone mineral to FFM varies across the lifespan (Lohman et al. 1984). Techniques that can be used for two-compartment body composition analysis include skinfold thicknesses, hydrodensitometry, air displacement plethysmography, BIA, DXA, and isotope dilution.

1.3.4 Three-Compartment Models

Three-compartment models improve the estimation body composition by further partitioning the FFM component of the body. Different three-compartment models can be derived based upon the technique and level of information obtained. DXA is commonly used to obtain a three-compartment model where the FFM is partitioned into *lean body mass* (LBM) and *bone mineral content* (BMC), represented by the equation

$$\text{Total body mass} = \text{fat mass} + \text{lean body mass} + \text{bone mineral mass}$$

The use of a DXA-based three-compartment model allows for the independent assessment of LBM and BMC in addition to FM. The information provided from this model therefore has much wider clinical and investigational utility compared to that of two-compartment models. Because DXA measures BMC directly, it eliminates a major source of FFM variability present in two-compartment models. This model still relies on the assumption that FM and LBM have constant densities, which is associated with the limitations discussed above.

An alternative three-compartment model can be obtained by combining a technique that provides density (such as hydrodensitometry) with a technique that determines total body water (such as isotope dilution). In this model, the FFM component is further portioned into water and nonaqueous solids, represented by the equation

$$\text{Total body mass} = \text{fat mass} + \text{total body water} + \text{non} - \text{aqueous solids}$$

This model addresses the variability associated with FFM hydration but is limited by a failure to account for the variable contribution of bone mineral to FFM across different populations.

1.3.5 Four- and Five-Compartment Models

Four-compartment models have been developed to address the limitations in the two- and three-compartment models noted above. DXA can be combined with techniques to estimate density and total body water to partition the FFM compartment into water, mineral, and protein (Wells et al. 1999), represented by the equation

$$\text{Total body mass} = \text{fat mass} + \text{total body water} + \text{total body mineral} + \text{protein}$$

The assumptions inherent in this model (constant hydration of protein and contribution of BMC to whole-body mineral content across individuals) are associated with less potential error than those present in the two- or three-compartment models (constant hydration of FFM and contributions of BMC to FFM across individuals) and therefore provide more accurate estimates of FM and FFM (Wells et al. 2012). A number of other four- and five-compartment models have been developed that incorporate techniques such as total body potassium counting, isotope dilution, and/or neutron activation to further improve estimation of body composition (Zemel and Barden 2004). These techniques are available only at specialized centers; as a result these models are not widely available for the analysis of body composition, and they are not routinely used in the assessment of cardiometabolic disease.

Extensive work in the field of body composition has been done to define the specific mathematical relationships between body compartments in a wide variety of human populations using the techniques described above. This has resulted in the development of numerous equations for the estimation of body mass within each of the five body levels, as well as equations relating body compartments between levels. Readers seeking a detailed methodological discussion regarding the in vivo assessment of body composition, complete with equations, examples, and references, are referred to the excellent reviews written by Steven

Heymsfield and Zi-Mian Wang (Heymsfield et al. 1997) and Kenneth Ellis (2000).

1.4 Functional Body Composition

Ultimately, the aim of using the five-level model or multi-compartment models described above is the integration of body compartments into whole-body regulatory systems and physical function. This emerging concept has been coined *functional body composition* (Muller et al. 2009) and is rooted in the idea that body compartments (particularly at the cellular and tissue level) are linked via hormonal, cytokine, metabolic, and neural networks. In these models, body compartments are understood to not only reflect but also contribute to the changes in body composition observed in the setting of environmental stressors such as undernutrition, overnutrition, and chronic disease. An ever-growing number of cytokines derived from fat "adipokines" (Ahima 2006), muscle "myokines" (Seldin and Wong 2012), and even bone (Clemens and Karsenty 2011) have been identified as potential mediators in this tissue cross talk.

An example of a functional body composition approach is the use of advanced medical imaging techniques to investigate determinants of *resting energy expenditure* (REE). FFM is known to be the primary determinant of REE (Korth et al. 2007). As discussed above, however, FFM is a heterogeneous compartment, and the contribution to REE is not constant among FFM components. FFM can be portioned into two functional components such that

$$\begin{aligned}\text{Body Mass} = {} & \text{metabolically active FFM} \\ & + \text{metabolically inactive FFM} + \text{FM}\end{aligned}$$

Equations for the estimation of REE can then be derived where whole-body REE is equal to the metabolic rate * mass of each of components above (Muller et al. 2014a). The metabolically active FFM compartment can be further partitioned into individual organs using MR- or CT-based assessment of organ size to improve estimates of REE (Elia 1992). The respective contributions of FFM and FM to REE are known to vary according to age, sex, race, and body weight and therefore must be accounted for when using these models (Bosy-Westphal et al. 2009). The explanation for the finding that the proportion of REE attributable to FM is greater at higher levels of FM is not fully understood, but may be related to larger adipocyte size, fat distribution, or increased adipocyte metabolic activity (Muller et al. 2009).

A further functional model of body composition related to cardiometabolic disease is the partitioning of FM into adipose depots. As noted above, traditional compartment-based models of body composition assume a constant density for FM. While the assumption of homogeneity of fat at the molecular, cellular, and tissue levels may be reasonable for estimating mass, there is growing evidence to suggest that body FM is not homogeneous from a functional standpoint. The partitioning of fat within the body can be described at several levels (Table 1). Certain fat depots including visceral adipose tissue (VAT), intramuscular adipose tissue (IMAT), and intrahepatic and epicardial fat appear to be more metabolically active and have greater associations with cardiometabolic disease in both adult and pediatric populations (Perseghin et al. 1999; Goodpaster et al. 2000; Brumbaugh et al. 2012; Katzmarzyk et al. 2013; Ogorodnikova et al. 2013). FM can also be partitioned into white and *brown adipose tissue* (BAT). BAT is a specialized form of adipose tissue involved in the maintenance of body temperature through non-shivering thermogenesis (Cannon and Nedergaard 2004). BAT activity has been shown to be negatively correlated with BMI and percentage body fat (van Marken Lichtenbelt et al. 2009); however, a potential protective role for BAT against the development of cardiometabolic disease has yet to be shown.

1.5 Techniques Used to Assess Body Composition

It is important to note that there is no gold standard for the assessment of body composition

Table 1 Fat partitioning within the human body and potential associations with cardiometabolic disease

Fat partition	Description	Assessment	Cardiometabolic consequences[a]
Android	Truncal fat distribution	DXA, anthropometry	Deleterious
Gynoid	Hip/thigh fat distribution		Protective
Marrow	Adipose tissue within the bone marrow	MRI, MRS	Deleterious, may be associated with skeletal fragility
Subcutaneous	Subcutaneous adipose tissue	CT, MRI, DXA	Protective
Visceral	Intra-abdominal adipose tissue	CT, MRI, DXA	Deleterious
Epicardial	Lipid deposits between visceral pericardium and myocardium	CT, MRI, MRS	Deleterious, especially for cardiovascular disease
Intermuscular	Lipid deposits between the muscle fibers	CT, MRI, MRS	Deleterious
Intrahepatic	Lipid deposits in the liver	MRI, MRS	Deleterious
Intramuscular	Lipid deposits within the muscle fibers	CT, MRI, MRS	Deleterious
Pancreatic	Lipid deposits within and around the pancreas	CT, MRI, MRS	Deleterious, especially related to β-cell function
Perivascular	Lipid deposits around the blood vessels	MRI, MRS	Evidence for both deleterious and protective
Brown fat	Thermogenic	PET	Protective
White fat	Energy storage	PET	Deleterious if excessive

[a]Deleterious in the setting of excess fat accumulation; protective in the absence of excess fat accumulation

in vivo. Instead, it is up to the clinician or researcher to select the technique or techniques that will provide the relevant information in a manner that is feasible, cost-effective, and with the appropriate risk/benefit ratio for the question of interest. While there are numerous techniques for body composition analysis available, they can be grouped together into a few fundamental categories based upon technical approach (Table 2). A brief discussion of the commonly used techniques to study body composition in relation to cardiometabolic disease is provided below.

1.5.1 Anthropometry

Anthropometric measures of body composition are relatively easy to attain, of low cost, and of low risk to patients. Because of these advantages, anthropometric assessment of body composition at the whole-body level is commonly used in research studies and in the development of practice guidelines to assess cardiometabolic risk in the clinical setting. A major benefit of these techniques is that reference data and prediction equations have been published for many different measures in diverse populations across the lifespan. Proper training of clinical or research staff and the development of measurement protocols are essential for accurate results.

Height and weight provide direct information about body size and body mass or can be combined into ratios such as weight for height (used in children <2 years of age) and BMI. Waist circumference can be used to assess abdominal adiposity and has been shown to be strongly correlated with CT or MRI measures of visceral adiposity (Han et al. 1997). Methods for the measurement of waist circumference vary; therefore, it is important to understand how the reference data to be used were determined. The US CDC recommends placing a measuring type around the midsection of the body at the level of the iliac crest while the patient/participant is standing (NHLBI 2000). This is in contrast to the WHO which states that the measurement should be obtained at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest (WHO 2008). There is no evidence to support the use of one technique over the other; however, as a recent systematic review found that all commonly used techniques were similarly

Table 2 Techniques used to assess body composition and information provided

Technique	Information provided
Anthropometry	
Height and weight	Weight for height, BMI (kg/m^2)
Skinfold thicknesses	Percentage body fat
Waist circumference and abdominal height	Estimates of abdominal obesity
Densitometry	
Hydrodensitometry	Percentage fat mass estimated from body density
Air displacement plethysmography	
Bioelectrical impedance	
Single-frequency BIA	FFM estimated from total body water
Multiple-frequency BIA	FFM estimated from intracellular and extracellular water
Isotope dilution	
Deuterium oxide, oxygen-18 hydride, others	FFM estimated from total body water
Imaging	
Dual-energy X-ray absorptiometry (DXA)	BMC, LBM, FM, visceral adipose
Computed tomography (CT)	BMC, LBM, FM, fat depots, organ size
Magnetic resonance imaging (MRI)	
Magnetic resonance spectroscopy (MRS)	Marrow adipose, mitochondrial function
PET	Brown fat, metabolic rate

associated with risk of adverse cardiometabolic outcomes (Ross et al. 2008).

Anthropometric measures can also be used to estimate other aspects of body composition through the use of prediction equations. This allows for estimates of body composition both within the same level and also at lower levels. For example, standing height (a Level V compartment) can be estimated from segment lengths such as knee height (another Level V compartment) (Chumlea et al. 1994). This is a useful technique for patients in whom standing height cannot be readily assessed due to disability. Other methods have been developed which allow for the estimation of *percentage body fat* (a Level IV compartment) from measurements of skinfold thicknesses. There are equations to do this directly in the pediatric population (Durnin and Rahaman 1967; Brook 1971; Slaughter et al. 1988; Dezenberg et al. 1999). In adults, a two-step process involving the estimation of body density from skinfold thickness (Jackson and Pollock 1978; Jackson et al. 1980; Durnin and Womersley 1974) and then the estimation of percentage body fat from body density (Siri 1961) is required.

1.5.2 Densitometry

Hydrodensitometry (also known as underwater weighing) and air displacement plethysmography rely on known relationships between body mass, volume, and density to estimate body composition. In hydrodensitometry, volume is calculated according to Archimedes' principle through the comparison of body mass in air and underwater (Brodie et al. 1998). Body density can then be calculated from body mass and body volume (density = mass/volume). Percentage body fat is subsequently estimated from body density using established equations (Siri 1961; Brozek et al. 1963; Lohman 1986); the remainder of body mass is assumed to be FFM. Hydrodensitometry requires specialized equipment and for the participant to be physically able to exhale completely while submerged underwater. These factors limit the use of this technique to relatively healthy populations.

Air displacement plethysmography is an alternative method used to determine body volume that is less arduous and can be used in a wider age range of participants. Commercially available systems such as the PEA POD (for infants) and BOD POD Gold Standard Body Composition Tracking System (Cosmed, Rome, Italy) measure body volume indirectly as a function of the changes in air pressure and volume when a participant enters an enclosed chamber. Body composition is estimated from body volume as described above for hydrodensitometry.

1.5.3 Bioelectrical Impedance Analysis (BIA)

BIA is a noninvasive method of body composition that utilizes measured impedance to the flow of electrical current to estimate total body water.

Impedance is a function of both resistance and length of travel. Because electrical current flows primarily through the electrolytes dissolved in the aqueous compartment, impedance is used to estimate total body water. Multiple equations in a wide variety of populations have been published which allow for the estimation of total body water and FFM from the results of BIA (Kyle et al. 2004). A limitation to the use of BIA is that estimates of FFM based upon impedance may be biased by hydration status. This may limit the accuracy of results obtained in individuals with chronic disease or other conditions known to affect FFM hydration. The use of multiple frequencies or more complex bioelectric spectroscopy allows total body water to be further partitioned into intracellular and extracellular water, which may improve estimates of body composition by accounting for hydration status (Chumlea and Guo 1994).

1.5.4 Isotope Dilution

Techniques utilizing *isotope dilution* provide another means of estimating FFM from total body water. Protocols have been developed that allow for the estimation of total body water following administration of stable isotopes such as deuterium oxide (^2H_2O) and oxygen-18 hydride. The concentration of the administered isotope in a body fluid sample is assessed by spectroscopy following a period of equilibration. Total body water volume can then be determined based upon the dose of the isotope and concentration of the sample. FFM is then determined using estimating equations from total body water (Schoeller et al. 1980). Stable isotopes are naturally occurring; therefore, isotope dilution is a low-risk means of assessing total body water. The technique is not widely used, however, in part because the protocols are costly and time-consuming.

1.5.5 Dual-Energy X-Ray Absorptiometry (DXA)

DXA is rapidly becoming the preferred means of assessing body composition for many applications. DXA is widely available, and whole-body and regional DXA scans can be performed quickly, are associated with minimal radiation exposure, and require no specific preparation on the part of the patient/participant. As a result, DXA can be used to assess body composition in populations of both healthy and diseased individuals across a wide age range. DXA-based body composition assessment is based upon the principle that X-ray beams will be attenuated differently by FM, LBM, and the bone as they pass through the body. The use of two beams of different intensity allows for the simultaneous calculation of FM and LBM in a given region using two separate equations (Roubenoff et al. 1993). Newer software has been developed that provides an estimate of visceral adipose tissue (Micklesfield et al. 2012), and it is likely that the estimation of IMAT will become possible in the near future. An example of a DXA body composition scan is shown in Fig. 1.

There are a number of limitations on the use of DXA. The machines and software are relatively expensive to purchase and operate compared to some other methods. Individuals who are excessively tall, obese, have metal surgical implants, or who cannot lay flat due to the presence of muscle contractures or other disabilities cannot be scanned. Additionally, estimation of LBM is affected by hydration status, which may be an important consideration when evaluating patients/participants with chronic disease.

1.5.6 CT, MRI, MR Spectroscopy (MRS), and Positron Emission Tomography (PET)

There is growing experience with the use of advanced medical imaging technologies such as CT, MRI, MRS, and PET for the determination of body composition. The information provided by these techniques is useful for body composition analysis using both traditional and functional approaches.

Similar to DXA, the estimation of body composition by *CT* is based upon the attenuation of X-ray beams as they pass through tissues of different densities. This allows for accurate quantification of lipid content present in fat depots (such as VAT) as well as fatty infiltration of organs (such as intrahepatic fat) and tissues (such as IMAT). Single-slice CT measurements of the trunk can be

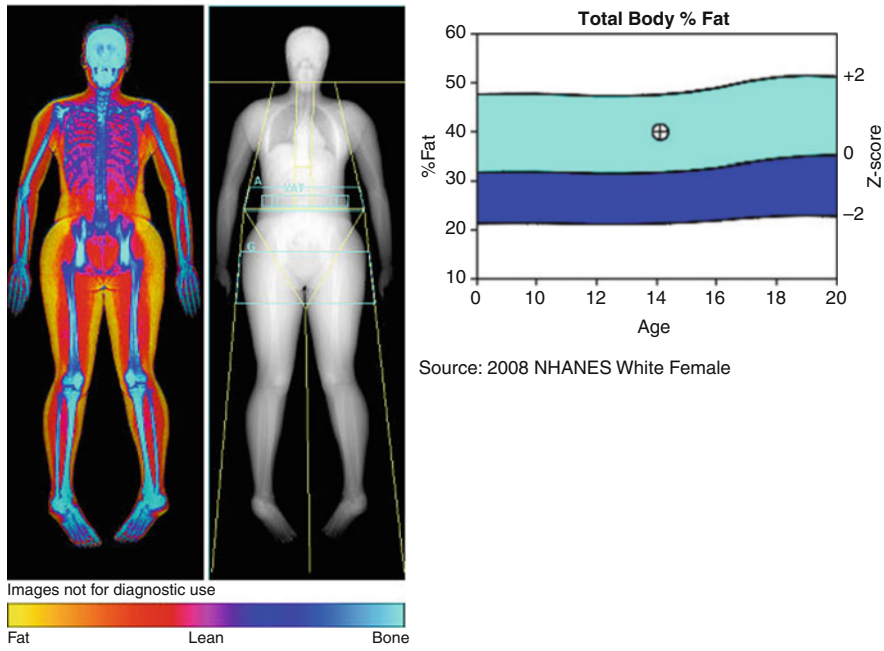

Fig. 1 DXA body composition report. DXA utilizes two beams of different radiation intensities to estimate fat mass, lean body mass, and bone mineral content. Integrated software allows for the calculation of measures such as percentage body fat and for the individual's data to be converted into a standard deviation score and compared to a reference population, as shown above. Scan shown was obtained on a Hologic Horizon scanner (Hologic, Inc., Bedford MA)

used to accurately quantify VAT with minimal radiation exposure. Typically, a 6–8-mm slice is obtained at the level of the umbilicus (ventral to L4–L5 vertebral bodies). Positioning is important because estimates of visceral adipose tissue vary by location (Kuk et al. 2006). Alternately, a single CT slice taken at the mid-thigh can be performed to quantify IMAT and SAT.

MRI provides another means of assessing fat partitioning without exposing the patient/participant to ionizing radiation (Hu and Kan 2013). MRI can also be used to obtain accurate estimates of organ size used for the investigation of REE (Gallagher et al. 2006). ^{1}H-MRS improves upon basic MRI for the quantification of lipid and can been used to estimate bone marrow adiposity (Abdalrahaman et al. 2015). ^{31}P-MRS allows for a functional assessment of muscle recovery by estimating mitochondrial function in skeletal muscle (McCormack et al. 2011).

PET can be used to assess the metabolic rate of fat and skeletal muscle. A common technique is to attach a positron-emitting tracer to 2-fluorodeoxy-D-glucose; the concentration of measured tracer activity reflects glucose uptake and thus metabolic activity (Wang et al. 2014). PET is particularly useful for the quantification and localization of BAT. PET is commonly combined with MRI or CT to provide both metabolic and anatomic information.

1.5.7 Whole-Body Counting and Neutron Activation

Whole-body counting (e.g., of potassium) and neutron activation are specialized techniques used to assess body composition at the molecular and atomic levels. They are not commonly employed in the analysis of cardiometabolic risk; interested readers are referred to detailed reviews published elsewhere (Ellis 2005).

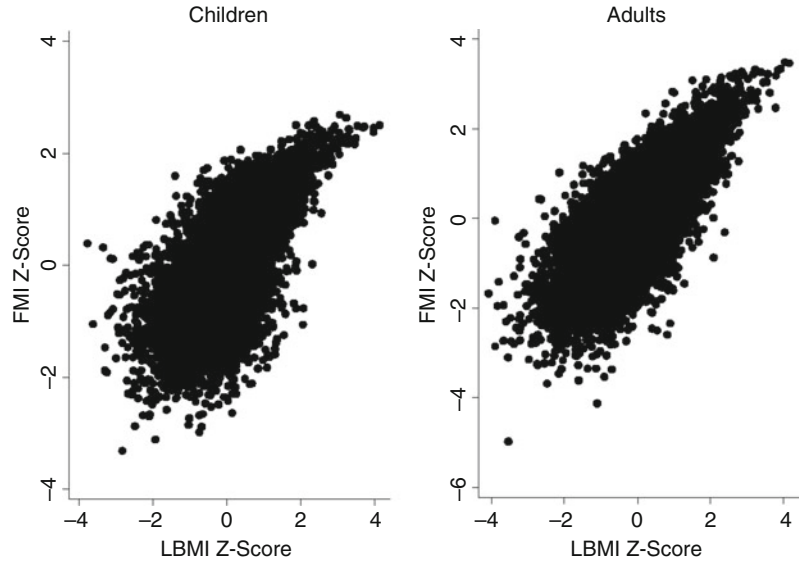

Fig. 2 Association between lean body mass (LBMI) and fat mass index Z-scores relative to age and sex. Body composition determined by DXA in participants from the National Health and Nutrition Examination Survey (NHANES)

1.6 Relationships Between Body Compartments and Cardiometabolic Disease

The relationships between body compartments and their respective impacts on cardiometabolic disease are complex. The use of multi-compartment body composition analysis has yielded important insights by allowing investigators to assess independent contributions of body compartments to disease.

1.6.1 Fat and Lean Body Mass

It is well established that increases in fat mass are associated with similar increases in lean body mass (Schautz et al. 2012). This relationship is true in both pediatric and adult populations as can be appreciated in Fig. 2. There is growing evidence to suggest that derangements in the relationships between FM and LBM due to aging or disease may have a negative impact on functional status and cardiometabolic health.

The term *sarcopenia* was originally used to describe the loss of muscle mass and physical function that occurs with aging (Rosenberg 1997). Early definitions of sarcopenia were therefore based solely on deficits in skeletal mass. Skeletal muscle mass is most commonly estimated using DXA-based assessment of *appendicular lean body mass* (ALM). ALM is simply the lean body mass of the upper and lower extremities. Skeletal muscle is the primary component of ALM, but other tissues such as the skin and connective tissue are also present (Heymsfield et al. 2014). Single-slice CT of the thigh has also been used to estimate whole-body skeletal muscle (Delmonico et al. 2009), as have BIA (Norman et al. 2009) and MRI (Muller et al. 2014b). Because of the strong relationship between height and ALM, ALM is typically expressed as an index [ALMI; ALM/height $(m)^2$].

Historically, the most commonly used definition of sarcopenia was an ALMI of two or more standard deviations below the mean of a young healthy reference population (Baumgartner et al. 1998). Recently, there has been growing interest in the use of two-compartment models that incorporate estimates of both skeletal muscle mass and fat mass into the definition of sarcopenia (Newman et al. 2003). It is thought that these definitions will provide better estimates of muscle quality and therefore correlate more strongly with functional outcomes compared to definitions based on skeletal muscle mass alone. Proposed fat-adjusted definitions of sarcopenia utilize equations based on DXA-based estimates of fat mass and appendicular

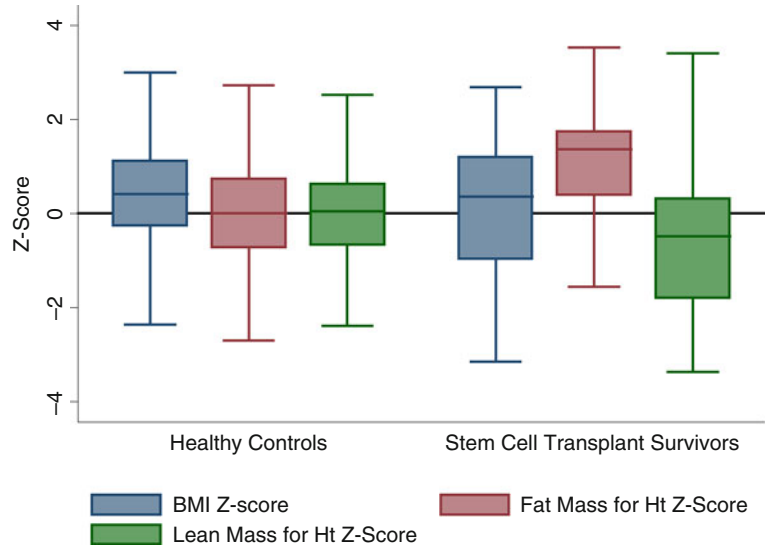

Fig. 3 Sarcopenic obesity in survivors of pediatric stem cell transplant. Fat mass Z-scores are higher, and lean body mass Z-scores are lower in survivors of pediatric stem cell transplant compared to healthy controls despite similar BMI Z-scores. The *black line* represents a Z-score of 0, which represents the average value for fat and lean mass in the reference population. Fat and lean mass determined by DXA and adjusted by height Z-score (Adapted with permission from Mostoufi-Moab et al. 2012)

lean mass (Delmonico et al. 2007; Dufour et al. 2013). In 2014 the Foundation for the National Institutes of Health Biomarkers Consortium Sarcopenia Project published a recommendation that sarcopenia be defined using a ratio of appendicular lean mass to BMI (McLean et al. 2014). Specifically, they define sarcopenia as a ratio of appendicular lean mass to BMI of <0.789 in males and <0.512 in females. Early evidence from the above studies suggests that fat-adjusted definitions of sarcopenia may correlate more strongly with functional outcomes such as grip strength, compared to prior definitions based on skeletal muscle mass alone, but larger studies in diverse populations are needed.

While much of the sarcopenia literature is focused on functional outcomes in the elderly population, the condition of *sarcopenic obesity* is emerging as a potentially important risk factor for the development of cardiometabolic disease in a wide variety of patient populations. Sarcopenic obesity is characterized by the coexistence of a simultaneous lean body mass deficit and fat mass excess (Stenholm et al. 2008). Because these individuals often have normal body weight, common one-compartment screening tools such as BMI may fail to identify the underlying derangements in body composition. Figure 3 illustrates sarcopenic obesity in a cohort of childhood cancer survivors treated with allogenic hematopoietic stem cell transplant (Mostoufi-Moab et al. 2012). Box plots of anthropometric and DXA-based measures of body composition show that stem cell transplant survivors have high fat mass and low lean mass, despite a BMI that is no different than healthy controls. Patients suffering from chronic disease are especially prone to the development of sarcopenic obesity. Chronic inflammation and exposure to glucocorticoids can result in the accumulation of excess fat mass, while immobility and malnutrition contribute to loss of lean body mass.

The effects of sarcopenic obesity on cardiometabolic health are just beginning to be understood. The presence of sarcopenia in addition to abdominal obesity was associated with an increased risk of metabolic syndrome compared to either abdominal obesity or sarcopenia alone in a large study of Asian adults (Park et al. 2014). Similarly, data from NHANES in the USA revealed that participants with sarcopenic obesity had higher insulin resistance [as measured by the homeostasis model assessment of insulin resistance (HOMA-IR)] and higher hemoglobin A1c levels compared to obese non-sarcopenic participants (Srikanthan et al. 2010). Skeletal muscle is the primary tissue responsible for glucose disposal and is also correlated with physical activity (Baxter-Jones et al. 2008). These factors may partially explain the higher cardiometabolic risk that accompanies muscle loss in obese individuals. Interestingly, a few

studies in both pediatric (Dai et al. 2011; Weber et al. 2014) and elderly populations (Barsalani et al. 2013) found that higher LBM was associated with cardiometabolic abnormalities independent of FM. These unexpected findings suggest that muscle quality, not just muscle quantity, may be an important factor in the development of cardiometabolic disease. The use of emerging techniques such as MRS and PET will allow investigators to more completely explore the relationships between fat, muscle, and cardiometabolic disease by allowing for the investigation of muscle quality and not just muscle quantity.

1.6.2 Fat and Bone

In recent years intriguing evidence has emerged supporting the existence of an endocrine hormone-mediated feedback loop linking together the bone, fat, and lean body tissue as regulators of whole-body glucose metabolism. Preclinical studies have identified the osteocyte-derived protein undercarboxylated osteocalcin (ucOCN) as a potentially novel hormone that acts to increase insulin secretion from pancreatic β (beta)-cells and also to increase insulin sensitivity in the periphery (Ferron et al. 2008). Further preclinical data suggests that insulin signaling regulates postnatal bone acquisition in mice (Fulzele et al. 2010) and that disruption of insulin signaling in osteoblasts leads to decreased ucOCN secretion and increased accrual of FM (Fulzele et al. 2010). Confirmation of these findings in humans could lead to an enhanced understanding of the skeletal fragility associated with diabetes and possibly to new treatments for obesity, insulin resistance, and type 2 diabetes (Vestergaard 2007).

1.7 Implementing Body Composition Analysis in the Clinical Setting

Given the scope of the obesity epidemic, there is great interest in translating the knowledge gained from clinical and translational body composition research into clinically relevant screening tools. Many of the techniques described above are not practical for clinical use due to cost or complexity. In addition to the specific limitations discussed above, there are other potential barriers to the accurate assessment and interpretation of body composition in the clinical setting. The composition of the human body changes over the life-span and is affected by the biological processes of growth, pubertal maturation, aging, and menopause (in women) (Butte et al. 2000; Davis et al. 2012). Comparison of an individual patient to a reference population requires knowledge of these underlying factors for an accurate determination of cardiometabolic risk. Additionally, the role of environmental factors such as the Western lifestyle (i.e., exposure to overnutrition and sedentary behavior) must be considered when assessing body composition, particularly when comparing measurements obtained in contemporary patients/research participants to reference data obtained in prior years.

Conceptually, obesity has been defined as the point at which accumulation of excess weight or adipose is sufficient to cause disease (Wells 2012). For example, in adults, the thresholds for BMI used to define overweight (BMI 25.0–29.9 kg/m^2) and obesity (BMI $\geq$30 kg/m^2) are based on the associated level of disease risk at these levels of excess relative weight. For other measures, definitions of obesity are derived mathematically, and the thresholds are defined by deviation from the population mean rather than from biologically relevant criteria. Therefore, knowledge of a few basic mathematical principles will aid the physician/investigator interested in using or interpreting the results of body composition analysis. To compare a result obtained in an individual to the broader reference population, one must calculate a standard deviation score (SDS). In its simplest form, an individual's SDS can be calculated using the mean and standard deviation of the reference population using the following equation:

$$\mathrm{SDS} = (x - \mu)/\sigma$$

where:

x = individual's value
μ = population mean
σ = standard deviation of population mean

The resultant SDS represents how many standard deviations the individual's value falls above or below the population mean. Approximately 68 % of all measurements are expected to fall ± 1 SDS from the mean, 95 % within ± 2 SDS, and >99.5 % within ± 3 SDS. However, for most soft tissue measures, such as fat mass, the distribution is skewed, and more complex computer-based calculations are required to determine the Z-score.

Two types of SDS are commonly used in the interpretation of body composition data: *Z-scores* and *T-scores*. A Z-score compares an individual to a population of the same age, whereas a T-score compares an individual to a younger population mean to represent peak health. T-scores are commonly used to define deficits in body composition associated with aging (i.e., osteoporosis is defined as a bone mineral density T-score of ≤−2.5; sarcopenia as an appendicular lean body mass index T-score of ≤−2). Z-scores are commonly used in the pediatric population who are still growing and in most cases have not yet obtained peak values. Z-scores may also be useful in some situations in adults, for example, when trying to assess disease effects.

The commonly used methods for clinical body composition analysis and the diagnosis of obesity are presented below, along with a discussion of their limitations.

1.7.1 Body Mass Index (BMI)

Body mass index, calculated as body weight (kg)/[height (meters)]^2, is currently the most widely used method of identifying individuals with excess adiposity and at risk for development of cardiometabolic disease. In adults aged 20 years and older, BMI is typically interpreted according to the following categories: underweight (BMI <18.5), normal weight (BMI between 18.5 and 24.99), overweight (BMI between 25 and 29.99), and obese (BMI ≥30) (WHO 2000). Obese individuals can be further classified into Class I, II, and III obesity based upon BMI level (Table 3).

In children, BMI is highly dependent on age and maturational status, so individuals less than 20 years of age are classified as overweight or obese based upon percentiles rather than absolute values of BMI. Current expert recommendations for the definition of overweight and obesity in childhood vary. The US Centers for Disease Control and Prevention (CDC) defines children with a BMI between the 85th and 95th percentile for age and sex as overweight and those with BMI greater than the 95th percentile as obese (Ogden and Flegal 2010). The WHO defines overweight as a BMI >1 standard deviation scores (SDS) above the median for age and sex in children aged 5–19 years (>2 SDS in children under 5 years of age) and obesity as a BMI >2 SDS (>3 SDS in children under 5 years of age) above the median (de Onis et al. 2007). Finally, the International Obesity Task Force provides age-specific cutoffs for children aged 2–18 years that correspond to the commonly used adult categories described above (Cole et al. 2000).

Table 3 Current expert guidelines for the use of BMI to classify nutritional status

BMI (kg/m^2)	Classification
Adult population	
<18.5	Underweight
18.5–24.99	Normal weight
25–29.99	Overweight
≥30	Obese
30–34.9	Class I obesity
35–39.9	Class II obesity
≥40	Class III obesity
Pediatric population[a]	
<5th percentile	Underweight
5th–84th percentile	Normal weight
85th–94th percentile	Overweight
≥95th percentile	Obese

[a]US Centers for Disease Control and Prevention (CDC) definition; percentiles based on comparison to CDC reference curves

The use of BMI has many advantages. It is easy to measure in the clinical or research setting, and online and mobile application-based calculators are readily available, as are reference curves for plotting BMI in children (Cole et al. 1995; Kuczmarski et al. 2000; WHO 2006). Numerous studies in both adult and pediatric populations have found that BMI is associated with a host of adverse health outcomes including type 2 diabetes, cardiovascular disease, metabolic syndrome, and mortality (Whitlock et al. 2009; de Mutsert et al. 2014; Sabin et al. 2015).

Despite the advantages, there are a number of limitations surrounding the use of BMI. BMI was developed as means of assessing obesity in populations and may not be an accurate screening tool for identifying individual patients with excess adiposity and/or at risk for the development of cardiometabolic disease. A key assumption underlying the use of BMI is that weight scales to height^2, such that BMI and height, are not correlated. This assumption has generally been found to be true in adults (Heymsfield et al. 2014) but not necessarily in pediatric populations where BMI is positively associated with height (Metcalf et al. 2011). Furthermore, as a one-compartment model, BMI is an index of weight and not fat and therefore does not take into account the independent contribution of fat and lean body mass to body weight. A recent Cochrane review including a multinational sample of studies found that BMI had a high specificity for the identification of excess fat mass (defined using two- or three-compartment models), but a sensitivity of only 50 % (95 % CI 43–57 %) (Okorodudu et al. 2010). Due to the lack of gold standard for the definition of excess fat mass using percentage body fat, these results must be interpreted with caution. Nevertheless, the data support the notion that BMI misclassifies a substantial proportion of individuals with excess adiposity as normal. Likewise, a study in NHANES found that almost one-fourth of adults with normal BMI had abnormal cardiometabolic profile (Wildman et al. 2008). A cross-sectional analysis of children in the Bogalusa Heart Study concluded that the optimal cutoff for BMI to identify the presence of cardiometabolic risk factors varied from the 50th to the 57th percentile across sex and racial groups (Katzmarzyk et al. 2004). The fact that such a low percentile for BMI is required to maximize sensitivity and specificity suggests that BMI may fail as a screening tool for metabolic disease in the pediatric population as well.

Additionally, there is evidence that the contributions of FM and LBM to BMI differ by racial/ethnic group (Gallagher et al. 1996). In a study of children in NHANES, it was found that non-Hispanic blacks had higher LBMI and lower FMI compared to non-Hispanic whites and Mexican Americans (Weber et al. 2013). This finding suggests that BMI is prone to overestimating excess adiposity in non-Hispanic black children. The risk of metabolic syndrome for a given BMI was also found to differ significantly between white and black obese adolescents, which may have been attributable in part to lower levels of visceral adipose tissue in blacks (Bacha et al. 2003). Finally, BMI fails to account for the distribution of fat within the body. This may be especially important given the evidence that different fat depots impart different cardiometabolic risk. These limitations of BMI have led experts in the field to call for alternative ways to assess cardiometabolic risk (Wells 2001; Ahima and Lazar 2013).

1.7.2 Waist Circumference

Criteria for the definition of abdominal obesity using *waist circumference* vary based on age, sex, race, and expert opinion. In the USA, abdominal obesity is typically defined as a waist circumference $\geq$40 in. (102 cm) in males and $\geq$35 in. (88 cm) in females (NCEP 2002). The WHO and International Diabetes Federation (IDF) recommend the use of population racial-/ancestry-specific cutoffs which vary in males from $\geq$85 cm in some Asian populations to $\geq$94 cm in Europeans and $\geq$80 cm in women (Alberti et al. 2009). Sex- and age-specific cutoffs are used for the pediatric population (Fernandez et al. 2004).

Waist circumference can be adjusted for height using a waist-to-height ratio (waist circumference/height) or waist-to-hip ratio (waist circumference/hip circumference). Waist-to-height ratio has been shown to provide better predictive ability than BMI or waist circumference to identify type 2 diabetes and cardiovascular disease in a meta-analysis of studies performed in multiethnic adult populations (Ashwell et al. 2012); however, other large studies have shown only marginal differences between the three measures (Gruson et al. 2010; Lawlor et al. 2010).

1.7.3 Percentage Body Fat

Percentage body fat is the product of a two-compartment model that can be obtained

using a variety of different techniques, including DXA (Fig. 1). There is no currently agreed upon definition for obesity using percentage body fat in either adults or children. An expert panel of endocrinologists proposed cutoffs of ≥25 % in adult men and ≥35 % women (AACE/ACE 1998); however, the use of percentage body fat to define obesity using these criteria has not become standard. Reference curves for percentage body fat have been published for children (Ogden et al. 2011), and a cross-sectional study using contemporary data from NHANES determined that the optimal cutoffs for percentage body fat to identify metabolic syndrome were the 85th percentile for boys and the 68th percentile for girls (Laurson et al. 2011).

1.7.4 Fat and Lean Body Mass Index

Fat mass index [FMI; FM/(height)^2] and *lean body mass index* [LBMI; LBM/(height)^2] are products of two-, three-, or four-compartment models. LBMI is differentiated from fat-free mass index in that it does not include the bone and is therefore a better estimate of lean tissue mass. Theoretically, the use of FMI and LBMI improves upon BMI by allowing for the independent assessment of FM and LBM. Reference data for FMI and LBMI derived from DXA have been published in both adult and pediatric populations (Kelly et al. 2009; Wells et al. 2012; Weber et al. 2013). A FMI of >80th percentile was determined to be the optimal cutoff for the identification of metabolic syndrome in NHANES youth and suggested as a possible criteria for the definition of obesity using FMI (Weber et al. 2014). Further studies are needed to determine the role for these indices in clinical practice.

2 Body Composition in the Definition of Metabolic Syndrome

The development of excess adiposity and the metabolic syndrome are closely intertwined. Multiple cross-sectional and longitudinal studies have found that the prevalence of metabolic syndrome increases with obesity in both adults (Maison et al. 2001; Katzmarzyk et al. 2005) and children (Weiss et al. 2004). Central (or abdominal) adiposity in particular has been identified as playing a critical role in the development of metabolic syndrome and may precede the appearance of other components (Cameron et al. 2008). Multiple different criteria have been proposed for the definition of metabolic syndrome in both adult and pediatric populations. Obesity is included in all commonly used criteria, but the requirements to meet the obesity component vary.

In adults, the presence of central obesity defined using waist circumference is included as a component in the commonly used NCEP ATP III (National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults) criteria (NCEP 2002) and is *required* for the diagnosis using the current International Diabetes Federation criteria (Alberti et al. 2005). Current consensus guidelines recommend the use of population- or country-specific reference data for waist circumference to determine thresholds for the definition of excess central adiposity (Alberti et al. 2009). Commonly used pediatric criteria require the use of age- and sex-specific percentiles for waist circumference (Cook et al. 2003; de Ferranti et al. 2004; Zimmet et al. 2007), although emerging evidence suggests that the use of racial-/ethnic group-specific thresholds may improve the ability of metabolic syndrome to predict cardiometabolic disease in diverse populations (DeBoer et al. 2011). Multiple attempts have been made to incorporate other measurements of body composition into the definition of metabolic syndrome. At this time, there is insufficient evidence to suggest that the incorporation of DXA or other imaging-based assessment of adiposity into the definition of metabolic syndrome is appropriate.

3 Summary

The use of body composition analysis has an important role in both the clinical evaluation of patients at risk for the development of cardiometabolic disease and in research aimed at investigating the relationships between body

compartments and disease. The field is moving rapidly toward the development of functional body composition models which seek not only to quantify the different body compartments, but to define the contributions of body tissue to health and disease. The continuing development of advanced medical imaging techniques will further advance this effort and is expected to lead to improved screening and treatment strategies for the millions of people with or at risk for cardiometabolic disease.

4 Cross-References

- Adipokines and Metabolism
- Adipose Structure (White, Brown, Beige)
- Diet, Exercise, and Behavior Therapy in the Treatment of Obesity and Metabolic Syndrome
- Epidemiology of Obesity in the United States
- Insulin Resistance in Obesity
- Linking Inflammation, Obesity, and Diabetes
- Overview of Metabolic Syndrome
- Prevention and Treatment of Childhood Obesity and Metabolic Syndrome
- Principles of Energy Homeostasis
- Sarcopenic Obesity

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Type 2 Diabetes: Etiology, Epidemiology, Pathogenesis, Treatment

32

Carrie Burns and Imali Sirisena

Contents

Abstract

Diabetes is one of the largest health problems facing the world today. It is estimated that by the year 2030 over 7 % of the world's adult population will have diabetes. Numerous risk factors play into an individual's risk of developing diabetes. Some are modifiable such as obesity, diet, and exercise. Other risk factors including genetic and environmental factors are topics of ongoing research. The physiology of diabetes is a complex interplay between beta-cell function and insulin resistance. Other hormones such as GLP-1 and leptin also play a role. The classic presentation of type 2 diabetes is polyuria, polydipsia, and unintentional weight loss. However, many people are diagnosed with diabetes on routine screening either with a hemoglobin A1c test or an oral glucose tolerance test. The treatment of type 2 diabetes is multifaceted and crosses multiple disciplines. Patient education regarding diet and exercise and adjustment of modifiable risk factors remain the cornerstone of treatment. Patients should be screened for microvascular and macrovascular complications. While studies have shown a benefit of intensive glycemic control for type 2 diabetes in reducing microvascular complications, the effect on macrovascular complications has been less clear. Long-term studies do suggest that good glycemic control near the time of diagnosis can have beneficial impact decades later.

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1 Etiology

The etiology of type 2 diabetes is multifactorial and diverse and spans a wide range of factors from genetic to lifestyle to environmental (see Box 1). There is clearly an association between *obesity* and type 2 diabetes. Analysis of large observational cohorts of men in the Health Professionals' Study and women in the Nurses' Health Study demonstrated that increased body mass index (BMI) is associated with an increased risk of developing diabetes (Chan et al. 1994; Hu et al. 2001). Population data in the United States showed that the lifetime risk of diabetes for men beginning at 18 years of age increased from 7.6 % for a BMI of <18.5 to 70.3 % for a BMI of 35 or higher. For women, the increase was similar, 12.2 % versus 74.4 % between lowest and highest BMI, respectively (Narayan et al. 2007).

Box 1: Risk Factors for Type 2 Diabetes

Modifiable
- Obesity
- Diet
- Physical inactivity
- Smoking
- Environmental

Non-modifiable
- Age
- Ethnicity
- Family history
- Gestational diabetes
- Intrauterine environment/birth weight

There are several lifestyle factors that, when modified, can lower the risk of type 2 diabetes. This includes a diet high in fiber and polyunsaturated fats but low in trans fat. Maintaining regular exercise and abstaining from smoking and consuming alcohol moderately also lower risk. Men who followed a prudent diet (characterized by higher consumption of vegetables, fruit, fish, poultry, and whole grains) had a modestly decreased risk of developing diabetes. Conversely, men who followed a "western" *diet* (characterized by higher consumption of red meat, processed meat, French fries, high-fat dairy products, refined grains, and sweets and desserts) had a significantly increased risk of diabetes (RR 1.6, 95 % CI 1.3–1.9) (van Dam et al. 2002). This risk was independent of BMI, physical activity, or family history. Similar results were found in women (Fung et al. 2004).

Sugar-sweetened beverages have been studied as an independent risk factor for diabetes. Women who consumed one or more sugar-sweetened soft drinks per day had almost twice the risk of developing diabetes compared to those who consumed less than one of these beverages a month (RR 1.8, 95 % CI 1.42–2.36). The risk remained significant even after adjustment for changes in *body mass index (BMI)* and caloric intake, suggesting that sweetened beverages may increase the risk of diabetes due to rapid absorption rate of carbohydrates (Schulze et al. 2004). Meat consumption also appears to be related to the incidence of type 2 diabetes. Individuals that reported an increase in red meat consumption over four years had a higher subsequent risk of developing diabetes, though this association was partly mediated by body weight (Pan et al. 2013). However, in a meta-analysis of meat consumption, consumption of processed meat was associated with a statistically significant increase in the risk of diabetes, whereas unprocessed red meat consumption showed a nonsignificant trend toward increased risk (Micha et al. 2010).

Moderate-intensity *exercise* is associated with a lower risk of developing type 2 diabetes. The association persists even after adjustment for BMI, suggesting that exercise can reduce the risk of developing diabetes independent of weight loss (Jeon et al. 2007). Additional studies have looked at associations between development of diabetes and sedentary behavior. One meta-analysis looked at television viewing as a risk

factor for development of diabetes and found TV viewing time was associated with a higher risk of *type 2 diabetes* (pooled RR, 1.20 95 % CI 1.14–1.27) (Grøntved et al. 2011). Retrospective analysis of prediabetic patients showed a 3.4 % increased risk of diabetes for every hour spent watching television ($p < 0.01$) (Rockette-Wagner et al. 2015).

Smoking is postulated to be a risk factor for type 2 diabetes. In a meta-analysis of 25 prospective cohort studies, active smoking was associated with an increased risk for type 2 diabetes, although only a few of the studies adjusted for other unhealthy behaviors associated with smoking, such as poor diet and lack of physical activity (Willi et al. 2007). There is some evidence that smoking acutely affects glucose metabolism. Subjects who smoked prior to an oral glucose tolerance test showed a significant rise in glucose compared with not smoking (Frati et al. 1996).

Aberrations in *sleep patterns* are associated with an increased risk of diabetes. A large meta-analysis of sleep and incidence of type 2 diabetes showed an increased risk for diabetes in both people who had a short duration of sleep (≤5–6 h a night) and a long duration of sleep (>8–9 h a night) (Cappuccio et al. 2010). However, it is difficult to determine if sleep duration is causal or rather related to obesity and associated comorbidities such as obstructive sleep apnea. Melatonin has been postulated to affect a person's risk of developing diabetes. Melatonin is regulated by light exposure, and its secretion peaks 3–5 h after sleep onset when it is dark, with almost no production during the daytime hours. One study looking at urinary excretion of melatonin metabolites showed lower melatonin secretion was independently associated with a higher risk of developing type 2 diabetes (McMullan et al. 2013).

Building on observational studies of obesity and lifestyle as a risk factor for diabetes, large prevention trials have investigated life style interventions to reduce the risk of developing diabetes. The Finnish Diabetes Prevention Study included a population of 522 middle-aged overweight subjects with impaired glucose tolerance and randomized them to an intervention group or control. The intervention group received intensive individualized counseling aimed at reducing weight and total intake of fat and increasing fiber and physical activity. The mean weight lost at 2 years was 3.5 ± 5.5 kg in the intervention group and 0.8 ± 4.4 kg in the control group. The cumulative incidence of diabetes after four years was 11 % in the intervention group compared with 23 % in the control group which translated to a 58 % reduction in the incidence of diabetes between the two groups (Tuomilehto et al. 2001).

The *Diabetes Prevention Program (DPP)* trial was a US multicenter trial that addressed preventing diabetes in a high-risk and ethnically diverse population. The DPP was a comparative effectiveness trial that recruited 3,224 participants with prediabetes and assigned them to one of three interventions: intensive lifestyle intervention, metformin, and a control group who received standard lifestyle recommendations and placebo. The intensive lifestyle intervention included an individual curriculum covering diet, exercise, and behavior modification intended to achieve a 7 % weight loss through a healthy low-calorie, low-fat diet and 150 min of exercise a week.

Over two years, those assigned to the *lifestyle intervention* had greater weight loss and a greater increase in physical activity than participants in the other groups (weight loss of 0.1, 2.1, and 5.6 kg in the placebo, metformin, and lifestyle intervention groups, respectively). The lifestyle intervention also reduced the incidence of diabetes by 58 % and metformin by 31 % compared with placebo. Subgroup analyses showed that lifestyle intervention was effective regardless of gender, ethnicity, or genetic predisposition to diabetes (Knowler et al. 2002).

Subsequently participants in the DPP were unmasked to their group and placebo was stopped. All participants were offered a group-administered version of the curriculum. The Diabetes Prevention Program Outcomes Study followed participants for 10 years and showed that the cumulative incidence of diabetes remained lowest in the lifestyle group with a reduction in diabetes incidence of 34 % (95 % CI 24–42) versus 18 % (7–28) in the metformin

group compared with placebo (Diabetes Prevention Program Research Group 2009).

Although previous guideliens stressed a low-fat diet for lowering risk of diabetes, a low-fat diet has not been shown to reduce the risk of diabetes (Tinker et al. 2008), and subsequent studies suggest the type of fat may be more important than the amount of fat. In one study by Salmerón et al., total fat and saturated fat were not associated with an increased risk of type 2 diabetes. However, increased *trans fats* were associated with increased risk of diabetes while polyunsaturated fatty acids were associated with reduced risk (Salmerón et al. 2001). The Mediterranean diet is characterized by high consumption of vegetables and legumes with moderate consumption of fish and wine and low consumption of red and processed meat. It contains high levels of monounsaturated and polyunsaturated fatty acids from sources like virgin olive oil and nuts. Adherence to a *Mediterranean diet* among nondiabetic subjects with at least one cardiovascular risk factor showed that a Mediterranean diet was associated with an over 50 % lower incidence of diabetes when compared with a low-fat diet (Salas-Salvado et al. 2011).

Nut consumption is inversely associated with risk of type 2 diabetes. Women eating five or more one ounce servings of nuts per week had a lower incidence of diabetes compared with women who did not consume any nuts (Jiang et al. 2002). High rates of coffee consumption have been associated with a decreased risk of diabetes. However, there is currently not enough evidence to recommend increased coffee intake as a prevention strategy for diabetes (van Dam and Hu 2005).

Certain medical conditions are associated with an increased risk of type 2 diabetes. *Gestational diabetes* is associated with a subsequent increased risk of developing type 2 diabetes. Studies of a large population-based cohort showed that nine years after gestational diabetes, 19 % of women had developed type 2 diabetes compared with only 2 % in women who did not have gestational diabetes (Feig et al. 2008). *Polycystic ovarian syndrome* (PCOS) (Lo et al. 2006), metabolic syndrome (Ford et al. 2008), and cardiovascular disease (Mozaffarian et al. 2007) have also been associated with increased risk of diabetes.

While obesity, lifestyle choices, and medical history are clearly strong risk factors for the development of diabetes, a person's risk of developing diabetes is affected by factors starting before conception.

Family history is clearly a risk factor of diabetes. Identical twins have a high concordance rate of type 2 diabetes (Barnett et al. 1981). Individuals with one parent with type 2 diabetes are two to three times more likely to have type 2 diabetes themselves. Individuals with both parents with diabetes have five times the risk of developing diabetes (Meigs et al. 2000). Even when controlling for potential confounding factors such as weight, diet, education, and genetic risk, family history remained a significant risk factor for developing diabetes (InterAct Consortium et al. 2013). Ethnicity is also a risk factor for diabetes as evidenced by the substantially higher rates of diabetes in certain ethnic groups, such as native Indians in North America.

Genetic factors contribute to an individual's risk of developing diabetes. Monogenic diabetes is a result of a genetic defect that leads to diabetes. The defect has a high penetrance, which leads to inherited diabetes in a classical Mendelian fashion (e.g., dominant or recessive). However, *monogenic diabetes* makes up a small proportion of all diabetes cases. Genomewide association studies or GWAS look for associations between specific genetic variations (most commonly, single-nucleotide polymorphisms) and a particular disease. While certain variants have been identified that are associated with an increased risk of type 2 diabetes, such as TCF7L2 in Europeans and KCNQ1 in Asians, genetic screening is not commonly used except for certain cases where monogenic diabetes is suspected (McCarthy 2010). Current research is ongoing on how best to integrate genetic and clinical risk factors to better predict a person's risk for developing type 2 diabetes.

Intrauterine factors affect an individual's risk of diabetes. Poor fetal nutrition has been associated with greater susceptibility to obesity and diabetes later in life. This was demonstrated through studies of the Dutch Hunger Famine birth cohort which showed that adults who had

been exposed to famine during fetal life had more glucose intolerance than unexposed people (Ravelli et al. 1998). This finding led to the *thrifty genotype* hypothesis that insulin resistance develops as a protective mechanism in response to intrauterine growth restriction. However, in adulthood when exposed to caloric excess, this thrifty genotype becomes maladaptive and leads to diabetes.

Low birth weight has been associated with increased risk of developing type 2 diabetes later in life. A large meta-analysis showed that in most populations a 1 kg increase in birth weight corresponds to a 20 % reduction in type 2 diabetes risk (Whincup et al. 2008). It is unclear if the relevant causal exposure is weight itself versus an underlying disturbance in fetal health or nutrition. Two native North American populations, however, showed the opposite result – higher birth weight was associated with a greater risk of type 2 diabetes. These groups have very high prevalence of type 2 diabetes and gestational diabetes, which seems to explain the increased incidence of diabetes in offspring. It is possible that as rates of diabetes in other ethnic groups continue to increase, the relationship between birth weight and diabetes risk may start to mimic that seen in native North American populations (Whincup et al. 2008).

There is growing evidence that environmental factors also affect an individual's risk of developing diabetes. The Endocrine Society defines an *endocrine disruptor* as an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action (Zoeller et al. 2012). Exposure to endocrine disruptors has been associated with an increased risk of metabolic disorders. One of the most studied endocrine disruptors is *bisphenol A (BPA)* which is used extensively in the lining of food and beverage containers and is detectable in urine of 90 % of the US population. Research into endocrine disruptors has mostly revolved around in vivo mouse studies and large population studies. In one study by Alonso-Magdalena et al. mice were exposed to BPA injections of 10 μg/kg per day during early pregnancy. At 6 months of age, males prenatally exposed to BPA displayed glucose intolerance, insulin resistance, hyperinsulinemia, and altered release from pancreatic β-cells as compared with control mice. Exposure of pregnant mice to higher dose of BPA (100 μg/kg per day) during the same period showed male offspring with glucose intolerance but normal insulin sensitivity and only a mild alteration in β-cell function. Also the pregnant mice that were exposed to BPA displayed glucose intolerance and were heavier than controls four months after delivery (Alonso-Magdalena et al. 2010).

In 2008 the US National Health and Nutrition Examination Survey (NHANES) 2003–2004 released the first large-scale data on BPA, and in a study by Lang et al. higher BPA urine concentrations were associated with a diagnosis of diabetes and cardiovascular disease (Lang et al. 2008). When the following NHANES data from 2005 to 2006 was evaluated, higher BPA concentrations were not associated with a diagnosis of diabetes. However, when the data from 2003–2004 to 2005–2006 was pooled together, there was a statically significant association with BPA and diabetes. This may have been because BPA concentrations in 2005–2006 were about 30 % lower than the earlier population (Melzer et al. 2010).

2 Epidemiology

The prevalence of diabetes is rapidly increasing in both the United States and throughout the world. This increase comes at a great cost to not only the individual but also on the community and the health system as a whole. The estimated national cost in the United States of diabetes in 2012 was $245 billion, of which $176 billion (72 %) represents direct health expenditures attributed to diabetes and $69 billion (28 %) represents lost productivity from absence in the workplace and premature mortality (American Diabetes Association 2013). It is estimated that in 2012, 29.1 million people or 9.3 % of the US population had diabetes and over 27 % of this group was undiagnosed, proving that type 2 diabetes is a public health crisis. Certain ethnic groups have a higher incidence of diabetes. In the United States,

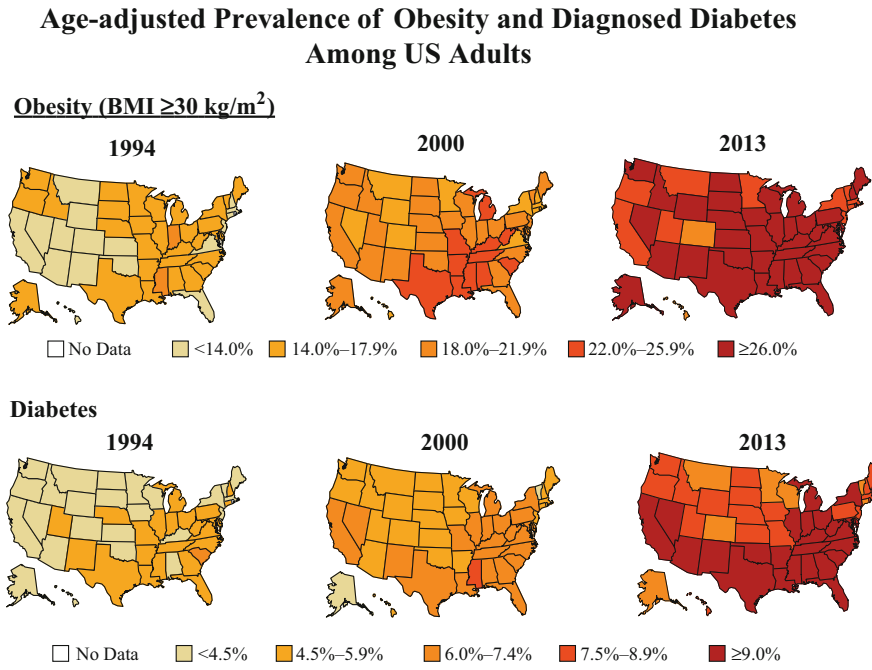

Fig. 1 Parallelism of diabetes and increased rates of obesity in the United States between 1994 and 2013

the highest incidence rate is in American Indians/Alaska natives (15.9 % 2010–2012). Non-Hispanic blacks, Hispanics, and Asian Americans also have a higher incidence rate than non-Hispanic whites (Centers for Disease Control and Prevention 2014). Worldwide, the number of people with diabetes has doubled over the past three decades increasing from an estimated 153 million in 1980 to 347 million in 2008 (Danaei et al. 2011). The number of people worldwide with diabetes is projected to increase even further to an estimated 439 million people by 2030, which represents 7.7 % of the world population aged 20–79 (Shaw et al. 2010).

The increase in diabetes largely parallels the increased rates of obesity seen in the United States and throughout the world (Fig. 1). The concomitant rise in diabetes and obesity worldwide is a result of a complex interplay between genetic, environmental and behavioral factors that have led to more sedentary behavior and an excess of calorie-rich food (Zimmet et al. 2001). While there is clearly an association between obesity and diabetes, there are individuals who are normal weight but have metabolic characteristics similar to obese people, such as hyperinsulinemia, insulin resistance, predisposition to type 2 diabetes, and high triglycerides (Ruderman et al. 1998). This "*metabolically obese" phenotype* might help explain why Asians tend to develop type 2 diabetes at lower BMI than people of European origin (Yoon et al. 2006).

While diabetes was once rare in the developing world, it is now growing rapidly, and Asia has emerged as the "diabetes epicenter" of the world (Chen et al. 2011). India and China have the largest number of diabetics which is expected to continue to increase, while the Middle East and areas of Africa also have growing diabetic populations. It is estimated that between 2010 and 2030 there will be a 69 % increase in the numbers of adults with diabetes in developing countries compared with a 20 % increase in developed world. Furthermore, patients in developing countries tend to present at a younger age leading to a greater effect on their productivity (Shaw et al. 2010).

Along with global shifts in diabetes epidemiology, there has also been a rise in diabetes in younger populations. While type 1 diabetes is

still the most common form of diabetes overall in youth in the United States, there has been a 30.5 % increase in the overall prevalence of type 2 diabetes between 2001 and 2009. Similarly to type 2 diabetes in adults, the highest prevalence is in American Indians, followed by black, Hispanic, and Asian Pacific Islander youth, with the lowest prevalence in white youth. This is almost the exact inverse of the pattern seen in type 1 diabetes which is more common in white youth and rare in American Indians (Dabelea et al. 2014). Prediabetes is also highly prevalent among adolescents. Analysis of National Health and Nutrition Examination Survey (NHANES) 2005–2006 showed an unadjusted prevalence of prediabetes of 16.1 % among a diverse cross section of US adolescents (Li et al. 2009). This increased population of young people diagnosed with diabetes will be at increased risk of complications given the long duration of disease.

3 Pathophysiology

The pathophysiology of diabetes is a complex interplay between insulin resistance, beta-cell dysfunction, and other hormones that regulate metabolism. Normal glucose metabolism can be separated into fasting and fed states (Fig. 2). In the fasting state, the body relies on endogenous glucose production, mainly through hepatic glycogenolysis and gluconeogenesis. Hypoglycemia is prevented by maintaining a low insulin-to-glucose ratio in plasma. The brain is dependent on glucose so other tissues are provided with alternative sources of fuel such as fatty acids from adipose tissue lipolysis. This preserves glucose for use by the brain. In the fed state, blood glucose levels increase as a result of absorption of carbohydrates from the gut. This stimulates *insulin* production from islet β-cells and simultaneously suppresses glucagon secretion from α-cells. Insulin helps to lower blood sugar in multiple ways – it suppresses endogenous glucose production by the liver. Insulin also mediates glucose uptake by peripheral tissues through both oxidation to carbon dioxide and water and non-oxidative disposal through glycogen synthesis (Nolan et al. 2011). Insulin induces the *glucose transporter 4 (GLUT4)* which catalyzes the uptake of glucose into adipose and muscle cells (Watson et al. 2004). This effect is mediated through the nuclear receptor *peroxisome proliferator-activated receptor-ϒ (PPARγ)*. PPARγ is critical for adipocyte differentiation and glucose homeostasis, and humans with mutations in PPARγ have partial lipodystrophy and insulin resistance (Ahmadian et al. 2013).

Extensive research has tried to elucidate the changes that lead from impaired fasting glucose to diabetes. Most of the initial research was based on cross-sectional studies of high-risk populations. The Pima Indians of Arizona have one of the highest documented rates of type 2 diabetes in the world (Knowler et al. 1990). Longitudinal studies followed Pima Indians who progress from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) to determine the course of events. Subjects who progressed from NGT to IGT showed both a lower rate of insulin-stimulated glucose disposal and decreased insulin secretion in response to a glucose load. This suggests that both *insulin resistance* and decreased insulin secretion occur well before the development of overt diabetes. The decrease in glucose uptake in response to insulin was almost entirely due to decreased non-oxidative glucose disposal, suggesting that insulin resistance is primarily mediated by insulin's action on skeletal muscle glycogenesis (Weyer et al. 1999). Inappropriate endogenous glucose production by the liver appears to occur later in the development of diabetes.

When subjects in the longitudinal Pima Indian trial who progressed to diabetes were compared to subjects who retained normal glucose tolerance, both groups had impaired glucose disposal suggesting insulin resistance. However, the subjects who did not progress were able to compensate for this by increasing insulin secretion, maintaining normal glucose tolerance. The subjects who progressed to diabetes were not able to increase insulin secretion to compensate for decreased insulin action, suggesting that *beta-cell dysfunction* is key in the development of diabetes (Weyer et al. 1999). This hyperbolic relationship has been confirmed in healthy individuals

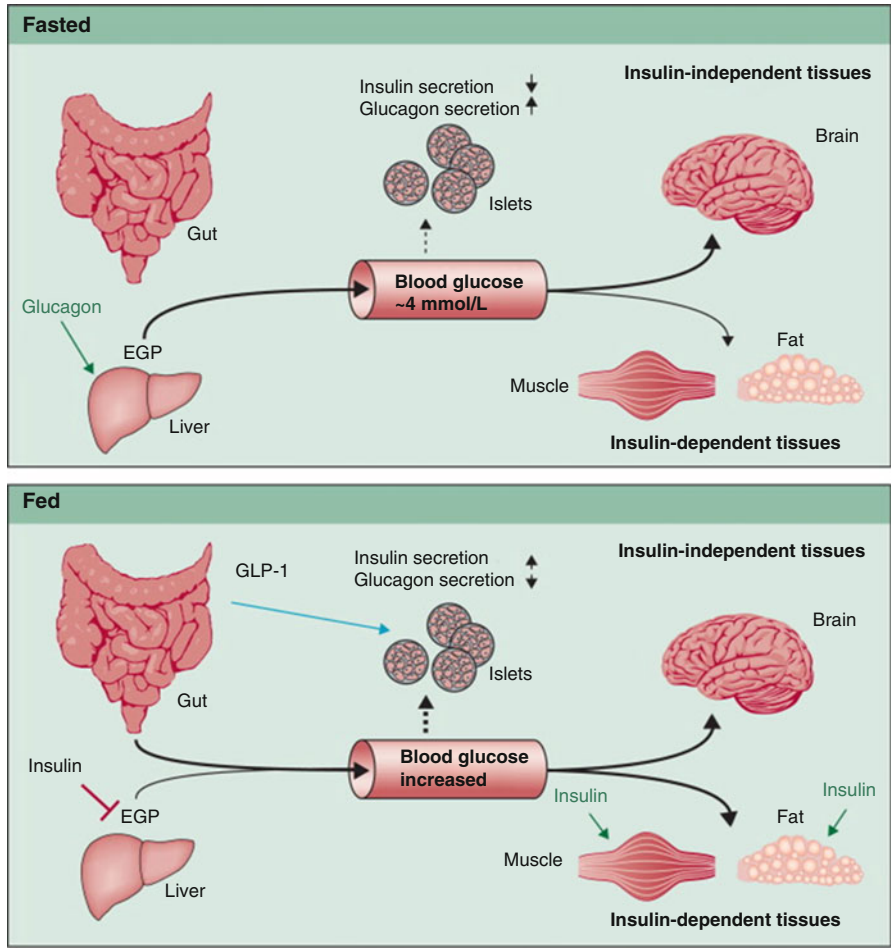

Fig. 2 Overview of normal glucose homeostasis. In the fasting state blood glucose concentration is determined by the balance between EGP production, mainly through hepatic glycogenolysis and gluconeogenesis, and use by insulin-independent tissues, such as the brain. EGP prevents hypoglycemia and is supported by a low insulin-to-glucagon ratio in plasma. The brain is dependent on glucose and, therefore, other tissues, such as heart and skeletal muscle, are mainly provided with nonglucose nutrients (e.g., nonesterified fatty acids from adipose tissue lipolysis). In the fed state (meal with carbohydrate), glucose concentrations in the blood rise because of absorption in the gut, which stimulates insulin secretion by islet β cells and suppresses glucagon secretion from α cells. EGP is suppressed (which helps to curtail total glucose input into blood) and uptake into insulin-sensitive peripheral tissues, such as the heart, skeletal muscle, and adipose tissue is activated (which increases the rate of glucose disposal). Neurohormonal processes include the release of the incretin hormones, such as GLP-1, which increases glucose-stimulated insulin secretion and glucose-suppression of glucagon secretion. Adipose tissue lipolysis is suppressed and anabolic metabolism is promoted. Glucose concentrations become close to the fasting level within 2 h. *GLP-1* glucagon-like peptide 1, *EGP* endogenous glucose production

as well – for any change in insulin sensitivity, there is a reciprocal change in beta-cell function to maintain euglycemia (Kahn et al. 1993; Kahn 2003). Similar results were shown in the UKPDS, which showed that beta-cell function had already decreased by 50 % at time of diagnosis of diabetes (Festa et al. 2006).

The causes of beta-cell loss are multifactorial. *Glucolipotoxicity* is a term that refers to the toxic effect of hyperglycemia and elevated plasma fatty acid level which occur early on in diabetes and may exert a destructive effect on beta-cells through increased oxidative stress (Poitout and Robertson 2008). *Amyloid* deposition in islet

bodies is associated with decreased beta-cell area and increased beta-cell apoptosis, suggesting that islet amyloid deposition may play a role in beta-cell destruction (Jurgens et al. 2011). Compounding the problem of beta-cell loss is the fact that most studies suggest beta-cell mass is established early in life with limited ability to regenerate (Cobo-Vuilleumier and Gauthier 2010). The reduction in beta-cell mass is not significant enough to explain the degree of impaired insulin release in type 2 diabetes, and further research is ongoing into the interplay between beta-cell mass and function (Kahn et al. 2014).

While insulin resistance and beta-cell dysfunction are the foundation of our understanding of diabetes pathophysiology, there are numerous other hormones involved. *Glucagon* levels are inappropriately elevated in patients with type 2 diabetes. This elevation is thought to contribute to greater rates of glucose production by the liver and attenuated reduction after meals (D'Alessio 2011).

Incretin hormones play an important role in promoting glucose-stimulated insulin secretion. The incretin effect is the phenomenon in which oral glucose load elicits a greater endogenous insulin secretion as compared with intravenous glucose. This suggested that factors from the gut are involved in signaling insulin production. The two hormones responsible for the incretin effect are glucose-dependent insulinotropic hormone (GIP) and *glucagon-like peptide-1 (GLP-1)*. They are secreted after oral glucose loads and help increase insulin secretion. While GIP loses its effect on insulin secretion in diabetes, GLP-1 retains its stimulatory effect on insulin; however its level is reduced in type 2 diabetes. This gave rise to GLP-1 as a target for type 2 diabetes (Nauck et al. 2004).

While obesity is clearly associated with type 2 diabetes, the mechanism by which obesity leads to diabetes is still an area of active research. Adipose tissue secretes several proteins and cytokines which are collectively termed *adipocytokines,* and it is thought that these may represent the link between obesity and diabetes. *Leptin* is produced by adipocytes and signals the hypothalamus regarding satiety and quantity of stored fat. Congenital leptin deficiency due to a mutation in the leptin gene leads to early-onset obesity, profound hyperphagia, and hyperinsulinemia with a dramatic response to treatment with leptin (Farooqi et al. 2002). This condition is rare and typically seen in consanguineous marriages. In addition, leptin appears to act on the pancreas as well. In studies of pancreas-specific leptin receptor knockout mice (KO), when fed a standard diet, the KO mice had improved glucose tolerance as compared with controls. However, when the KO mice were challenged with a high-fat diet, they demonstrated poor compensatory islet growth and glucose intolerance when compared with controls (Morioka et al. 2007).

Adiponectin is a hormone secreted by adipocytes that has anti-inflammatory and insulin-sensitizing properties. Adiponectin secretion is decreased in obesity, and higher adiponectin levels are associated with better glycemic control, more favorable lipid profile, and reduced inflammation in diabetic women (Mantzoros et al. 2005).

Numerous other signaling molecules have been studied, mainly in mouse models with some association studies in humans. *Tumor necrosis factor-alpha (TNFα)* released from adipose tissue may lead to impaired insulin action. Injection of TNFα into obese mice led to a two- to threefold increase in insulin-stimulated glucose utilization (Hotamisligil et al. 1993). Plasminogen activator inhibitor 1 (PAI-1) is a prothrombotic factor released by adipocytes which negatively regulates fibrinolysis by inhibiting tissue plasminogen activator. In a prospective study looking at incidence of type 2 diabetes, PAI-1 was an independent predictor of diabetes after controlling for other metabolic factors such as BMI and visceral fat (Kanaya et al. 2006). Further research is needed to elucidate the relationship between obesity and diabetes with the goal of developing new therapeutic targets.

4 Diagnosis

The word diabetes was first coined by the ancient Greeks and literally means siphon, relating to the finding of frequent urination in those inflicted.

The term mellitus which is derived from the Latin word for sweet was added by Englishman Thomas Willis in 1675 after noting the sweet taste of urine from patients with diabetes. In fact, sweet urine has been noted by physicians in ancient Egyptian, Persian, Indian, and Chinese societies. Today the most classic presenting symptoms of type 2 diabetes are polydipsia (frequent thirst), polyuria (frequent urination), blurry vision, and unintentional weight loss. Typical physical exam findings include visceral adiposity and *acanthosis nigricans* – a velvety, hyperpigmented skin plaque often found on the neck and axilla. In more advanced cases of diabetes, one may see evidence of *diabetic retinopathy* on fundoscopic exam and decreased sensation in the feet.

The diagnosis of diabetes is mainly established through demonstrating hyperglycemia. If a patient has the above symptoms and a random blood glucose of 200 mg/dL (11.1 mmol/L), this establishes the diagnosis of diabetes. Asymptomatic individuals can be identified by any of the following criteria: fasting plasma glucose (FPG) value ≥126 mg/dL (7.0 mmol/L), 2-h post oral glucose 75 g tolerance test (OGTT) value of ≥200 mg/dL (11.1 mmol/L), and *glycated hemoglobin (A1C)* values ≥6.5 % (48 mmol/mol) (Table 1). These criteria have been adopted by both the American Diabetes Association (ADA 2015) and the World Health Organization (WHO 2011). While the ADA places less importance on the OGTT to diagnose diabetes citing its inconvenience, greater cost, and less reproducibility, the WHO encourages the use of the OGTT in diagnosing diabetes because of its greater sensitivity in diagnosing diabetes compared with FPG and evidence of worse health outcomes for patients diagnosed with diabetes by OGTT (WHO 2006).

Glycated hemoglobin (A1c) is a product of hemoglobin's exposure to plasma glucose through nonenzymatic glycation and correlates to the average blood sugar for the prior three months. The ADA emphasizes using A1c because in some studies it is a stronger predictor of subsequent diabetes and cardiovascular events than fasting glucose (Selvin et al. 2010). Recent improvements in A1c assays have allowed its use for screening for diabetes. The National Glycohemoglobin Standardization Program (NGSP) has standardized the majority of the assays used in the United States to the Diabetes Control and Complications Trial (DCCT) standard. The A1c has many advantages including its convenience (fasting not required) and the stability of averaging blood sugars over a longer period of time. The disadvantages include greater cost, limited availability in certain regions, and factors that can alter A1c. Racial variations have been noted in A1c measurements. African Americans with and without diabetes have higher A1c levels than non-Hispanic whites when matched for fasting plasma glucose. Furthermore,

Table 1 Diagnostic Criteria for Diabetes and Prediabetes

	Diabetes ADA and WHO	
	mg/dL	mmol/L
Fasting plasma glucose **OR**	≥126	7.0
OGTT after 75 g oral glucose load **OR**	>200	11.1
Hemoglobin A1c	>6.5 %	48 mmol/mol

	Prediabetes ADA		Prediabetes WHO	
	mg/dL	mmol/L	mg/dL	Mmol/L
IFG Fasting plasma glucose	100–125	5.6–6.9	110–125	6.1–6.9
IPG OGTT after 75 g oral glucose load	140–199	7.8–11.0	140–199 + FPG < 126	7.8–11.0 + FPG < 7.0
Prediabetes Hemoglobin A1c	5.7–6.4 %	39–46 mmol/mol		

conditions that alter hemoglobin such as hemoglobinopathies and anemia can cause variations in A1c measurements. The A1c test is also the least sensitive test, and it identifies one-third fewer cases of undiagnosed diabetes than a fasting glucose of ≥126 mg/dL (7.0 mmol/L) (ADA 2015). This lower sensitivity may be offset by the ease of testing which facilitates screening larger numbers of people (Picon et al. 2012).

Patients can also be categorized as *prediabetic*, which confers an increased risk for diabetes. The ADA characterizes prediabetes as one of the following: impaired fasting glucose (IFG) defined as a FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L), impaired insulin glucose tolerance (IGT) defined as a 2-h plasma glucose in the 75-g OGTT of 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L), or an A1c of 5.7–6.4 %. This differs from the WHO which defines IFG as a fasting glucose between 110 and 125 mg/dL (6.1–6.9 mmol/L) and defines IGT as both a fasting glucose <126 (7.0 mmol/L) and a 2-h glucose ≥140 mg/dL (7.8 mmol/L) but <200 mg/dL (11.06 mmol/L). The WHO criteria use a higher threshold for defining IFG citing concerns that lowering the cut point would cause an overdiagnosis of IFG.

In general, *screening for diabetes* should be considered in overweight adults (defined as a BMI ≥25 kg/m^2 or 23 kg/m^2 in Asians) with additional risk factors including family history, hypertension, or a history of gestational diabetes. It is important to distinguish type 2 diabetes, which is the most common form, from other types of diabetes. The American Diabetes Association classifies diabetes into four categories: (1) type 1 diabetes, (2) type 2 diabetes, (3) gestational, and (4) other. *Type 1 diabetes* is due to autoimmune destruction of beta-cells arising in absolute insulin deficiency. Patients often present with markedly elevated blood sugar and are prone to diabetic ketoacidosis, which is less common in type 2 diabetes. Autoimmune markers are sometimes tested to confirm the diagnosis; these include islet cell autoantibodies, glutamic acid decarboxylase (GAD) antibodies, autoantibodies to insulin, autoantibodies to tyrosine phosphatases IA-2 and IA-2β, and autoantibodies to zinc transporter 8 (ZnT8). Gestational diabetes (GDM) is defined as diabetes diagnosed for the first time during pregnancy and as mentioned earlier is a risk factor for developing type 2 diabetes later in life.

Other less common forms of diabetes include monogenic diabetes syndrome, where a monogenic defect causes β-cell dysfunction. These include *mature-onset diabetes of the young (MODY)* which is characterized by impaired insulin secretion and is inherited in an autosomal dominant pattern. Numerous mutations have been identified. The most common mutation is on chromosome 12 in hepatocyte nuclear factor (HNF)-1α. This mutation leads to reduced insulin secretion and often responds well to treatment with a sulfonylurea. Another common mutation is in the glucokinase gene on chromosome 7p. Glucokinase converts glucose to glucose-6-phosphate which stimulates insulin secretion and acts as a glucose sensor. Mutations in this gene lead to a higher glucose threshold for insulin secretion with consequently higher baseline fasting blood sugars, which in most cases do not require treatment. Other forms of diabetes include *cystic fibrosis-related diabetes (CFRD)* which is due to insulin deficiency secondary to partial fibrotic destruction of islet mass. Diabetes can also be drug induced and is commonly seen after treatment of HIV/AIDS and with immunosuppression for organ transplantation.

5 Treatment

The main goal of treating diabetes is lowering blood glucose to minimize the risk of both microvascular and macrovascular complications. *Microvascular complications* from diabetes include retinopathy, nephropathy, and neuropathy. *Macrovascular complications* in diabetes include stroke, coronary artery disease, and peripheral vascular disease.

The cornerstone of diabetes treatment has been education on diet, exercise, and weight loss. The Look AHEAD trial was designed to evaluate if intensive *lifestyle intervention for weight loss* would decrease cardiovascular morbidity and

mortality in type 2 diabetics. The trial was ended after a median follow-up of 9.6 years when it was determined that despite a greater weight loss in the intervention group, there was no difference in the primary endpoints (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and later added hospitalization for angina) between the two groups (1.83 and 1.92 events per 100 person-years, in intervention and control groups, respectively; hazard ratio in the intervention group, 0.95; 95 % confidence interval, 0.83–1.09; $p = 0.51$). However, the intensive lifestyle intervention group did have greater reductions in A1c, greater initial improvements in fitness, and greater reductions in all cardiovascular risk factors except for low-density-lipoprotein cholesterol levels (Look AHEAD Research Group et al. 2013). Other trials have shown lifestyle interventions in diabetics can provide other benefits such as decreasing need for medications, improved well-being (Williamson et al. 2009), and in some cases remission of diabetes completely (Gregg et al. 2012). Given that most lifestyle modifications have few risks and some benefit, they remain the cornerstone of diabetes treatment.

In regard to medical therapy for glycemic control, the *Diabetes Control and Complications Trial (DCCT)* demonstrated that intensive therapy in type 1 diabetics delayed the onset and progression of microvascular complications such as diabetic retinopathy, nephropathy, and neuropathy (Diabetes Control and Complications Trial Research Group 1993). Long-term follow-up of these patients showed a beneficial effect on the risk of cardiovascular disease as well (Nathan et al. 2005). For type 2 diabetics, most, but not all, trials showed a benefit of intensive treatment on preventing microvascular complications. The effect of intensive glucose control on macrovascular outcomes has proved more difficult to delineate.

The *United Kingdom Prospective Diabetes Study (UKPDS)* followed over 5,000 newly diagnosed persons with type 2 diabetes and evaluated the effect of conventional versus intensive management on diabetes complications. The intensive therapy arm was treated with medication, while the conventional therapy arm was treated with diet alone with the addition of medications if their fasting blood glucose concentration was greater than 270 mg/dL (15 mmol/L). The average A1c was 7.0 % in the intensive therapy group compared with 7.9 % in the conventional therapy group. Over a 10-year period, the intensive treatment group had a 25 % reduction in the risk of microvascular endpoints (7–40, p = 0.0099), most of which was due to reduced need for photocoagulation for diabetic retinopathy. However, the intensive therapy arm had more weight gain (4.0 kg for those receiving insulin and 1.7–2.7 kg for those receiving sulfonylurea) and increased incidence of hypoglycemia (UK Prospective Diabetes Study (UKPDS) Group 1998). Other later studies showed reduction in microvascular endpoints such as nephropathy, while other studies did not show a reduction in microvascular endpoints (ADVANCE Collaborative Group et al. 2008; Duckworth et al. 2009).

The major trials looking at diabetes control and macrovascular complications are summarized in Table 2.

These trials were designed to evaluate the effect of intensive versus conventional therapy on cardiovascular outcomes in patients with long-standing diabetes (duration 8–12 years), and many who had already had one cardiovascular event. VADT and ADVANCE showed no

Table 2 Trial data for intensive glycemic control and macrovascular complications

	ACCORD	ADVANCE	VADT
N	10,251	11,140	1,791
Mean duration T2DM	10 years	8 years	11.5 years
Known CVD	32 %	35 %	40 %
A1c decrease	1.1 % (6.4 vs. 7.5 %)	0.7 % (6.5 vs. 7.3 %)	1.5 % (6.9 vs. 8.4 %)
Renal outcomes	−21 %	−32 %	−33 %
CV outcomes	No effect*	No effect	No effect
NEJM publication	2008; 358: 2545	2008; 358: 2520	2009; 360: 129

ACCORD showed 22 % in all cause mortality

difference in rates of macrovascular complications between intensive and conventional treatment arms (ADVANCE Collaborative Group et al. 2008; Duckworth et al. 2009). The *ACCORD trial* was ended early secondary due to an increased mortality rate in the intensive glucose control group compared with conventional therapy (Action to Control Cardiovascular Risk in Diabetes Study Group et al. 2008). The higher incidence of total and cardiovascular death in the intensive group versus standard persisted even after the intensive arm was transitioned to the standard therapy (HR for death from any cause 1.19, 95 % CI 1.03–1.38) (ACCORD Study Group et al. 2011). While it was initially thought that the increased rate of mortality may be due to hypoglycemia or the medications used, follow-up analysis has failed to demonstrate this conclusively (Bonds et al. 2010).

Returning to the UKPDS trial discussed above, it continued with a post-trial monitoring phase in which all patients returned to community-based diabetes care with no attempt to maintain their previously randomized therapy. While initially the intensive group had a lower A1c, after 5 years, there was no significant difference in A1c between the two groups (A1c of around 7.8 %). After a median follow-up of 17 years, there was still a significant reduction in microvascular complications with the intensive control group compared with the conventional treatment group (RR 0.76, 95 % CI 0.64–0.89). Furthermore, while there was no significant difference in macrovascular outcome in the initial phase, a significant risk reduction for myocardial infarction (15 %, $p = 0.01$) and death from any cause (13 %, $p = 0.007$) emerged over time as more events occurred (Holman et al. 2008). This gave rise to the term the "legacy effect," suggesting that good glycemic control in the initial stages of diabetes can lower ones risk of both microvascular and macrovascular outcomes over a long period of time. This is in comparison to the initial phase of UKPDS and ADVANCE, which showed no benefit of good or near normal blood glucose control on macrovascular outcomes in the short term.

Based on these studies above, the ADA recommends an A1c target of 7 % or less for most patients with diabetes, especially if implemented soon after diagnosis. A more stringent goal of 6.5 % or less can be considered if this can be achieved without significant hypoglycemia, especially in patients with a long life expectancy and little or no significant cardiovascular disease. Less stringent A1c goals such as 8 % or less may be appropriate for patients with history of severe hypoglycemia and those patients who already have long-standing diabetes with complications or a decreased life expectancy.

6 Diabetes Management

Comprehensive care of the diabetic patient requires a multifaceted approach across multiple disciplines. Educating the patient about their disease and stressing modifiable risk factors for complications is the cornerstone of diabetes management. Patients should be informed of the benefit of weight loss, exercise, and dietary changes. While no one diet has proved itself superior in diabetics, it is reasonable to counsel patients to avoid trans fat and highly refined carbohydrates that are often found in processed food in favor of increased fruits and vegetables, unprocessed meats, and omega-3 fatty acids. Emphasis should also be placed on smoking cessation, screening and treatment for depression, and routine immunizations.

Screening for diabetes complications should be done routinely and the American Diabetes Association provides recommendations for standards of care for diabetic patients. This includes an annual dilated eye exam to look for *retinopathy* and an annual foot exam to identify risk factors for ulcers and amputations. Urinary albumin and estimated glomerular filtration should be evaluated once a year in all patients with type 2 diabetes annually to screen for nephropathy. Treatment with an ACE inhibitor or angiotensin receptor blocker (ARB) is suggested for patients with elevated urinary albumin.

For cardiovascular disease and risk management, *blood pressure* should be measured at every visit with goal systolic blood pressure (SBP) of <140 mmHg and diastolic blood

Table 3 Type 2 diabetes medications

Intervention	Action	Advantages	Disadvantages
Lifestyle	(+) Insulin sensitivity	Low cost Multiple benefits	Fails for most in first year
Metformin	Decreases gluconeogenesis	Low cost Weight neutral	Gastrointestinal (GI) side effects Rare lactic acidosis
Sulfonylureas	Insulin secretagogue	Low cost	Hypoglycemia Weight gain
Thiazolidinediones	(+) Insulin sensitivity	No hypoglycemia Improved lipids	Weight gain High cost
Alpha glucosidase Inhibitors	(−) Carb absorption	No hypoglycemia Weight neutral	GI side effects, frequent dosing
GLP-1 agonists	(+) Incretin effect	Weight loss No hypoglycemia	Injectable High cost GI side effects
DPPIV-inhibitors	(+) Incretin effect	Weight neutral No hypoglycemia	High cost Lower potency
Glinides/meglitinides	Insulin secretagogue	Short acting	Frequent dosing Higher cost
SGLT-2 inhibitors	Increases glycosuria	Weight loss	Genitourinary (GU) side effects High cost Hyperkalemia
Insulin	Increases insulin concentration	Efficacious	Injectable Can be high cost Weight gain

pressure (DBP) < 90. A fasting *lipid profile* should be obtained at time of diagnosis and every 1–2 years afterwards. Statin therapy is indicated in most patients aged 40 or older and can vary between moderate- and high-intensity statin therapy depending on age and risk factors. *Antiplatelet agents* such as aspirin have been shown to be effective in reducing cardiovascular morbidity in high-risk patients with previous myocardial infarction or stroke (secondary prevention). Evidence for its use for primary prevention in diabetics is less clear, but it is reasonable to consider aspirin therapy for primary prevention in diabetics with increased cardiovascular risk (10-year risk > 10 %).

Medications commonly used for the treatment of type 2 diabetes are summarized in Table 3. Recent interest has focused on surgical treatments of type 2 diabetes through gastric bypass. Recent studies of gastric bypass in diabetic patients show that surgery often leads to improvements in diabetes control but at a cost of increased adverse events such as fracture and nutritional deficiency (Ikramuddin et al. 2015).

7 Cross-References

- Adipokines and Metabolism
- Endocrine Disorders Associated with Obesity
- Genetics of Type 2 Diabetes
- Insulin Resistance in Obesity
- Linking Inflammation, Obesity, and Diabetes
- Nonalcoholic Fatty Liver Disease
- Overview of Metabolic Syndrome
- Pancreatic Islet Adaptation and Failure in Obesity and Diabetes

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Obesity and Cardiac Disease

33

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Abstract

Obesity contributes to the development of cardiac disease in several ways. It is both an independent risk factor for cardiovascular disease and a facilitative risk factor for coronary artery disease and its complications through its association with a variety of other traditional and nontraditional risk factors. Central obesity is a key component of the metabolic syndrome. There is substantial epidemiologic evidence of an association between overweight and obesity and coronary heart disease. Evidence of an association based on autopsy and coronary angiography is less convincing. An increasing body of evidence supports the existence of an obesity paradox with respect to mortality in patients with coronary heart disease once it is established. Whether purposeful weight loss improves cardiovascular outcomes in overweight or obese patients is uncertain. Obesity is also a risk factor for the development of heart failure and may serve as the sole or predominant cause in individuals who are severely obese. Obesity produces alterations in cardiac hemodynamics and cardiac morphology that may predispose to left ventricular diastolic and less commonly systolic dysfunction. Prolonged exposure to these conditions and the presence of comorbidities such as hypertension, sleep apnea, and obesity hyperventilation predispose to heart failure. Purposeful weight loss is capable of reversing most of the abnormalities of cardiac structure and function associated with obesity. To an even greater extent than with coronary artery disease, an obesity paradox exists with respect to heart failure such that the risk of mortality is lower in overweight and mildly obese persons than in underweight or normal weight individuals.

Keywords

Obesity • Overweight • Metabolic syndrome • Coronary heart disease • Cardiovascular disease • Coronary artery disease • Heart failure • Left ventricular hypertrophy and weight loss

The relation of overweight and obesity to cardiac disease has been the subject of ongoing investigative interest for many decades. Coronary heart disease (CHD), defined as coronary artery disease (CAD) and its complications, has been the prime focus. Obesity is strongly associated with a variety of cardiovascular (CV) disease (CVD) risk factors including diabetes mellitus, hypertension, and dyslipidemia but is also considered an independent risk factor for CVD (Poirier et al. 2006; Alexander 1998, 2001; Poirier and Eckel 2002; Barrett-Connor 1985; Jahangir et al. 2014; Sjostrum 1992; Krauss and Winston 1998; Miller et al. 2008; 27th Bethesda Conference). Clustering of risk factors in the form of the metabolic syndrome identifies a population that is at particularly high risk for CVD, especially CHD (Poirier et al. 2006; Jahangir et al. 2014; Miller et al. 2008). From a pathophysiologic point of view, obesity serves as a central component of the metabolic syndrome (Lakka et al. 2002; Isomaa et al. 2001). In addition, obesity is capable of producing alterations in cardiac structure and function separate from CHD that may predispose to the development of heart failure (HF) (Abel et al. 2008; Wong and Marwick 2007; Alpert et al. 2014a, b; Alpert 2001; Massie 2002). This chapter discusses the relation of obesity to CVD risk factors; reviews the literature linking obesity with CVD and CHD based on epidemiologic, autopsy, and angiographic studies; and describes evidence that suggests the presence of an obesity paradox with respect to CHD. Also discussed in this chapter are the effects of obesity on cardiac structure and function and the mechanisms by which it predisposes to HF.

1 Definitions

The World Health Organization classifies body weight on the basis of body mass index (BMI) as follows: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), class I obesity (30–34.9 kg/m^2), class II obesity (35.0–39.9 kg/m^2), and

class III obesity also known as severe, extreme, or morbid obesity (≥40 kg/m^2) (WHO 2000). Some experts have recommended two additional classes: class IV (≥50 kg/m^2) and class V (≥60 kg/m^2) (Poirier et al. 2006; Bastien et al. 2014). The term super-obesity is sometimes applied to persons whose BMI is ≥50 kg/m^2 (Bastien et al. 2014). Central obesity (also referred to as abdominal or visceral obesity) is defined in terms of waist circumference (>102 cm in men and >88 cm in women) or waist-hip ratio (WHR, >1.0 in men and >0.8 in women) (Poirier et al. 2006; Nicklas et al. 2014). The metabolic syndrome is commonly defined as three or more of the following: (1) waist circumference >102 cm in men and >88 cm in women, (2) serum triglyceride levels ≥150 mg/dl, (3) serum levels of high-density lipoprotein <40 mg/dl in men and <50 mg/dl in women, (4) blood pressure ≥135/85 mmHg, and (5) serum glucose levels >100 mg/dl (Miller et al. 2008; Bastien et al. 2014; Lakka et al. 2002; Isomaa et al. 2001).

2 Risk Factors for CVD

Atherosclerosis, and by extension CHD, is multifactorial in origin. A variety of genetic, environmental, physiologic, and biochemical mechanisms contribute to its presence, progression, and complications. Risk factors for CVD are commonly classified as traditional and nontraditional. Traditional CVD risk factors associated with obesity include type 2 diabetes mellitus (there is a 9 % increase in risk of type 2 diabetes mellitus for every 1 kg increase in body weight), hypertension (related in part to activation of the renin-angiotensin aldosterone and sympathetic nervous systems; there is an 8 % increase in risk of hypertension for every 1 kg/m^2 increase in BMI), and various dyslipidemias (hypertriglyceridemia, decreased serum levels of high-density lipoprotein, increased serum levels body of small dense low-density lipoprotein associated with increased apoprotein B levels) (Poirier et al. 2006; Jahangir et al. 2014; Miller et al. 2008; Bastien et al. 2014; Freedman et al. 1999; Berenson et al. 1992; Despres 2012; Wormser et al. 2011; Lakka et al. 2002; Isomaa et al. 2001; Schulte et al. 1999). Nontraditional risk factors for CVD associated with obesity include insulin resistance with hyperinsulinemia, endothelial dysfunction, inflammation (characterized by increased circulating levels of interleukin-6, C-reactive protein, and tumor necrosis factor alpha), and various prothrombotic alterations (increased serum levels of fibrinogen, von Willebrand factor, plasminogen activating factor-1, factor VII, and factor VIII) (Poirier et al. 2006; Jahangir et al. 2014; Miller et al. 2008; Bastien et al. 2014; Wormser et al. 2011). In recent years, it has become increasingly clear that the metabolic syndrome is a potent risk factor for CAD and its complications. Central obesity is a key component of the metabolic syndrome, contributing by biochemical and physiologic mechanisms to each of the other components (Despres 2012; Emerging Risk Factors Collaboration et al. 2011). Obesity is primarily a facilitative risk factor. Controversy exists as to extent to which CVD in overweight and obese persons is attributable solely to CVD risk factors (Poirier et al. 2006; Schulte et al. 1999). Nevertheless, the 27th Bethesda has classified obesity as an independent risk factor for CVD, primarily because of epidemiologic evidence that will be presented in the following section (27th Bethesda Conference 1995).

3 Relation of Obesity to CVD: Epidemiologic Studies

Numerous epidemiologic studies have explored the relation between CVD and obesity. Some have included patients with CVD which is not necessarily restricted to CHD. Most studies have focused on risk of CVD or risk of CHD and its complications. Others have focused on CVD or CHD mortality.

Multiple reports derived from the Framingham Heart Study database have provided insights into the relation of overweightness and obesity to CHD risk and outcomes. Hubert et al. reported the results

of a 26-year follow-up of 2,252 men and 2,818 women whose age ranged from 28 to 62 years (Hubert et al. 1983). Minimum relative weight was a risk factor for CHD and stroke independent of age, cholesterol, systolic blood pressure, smoking, left ventricular (LV) hypertrophy, and glucose intolerance. A study by Harris and colleagues reported a U-shaped mortality curve for BMI in 597 men and 1.126 women whose age ranged from 55 to 65 years and who were followed for up to 23 years (Harris et al. 1998). Kannel and coworkers showed that CVD risk was linearly related to abdominal and general adiposity in 2,039 men and 2,871 women whose age ranged from 35 to 70 years and who were followed for 24 years (Kannel et al. 1991; an update: follow-up of 26 years). Kannel et al. also noted that each standard deviation in relative weight gain conferred a 15 % (men) and 22 % (women) increase in CHD and stroke risk (Kannel et al. 1996). The optimal BMI for avoidance of CVD was 22.6 kg/m^2 for men and 21.1 kg/m^2 for women. Wilson and colleagues reported that overweight and obesity (based on BMI) were associated with increased CVD incidence in men and women whose age ranged from 35 to 75 years and who were followed up to 44 years (Wilson et al. 2002).

Several reports from the Nurses Health Study have addressed the relation of various indices of body weight to CHD risk in women. Manson et al. reported the results of a study of 115,886 women whose age ranged from 30 to 56 years and who were followed for 8 years (Manson et al. 1990). There was a strong association between obesity and CHD risk in these women. An update of this study by Manson and colleagues reported that CHD mortality in the women in this study was 15 % less than the US average for women (Manson et al. 1995). Willett et al. reported a 14-year follow-up of the Nurses Health Study (Willett et al. 1995). They noted that the highest level of body weight (BMI) within the range of modest weight gains after 18 years of age increased CHD risk in middle-aged women. In a substudy of the Nurses Health Study consisting of 44,702 women who were followed for 12 years, Rexrode and coworkers demonstrated that WHR and waist circumference were independently associated with CHD risk in women (Rexrode et al. 1997). In another substudy of the Nurses Health Study women with a BMI $\geq$32 kg/m^2 who had never smoked had a relative risk of CVD mortality of 4.1 compared to women whose BMI was less than 19 kg/m^2 (Rexrode et al. 1998). In still another subgroup analysis involving 44,636 women, Zhang et al. reported that the relative risk of CVD mortality increased from the lowest to the highest quintile of waist circumference (1.00, 1.04, 1.04, 1.28, 1.99) after adjustment for BMI and various CVD risk factors (Zhang et al. 2008). Cho and colleagues, studying 5,897 women, reported that weight gain prior to the onset of diabetes mellitus predicted increased risk of CHD (Cho et al. 2002).

In the Health Professionals Follow-up Study, Baik et al. monitored 39,756 males whose age ranged from 40 to 75 years (Baik et al. 2000). The follow-up period was 10 years. In men $<$65 years of age, the risk of CVD mortality rose with increasing BMI. In a previous substudy, BMI was more effective than WHR in predicting CVD risk. In men $\geq$65 years of age, there was no relation between BMI and CVD mortality; however, WHR predicted CVD mortality in this group. In a study of 29,112 whose age ranged from 40 to 75 years of entry, Rimm and colleagues reported that BMI, WHR, and weight gain after the age of 21 years predicted increased risk for CAD (Rimm et al. 1995). In those $>$65 years of age, WHR was superior to BMI in predicting risk of CAD.

Field and coworkers, in a study combining subgroups from the Nurses Health Study (77,690 women) and the Health Professionals Follow-up Study (40,060 men) who were followed for 10 years, showed that the risk of CHD or stroke increased with severity of overweightedness or obesity (Field et al. 2001).

Two reports from the Epidemiologic Follow-up Study of NHANES I addressed the relation between body weight and CHD risk. Harris and colleagues demonstrated that in 1,259 females, aged 65–74 years and followed for 14 years, overweight/obesity (BMI $\geq$ 29 kg/m^2) was an independent risk factor for CHD in older women, a finding strengthened after accounting for previous weight loss (Harris et al. 1993). In a report of

621 men and 960 women whose mean age was 77 years and who were followed for up to 13 years, Harris and coworkers noted that heavier weight in late middle age was a risk factor for CHD in later life (Harris et al. 1997). Heavier weight in older age was a risk factor for CHD after adjusting for those who lost substantial amounts of weight.

In a study of more than one million adults followed for 14 years, increased BMI (>26.5 kg/m^2 in men and >25.0 in women) predicted CVD in men (relative risk of 2.9) and women (Calle et al. 1999). The relative risks of CVD were 2.7 in men and 1.9 in women whose BMI was >40 kg/m^2.

Adams-Campbell et al. retrospectively studied 866 African-American men and women to assess the relation between BMI and CAD (Adams-Campbell et al. 1995). Patients were followed for 7 years. They reported an inverted "U"-shaped relation between BMI and CAD. A study of 14 target populations consisting of 1,974 men and women whose age ranged from 30 to 59 years on who were followed for 9 years reported by Zhou and colleagues showed that overweightness was an independent predictor of CHD (Zhou et al. 2002). In the Manitoba Study of 3,983 men whose mean age was 30.8 years at entry and who were followed for 26 years, Rabkin et al. reported 390 cases of CHD (Rabkin et al. 1977). A high BMI was significantly associated with myocardial infarction, sudden death, and coronary insufficiency. These observations were not evident until 16 years of follow-up. Overweight/obesity was the best predictor of myocardial infarction occurring after 20 years of observation. In contrast, the Pooling Project reported no specific age-adjusted or age-associated association of obesity and CHD in male cohorts (Barrett-Connor 1985).

Kramer and coworkers reported the results of a meta-analysis of eight studies involving 61,386 adults followed for more than 10 years (Kramer et al. 2013). There were approximately 4,000 adverse cardiac events. They noted that obese subjects without the metabolic syndrome had a 24 % higher risk of cardiac events than normal weight participants without the metabolic syndrome. In the Copenhagen General Population Study involving 71,527 adults followed for a mean duration of 3.6 years, Thomsen et al. reported that overweight and obese adults with the metabolic syndrome had an increased risk for myocardial infarction (Thomsen and Nordestgaard 2014). Hazard ratios were 1.26 (95 % CI: 1.0–1.6) in overweight subjects and 1.88 (95 % CI: 1.3–2.6) in obese persons.

Multiple smaller studies have focused on CVD and CHD mortality. Jousilahti et al. reported the results of a study of 16,113 men and women from eastern Finland whose age ranged from 30 to 59 years and who were followed for 15 years (Jousilahti et al. 1996). In this study obesity was an independent risk factor for CHD mortality among men and contributed to CHD mortality risk in women. In the Adventist Mortality Study of 12,576 women whose age range was 30–74 years and who were followed for 26 years, Singh and Landsted reported a U-shaped curved for risk of CHD, hypertensive disease, and stroke mortality, particularly in the fifth to seventh decades of life (Singh and Lanstead 1998).

Spadaro et al., in the Western Electric Study of 1,707 males whose age range was 40–55 years followed for 22 years, showed that after 15 years of follow-up, all adiposity measures except triceps skinfold were significantly associated with CHD mortality (Spadaro et al. 1996). In contrast, in the Charleston Heart Study, Stevens et al. reported that neither BMI nor fat patterning predicted CHD mortality in African-American females followed for 25–28 years (Stevens et al. 1992).

A prospective study of 7,735 males, age range of 40–59 years followed for a mean of 14.8 years reported by Shaper et al., identified a BMI of 22 kg/m^2 as being associated with the lowest risk of CV mortality (Shaper et al. 1997).

As suggested in some of the larger epidemiologic studies, central (visceral, abdominal) obesity may be a better predictor of CVD and CHD morbidity and mortality than general indices of body weight. Yusuf et al. studied 27,098 adults from 52 countries to determine the relation of BMI and WHR to risk of myocardial infarction. BMI was minimally associated with myocardial infarction after adjustment for other risk factors

(adds ratio of 1.12, 95 % CI: 1.03–1.22) (Yusuf et al. 2005). In contrast, odds ratios for WHR were more robust (1.90 in the 4th and 2.52 in the 5th quintile). In the INTERHEART Study, Yusuf and colleagues noted that WHR was the strongest predictor of myocardial infarction. In this study, other measures of abdominal obesity were also stronger predictors of myocardial infarction than BMI (Yusuf et al. 2004). A review of multiple studies reported by Rao and colleagues in 1991 showed that both high BMI and high WHR were independent risk factors for CHD mortality (Rao et al. 2001). Multiple epidemiologic studies of regional fat distribution have shown an association of various indices of central adiposity and CHD morbidity and mortality.

In a study combining the results of the Health Study of England and the Scottish Health Survey involving 22,308 whose mean age was 54 years, Hamer et al. reported that obese subjects with lower metabolic risk (waist circumference <102 cm for men and <88 cm for women, normotensive, no diabetes mellitus, normal C-reactive protein, normal high-density lipoprotein cholesterol) had no increase in CVD risk compared to healthy nonobese individuals (Hamer and Stamatakis 2012). In a case control study (217 cases, 261 controls) consisting of men and women <70 years of age, Kahn et al. showed that increased mid-thigh girth and subcutaneous fat mass were associated with a protective effect against CHD (Kahn et al. 1996).

Brown et al., in the Women's Health Australia Project, studied 13,431 female whose age ranged from 45 to 49 years to determine the relation between BMI and CVD risk (Brown et al. 1998). They identified a BMI of 19–24 kg/m^2 as the optimal BMI for reducing CVD risk.

4 Relation of Obesity to CVD: Autopsy Studies

Studies based on autopsy findings have produced conflicting results concerning to the relation between overweight/obesity and CHD. In a report of the International Atherosclerosis Project conducted from 1960 to 1964 and involving autopsy data on 350 persons from six geographic regions, Montenegro and Salberg noted that in those who died accidently, the extent of atheromata related to none of the weight indices used Montenegro and Salsberg (1968). A World Health Organization Study in Europe, which excluded those with wasting diseases, reported that neither the prevalence of coronary stenosis nor the extent of atherosclerosis differed between normotensive, nondiabetic obese, and lean subjects (Sternby 1976). Giertsen et al. showed no significant difference in the extent of coronary atheromata between 408 underweight and overweight patients whose age ranged from 15 to 89 years (Giertsen 1966). A retrospective autopsy study by Ackerman and colleagues demonstrated that the degree of coronary atherosclerosis in persons of average weight was comparable to those who were overweight (Ackerman et al. 1950). Yater and coworkers reported no significant difference in body weight between 237 men who died of CHD and 297 men who suffered accidental death (Yater et al. 1948). Lee and Thomas showed no significant difference in body weight between 450 persons whose age ranged from 30 to 60 years and who died of acute myocardial infarction and average body weight for the general population matched for age and sex (Lee and Thomas 1956).

A study of 1,260 autopsy cases reported by Wilens et al. in 1947 showed that advanced coronary atherosclerosis occurred twice as often within those with an abdominal panniculus greater than 3 cm as in persons with poor nutritional status (Wilens et al. 1947). In 2002, McGill and colleagues reported the results of the PDAY (Pathobiological Determinants of Atherosclerosis in Youth) Study which involved 3,000 males and females whose age ranged from 15 to 34 years (McGill et al. 2002). Increased BMI in adolescents and young men was associated with fatty streaks in the right coronary artery and stenosis of the left anterior descending coronary artery. Right coronary artery lesions were greater in young men with a thick abdominal panniculus. BMI was not associated with coronary atherosclerosis in young women, although there was a trend toward an association in young women with a thick abdominal

panniculus. A prior study by McGill and coworkers of 1,532 young persons who died of non-CHD causes showed that in males the percentages of fatty streaks and raised right coronary lesions were two to four times higher in those with an abdominal panniculus greater than 17 mm than in men with a panniculus $\leq$17 mm (McGill et al. 1995).

In a study of 1,108 males whose age ranged from 13 to 34 years who died of diseases other than CHD, there was a positive correlation between body weight-height indices and raised coronary lesions in Caucasians, but not in African-Americans (Strong et al. 1984). However, there were relatively small differences in panniculus thickness in this group and those who died of CHD. A study of 672 autopsy cases of men aged 25–64 years, 70 % of which followed accidental death reported by Patel et al. showed a weak correlation between abdominal panniculus thickness and raised coronary artery lesions in Caucasian men, but not in African-American men (Patel et al. 1983).

Bjurulf et al., in an autopsy study of 110 subjects in which biopsies of subcutaneous but were obtained, demonstrated that the severity of coronary atherosclerosis correlated with the size, but not the number of fat cells (Bjurulf 1959).

In an autopsy study of 37 Japanese-American men, Rhoads and colleagues reported a correlation between CHD severity and relative weight $>$116 % (Rhoads and Kagan 1983). Wilkens and coworkers reported greater severity of CHD on autopsy and incidence of catastrophic coronary events in normotensive obese men, but not in women (Wilkens et al. 1959).

5 Relation of Obesity to CVD: Coronary Angiographic and Computed Tomographic Studies

A relatively small number of studies have assessed the relation between overweight/obesity and CAD using invasive coronary angiography or computed tomography.

In the Honolulu Heart Program, 357 men from a cohort of 7,591 free from CHD at entry had repeat invasive coronary angiography during a 20-year follow-up period (Reed and Yano 1991). Thirty-five men with less than 50 % stenosis represented controls. BMI did not separate controls from those with greater degrees of stenosis. Cramer et al. studied 262 patients with established CHD repeat invasive coronary angiography 2–182 months after the first angiogram (Cramer et al. 1966). There was no difference in progression of coronary lesions between those with a relative weight greater than 120 % compared with those with lower relative weights. Using an invasive coronary angiographic database of 33,119 patients, Stalls and colleagues reported that although African-Americans had higher rates of CVD risk factors and morbid obesity, they were significantly less likely to have significant coronary stenosis on angiography (Stalls et al. 2014). In total, cross-sectional invasive coronary angiographic studies have shown little or no correlation between BMI and severity of CAD (Reed and Yano 1991; Cramer et al. 1966; Stalls et al. 2014; Hujamuta et al. 1990; Flynn et al. 1993; Rossi et al. 2011; Morricone et al. 1996; Anderson et al. 1978; Hauner et al. 1990; Clark et al. 1994; Kramer et al. 1991; Zamboni et al. 1992; Mahoney et al. 1996).

Several studies employing computed tomography have shown a positive correlation between BMI or indices of abdominal obesity and CAD and its complications. In the Muscatine Heart Study, Mahoney et al. reported that among 384 males and females who were 15 years old at entry and were followed for 15 years, obesity (assessed by BMI and triceps skinfold thickness) was strongly associated with coronary artery calcium detected by computed tomography (Mahoney et al. 1992). In the Dallas Heart Study, WHR was the only anthropometric measure of obesity that was associated with coronary artery calcium on computed tomography (odds ratio: 1.91) (See et al. 2007). Labounty et al. studied 13,874 patients suspected of having CAD using coronary computed tomographic angiography (Labounty et al. 2013). Those with and increased BMI had a greater prevalence, extent, and severity of CAD that was not fully explained by CVD risk factors. There was an

independent association between BMI and risk of myocardial infarction.

6 The Obesity Paradox and CHD

Epidemiologic studies strongly suggest that overweightness and obesity are associated with increased risk for CVD and CHD mortality, particularly when excess bodyweight is present for long periods of time. There is increasing evidence that an obesity paradox exists with respect to CVD and CHD mortality once CHD is established. Multiple studies have demonstrated lower total and CVD mortality in overweight and class I obese persons than in normal weight or underweight persons (Jahangir et al. 2014; Miller et al. 2008; Lavie et al. 2009a, b; Romero-Corral et al. 2006). Romero-Corral et al. reported the results of a systematic review and meta-analysis of 40 studies comprising more than 250,000 patients with established CAD (Romero-Corral et al. 2006). In this analysis, normal weight (BMI of 19.0–24.9 kg/m^2) was used as a referent. Total mortality was lower in both overweight and class I obese patients. Compared to the referent, underweight subjects possessed the highest risk for total mortality, and those with a BMI $\geq$35 kg/m^2 had a relative risk for total mortality similar to the referent. Similar observations were noted for subgroups with myocardial infarction and those receiving percutaneous coronary interventions. Relative risks for total mortality in overweight and class I obese patients undergoing CABG were similar to the referent, but were higher in underweight patients and in those whose BMI was $\geq$35 kg/m^2. Unadjusted and adjusted relative risk for CV mortality was slightly lower in overweight and class I obese patients, but was higher than the referent in underweight subjects and in those whose BMI was $\geq$35 kg/m^2. In contrast to these findings, a meta-analysis by Flegal et al. failed to show clear-cut evidence of an obesity paradox with respect to CAD (Flegal et al. 2013).

Multiple studies have demonstrated an obesity paradox in subsets of patients with CHD, including those receiving surgical or percutaneous revascularization (Das et al. 2011; Lavie et al. 2009a, b; Kragelund et al. 2005; Pingitore et al. 2007; Mehta et al. 2007). In a study of 50,000 patients with ST segment elevation myocardial infarction, Das et al. noted that those with a BMI of 30–35 kg/m^2 had the lowest mortality of the weight groups studied (Das et al. 2011). Lavie and colleagues and others reported that adjusted in-hospital mortality was lower in patients suffering ST segment or non-ST segment elevation myocardial infarction whose BMI was $\geq$40 kg/m^2 than in those whose BMI was $<$40 kg/m^2 (Lavie et al. 2009a). In the TARGET trial of 4,800 patients who received a bare metal stent and either abciximab or tirofiban, there was no difference in death or myocardial infarction at 30 days or 6 months between obese and nonobese patients (Miller et al. 2008; Jahangir et al. 2014). However, target vessel revascularization at 6 months occurred more commonly in obese subjects $<$65 years old in this trial. Other studies have also demonstrated a greater propensity for use of percutaneous revascularization in obese subjects (Gruberg et al. 2002; Li et al. 2013; Lancefield et al. 2010; Park et al. 2013; Sarno et al. 2010, 2011; Nikolsky et al. 2005; Wang et al. 2012). In contrast, Akin et al. failed to identify better outcomes in obese patients following persons' intervention in a German Registry (Akin et al. 2012). A study of 6,068 patients undergoing coronary artery bypass showed that 12-year mortality was similar between normal weight subjects and those whose BMI ranged from 32 to 36 kg/m^2, but was greater in those whose BMI was $\geq$36 kg/m^2 (Jahangir et al. 2014; Miller et al. 2008). Oreopoulos et al., in a study of 31,021 patients with CHD followed for 46 months, showed that medically treated overweight and class I obese patients had significantly lower mortality than underweight and normal weight subjects (Oreopoulos et al. 2008a). In patients undergoing coronary artery bypass grafting, subjects with a BMI of 35–39.9 kg/m^2 had the lowest mortality rate among weight groups studied. Similar results were reported by other investigators (Stamou et al. 2011; Wagner et al. 2007; Moulton et al. 1996; Benedetto et al. 2014). As with other studies, those with class I and class II obesity were

more likely to be revascularized than other BMI subgroups.

The preponderance of evidence suggests that mortality in overweight and class I obese subjects is similar to or lower than that of normal weight individuals. Underweight subjects consistently have the highest risk for mortality. There is some variability in mortality among patients with more severe degrees of obesity. A variety of reasons for the obesity paradox in CHD have been suggested (Miller et al. 2008). It is postulated that overweight and obese patients may have greater metabolic reserves, less cachexia, greater muscle mass, better cardiorespiratory fitness, and attenuated responses to activation of the renin-angiotensin-aldosterone system. They also suggest that obese subjects may present at a younger age and may receive more aggressive medical therapy, diagnostic evaluation, and revascularization therapy than underweight or normal weight individuals (Miller et al. 2008).

7 Effects of Weight Loss

It is well established that purposeful weight loss is capable of favorable modifying traditional CVD risk factors associated with obesity including hypertension, atherogenic dyslipidemia, and type 2 diabetes mellitus. Weight loss is also known to reduce insulin resistance and inflammation, improves endothelial function, and reduces the incidence of the metabolic syndrome. Lavie et al. reported a trend toward decreased mortality in patients who had suffered a cardiac event and then lost weight while entered in a cardiac rehabilitation program (Lavie et al. 2009a, b). Others have reported increased mortality following weight loss, but many of these studies failed to exclude patients with non-purposeful weight loss (Allison et al. 1999; Jahangir et al. 2014; Miller et al. 2008). While it is likely that risk factors' modification and improvement in cardiopulmonary fitness contribute to well-being and perhaps a decrease in cardiovascular events, the effect of purposeful on total and CV mortality in patients with established CHD remains uncertain.

8 Conclusions

Obesity is closely associated with a variety of traditional and nontraditional CVD risk factors, both individually and in the setting of the metabolic syndrome. There is strong epidemiologic evidence of a link between obesity and CVD in general as well as CHD morbidity and mortality. This relation is less well established in studies based on autopsy and coronary angiographic data. Nevertheless, obesity has been classified as an independent risk factor for CVD and CHD. An increasing body of evidence suggests the presence of an obesity paradox with respect to total and CVD mortality. Although purposeful weight loss is capable of favorably modifying many CV risk factors, direct evidence of a relation between weight reduction and regression of CAD or improvement in CVD outcomes is sparse.

8.1 Obesity and Heart Failure

Obesity serves as both a risk factor for and a primary cause of heart failure (HF). This section discusses epidemiologic and prognostic considerations as they relate to obesity, describes changes in cardiac performance and morphology associated with obesity, reviews clinical manifestations in patients with HF due entirely or predominantly to obesity (obesity cardiomyopathy), and discusses the effects of purposeful weight loss on cardiac structure and function and on HF itself.

9 Epidemiologic Considerations

Obesity is a common comorbidity in patients with HF. Owan et al., in a study of 6,016 in-patients discharged with a diagnosis of HF reported an incidence of obesity of 41.4 % in subjects with a preserved left ventricular (LV) ejection fraction (LVEF) and 35.5 % in those with a reduced LVEF (Owan et al. 2006). Kenchaiah and colleagues, in a study of 5,881 patients from the Framingham Heart Study, demonstrated that 8.4 % of class I and class II subjects developed HF over a mean follow-up period of 14 years

(Kenchaiah et al. 2002). Each kg/m^2 increase in BMI was associated with an increased risk of HF of 5 % in men and 7 % in women. The risk of HF was significantly greater in overweight than in normal weight persons and significantly greater in obese than in overweight subjects. Baena-Diaz and coworkers identified obesity as an independent risk factor for HF in a low-risk Mediterranean population (Baena-Diez et al. 2010). Alpert et al. found that nearly one-third of 74 class III obese subjects had clinical evidence of HF (Alpert et al. 1997a). Retrospective analysis of data from the NHANES 1 study supports the designation of obesity as a risk factor for HF (He et al. 2001).

10 Hemodynamic Alterations Associated with Obesity

Total and central blood volume and cardiac output are elevated in obese persons, roughly in proportion to the excess in body weight (Alexander and Alpert 1998a; Alexander et al. 1962; Alexander 1964; DeDivitiis et al. 1981). In most studies, heart rate changed little, if at all with weight gain (Alexander and Alpert 1998a). Thus, the increase in cardiac output occurs due to increased LV stroke volume. This is facilitated by a decrease in systemic vascular resistance in normotensive patients. LV dP/dt is higher and Vmax is lower than that predicted for normal in class II–III obese patients (DeDivitiis et al. 1981). Myocardial oxygen consumption and arteriovenous oxygen difference values also exceed those predicted for normal weight in such patients (Poirier et al. 2006; Alexander and Alpert 1998a; DeDivitiis et al. 1981). LV end-diastolic pressure and pulmonary artery capillary wedge pressure are commonly elevated in obese subjects, particularly in those who are severely obese (Alexander and Alpert 1998a; DeDivitiis et al. 1981). Right ventricular end-diastolic pressure and right atrial pressure are commonly elevated in severely obese persons (Alexander and Alpert 1998a; DeDivitiis et al. 1981; Kasper et al. 1992). Pulmonary vascular resistance is more variable. Sleep apnea and obesity hypoventilation may produce increases in pulmonary artery and right heart pressures over and above that caused by elevated LV filling pressure resulting in increases of pulmonary vascular resistance (Alexander and Alpert 1998a; Alaud-din et al. 1982).

Exercise has been shown to substantially increase central blood volume and LV dP/dt in obese subjects (Kaltman and Goldring 1976; Backman et al. 1973). In one study, exercise caused LV end-diastolic pressure to increase from a mean of 21 to 31 mmHg. At workloads greater than three times the resting level, the rise in cardiac output is blunted (Alexander and Alpert 1998a). In severely obese patients, LV end-diastolic pressure increases disproportionally to LV stroke work suggesting reduced LV compliance (Backman et al. 1973; Alexander and Alpert 1998a).

In class II and class III obese subjects, cerebral blood flow and renal blood flow are low normal or reduced, whereas splanchnic blood flow is increased (Alexander and Alpert 1998a). Blood flow in adipose tissue is 2–3 ml/min less than in other organs and does not fully account for the increase in cardiac output noted in obese subjects (Poirier et al. 2006; Alexander and Alpert 1998a). The difference is attributable to increased fat-free mass (Poirier et al. 2006).

11 Cardiac Morphology in Obesity

Postmortem studies, consisting primarily of severely obese persons during life, have shown that nearly all have LV hypertrophy on both gross and microscopic examination LV dilation was commonly, but not invariably present (Alpert and Alexander 1998a; Smith and Willius 1933; Amad et al. 1965; Alexander and Pettigrove 1967; Warnes and Roberts 1989). Right ventricular hypertrophy was present in approximately one-third of patients. Excess epicardial adipose tissue was reported in approximately two-thirds of subjects.

Kasper et al. studied 43 obese patients and 409 lean patients with HF (Kasper et al. 1992). Of those who underwent myocardial biopsy, a specific etiology was identified in 64.5 % of lean patients and in only 23.3 % of obese patients. LV hypertrophy was the most common pathologic

finding in obese subjects. These findings support the concept of a cardiomyopathy of obesity.

Noninvasive cardiac imaging techniques (echocardiography, magnetic resonance imaging) have allowed us to study more patients than is possible with postmortem studies. Studies using these techniques have identified similar morphologic abnormalities as autopsy studies, but their reported incidence is more variable due to inclusion of patients with lesser degrees and variable duration of obesity (Alpert and Alexander 1998a; Zema and Cacavano 1982; Garcia et al. 1982; Alpert et al. 1985).

Numerous studies have compared LV morphology in lean and obese subjects (Alpert and Alexander 1998a). In virtually all studies, indices of LV mass or wall thickness were significantly greater in obese than in lean patients. LV diastolic chamber size was significantly greater in patients with uncomplicated obesity than in lean subjects. Multiple studies have reported strong positive correlations between indices of LV mass and body weight indices (Alpert and Alexander 1998a; Alpert et al. 1998; Lauer et al. 1991). Correlation between LV diastolic chamber size and body weight indices has been less consistent. Factors contributing to increased LV mass in obesity include blood pressure (predominantly systolic blood pressure), LV end-systolic wall stress, duration of obesity, and possibly, abdominal adiposity (Alpert and Alexander 1998a; Alpert et al. 1994). As with cardiac output, fat-free mass appears to be as important or more important than fat mass in predicting increased LV mass (Bella et al. 1998).

Controversy exists concerning LV geometry in obesity. Based on known hemodynamic alteration in obesity, eccentric LV hypertrophy would be expected to predominate. However, multiple recent studies have reported that concentric LV hypertrophy or remodeling occurs as frequently or more frequently in obese subjects (Aurigemma et al. 2013; Turkbey et al. 2010; Danias et al. 2003; Woodwiss et al. 2008; Smalcelj et al. 2000; Peterson et al. 2004). In most studies of uncomplicated (normotensive) obesity, when LV hypertrophy was present, it was predominantly eccentric (Alpert and Alexander 1998a; Okpura et al. 2010; Iacobellis et al. 2002, 2004). All but one of the studies reporting a predominance of concentric LV hypertrophy or remodeling have failed to exclude hypertensive patients or to account for the relative duration and severity of hypertension and obesity. For example, a patient with a long-standing severe obesity and treated hypertension might be expected to have eccentric LV hypertrophy, whereas a patient with long-standing poorly controlled hypertension and class I obesity might be expected to have concentric LV hypertrophy or remodeling. It is possible that various neurohormonal and metabolic factors may contribute to the development of concentric LV hypertrophy or remodeling in the absence of hypertension in obese persons. This issue remains unresolved.

12 Ventricular Function in Obesity

As previously noted, LV end-diastolic pressure is commonly elevated is severely obese persons and rises substantially with exercise. LV diastolic function in obesity has also been evaluated using noninvasive cardiac techniques including transthoracic echocardiography, Doppler echocardiography, tissue Doppler imaging, radionuclide angiography, and magnetic resonance imaging. Studies comparing LV diastolic function, regardless of the technique used, have shown impairment of LV diastolic function in obese subjects relative to lean controls (Chakko and Alpert 1998; Stoddard et al. 1992; Chakko et al. 1991; Herszkowicz et al. 2001; Ku et al. 1994; Ferraro et al. 1996). In some studies, indices of diastolic filling became progressively more impaired with increasing LV mass (Chakko and Alpert 1998; Alpert et al. 1997; Tian et al. 2007; Kossaify and Nicolais 2013). In one study, impaired diastolic filling occurred only in those with LV hypertrophy (Alpert et al. 1997). Other factors that may contribute to LV diastolic dysfunction included systolic blood pressure, LV end-systolic wall stress, duration of obesity, and type 2 diabetes mellitus with insulin resistance (Chakko and Alpert 1998; Alpert et al. 1996; Nakajima et al. 1985). Pascual et al. reported abnormal LV diastolic filling in 12 % of class I, 35 % of class II, and 45 % of

class III obese subjects using Doppler echocardiographic techniques (Pascual et al. 2003). More recently, studies using tissue Doppler echocardiography (a presumably load-independent technique) have shown decreased mitral annular velocities in diastole in obese subjects (Kossaify and Nicolais 2013).

Most studies assessing LV systolic function have shown normal or supernormal LV ejection phase indices (LVEF, LV fractional shortening) (Alpert and Alexander 1998b; Alpert et al. 1993). In several studies, LV ejection phase indices in obese subjects were lower than in lean subjects. Most however, remained with the normal range are those that did not were typically only mildly reduced. Severely depressed LV systolic dysfunction should elicit a search for comorbid CV diseases in all classes of obesity (Alpert et al. 1993). Recent studies have identified decreased mitral annular velocities in systole and abnormal LV strain and strain rates in obese patients with normal LV ejection phase indices (Alpert et al. 2014a; Tumuklu et al. 2007; Barbosa et al. 2011; Talano et al. 2008). This suggests that subclinical LV systolic dysfunction occurs in obesity more commonly than was previously appreciated.

Little information exists concerning right ventricular function in obesity. Tissue Doppler studies have shown decrease systolic velocities in the lateral tricuspid annulus suggesting right ventricular systolic dysfunction in such patients (Otto et al. 2004; Orhan et al. 2010; Chahai et al. 2012).

13 Obesity, Hypertension, and the Heart

Hypertension occurs in up to 50 % of class I and II obese persons and in approximately 60 % of severely obese individuals (Alexander and Alpert 1998a). Intravascular volume is normal to increased in such individuals. Cardiac output and LV stroke volume remain increased in obese hypertensives, but to a lesser extent than in normotensive obese persons (Thakur et al. 2001; Fazio et al. 1989). LV stroke work is increased to a greater extent in hypertensive obese subjects than in those who are normotensive and obese. Systemic vascular resistance is higher in hypertensive obese patients than in normotensive obese subjects (Thakur et al. 2001; Alexander and Alpert 1998a). It is sometimes described as inappropriately normal and is frankly elevated in some individuals. LV end-diastolic pressure is commonly elevated in hypertensive obese subjects, particularly when obesity and hypertension are long-standing. In patients with chronic poorly controlled hypertension and severe obesity, a hybrid form of LV hypertrophy may occur known as eccentric-concentric hypertrophy (now classified as a form of concentric LV hypertrophy) (Thakur et al. 2001; Lavie et al. 2009a, c; Messerli et al. 1983; Iacobellis et al. 2003). In such individuals, LV chamber size is dilated, but to a lesser extent than in normotensive obese subjects, and LV wall thickness is normal to increased in hypertensive obese individuals. Left atrial enlargement is common in both states. LV diastolic dysfunction is present in both states. LV systolic function typically remains normal in hypertensive obese persons (Thakur et al. 2001; Lavie et al. 2009c).

14 Metabolic Abnormalities Affecting Cardiac Performance and Morphology

Increased sympathetic nervous system activity, activation of the renin-angiotensin-aldosterone system, hyperleptinemia due to leptin resistance and insulin resistance with hyperinsulinemia have been linked to LV hypertrophy and to impaired LV function in animal and in some human studies (Amador et al. 2004; Abel et al. 2008; Wong and Marwick 2007; Alpert et al. 2014a; McGavock et al. 2006). Myocardial lipotoxicity is a process by which triglycerides and excess fatty acids accumulate in myocardial cells causing cellular dysfunction and death and eventually myocardial dysfunction (McGavock et al.). Myocardial lipotoxicity has been linked to LV hypertrophy and to LV systolic and diastolic dysfunction in genetically obese rats and transgenic murine models of lipotoxicity (McGavock et al. 2006; Abel et al. 2008; Wong and Marwick 2007). Whether myocardial lipotoxicity produces

alterations in cardiac performance and morphology in humans is unknown.

15 Obesity Cardiomyopathy: Clinical Manifestations

Severe obesity is capable of causing HF in the absence of other underlying causes or precipitating factors. HF due predominantly or entirely to severe obesity is termed obesity cardiomyopathy. Clinical manifestations of obesity cardiomyopathy are similar to those of HF from other causes in some respects and unique in other respects (Alexander and Alpert 1998b; Lillington et al. 1957). Nearly all patients with obesity cardiomyopathy have a relative weight $\geq$175 % or a BMI $\geq$40 kg/m^2 and have been severely obese for at least 10 years. HF tends to be episodic and typically occurs following a recent weight gain. Sleep apnea occurs in up to 50 % of severely obese patients. Obesity hypoventilation occurs in 10–20 % of such individuals. The pathophysiology of obesity cardiomyopathy is summarized in Fig. 1. Symptoms include dyspnea on exertion, paroxysmal nocturnal dyspnea, edema of the lower extremities, increased abdominal girth, mental confusion and disorientation, somnolence, and death. Physical signs include jugular venous distension with hepatojugular reflux, pulmonary crackles, gallop rhythm, ascites, brawny edema, cyanosis, periodic breathing, conjunctival suffusion, retinal venous congestion, and papilledema (Alexander and Alpert 1998b). Cardiac murmurs are usually absent (Alexander and Alpert 1998b; Lillington et al. 1957).

16 Prognostic Considerations: The Obesity Paradox

An increasing body of evidence suggests that mortality risk is lower in obese patients with HF than in lean patients with comparable degrees of severity of HF (Lavie et al. 2013a, b; Oreopoulos et al. 2008; Horwich et al. 2001; Davos et al. 2003). To an even greater extent than with CAD, there exists an obesity paradox with respect to HF. Oreopoulos et al. published the results of a meta-analysis of 28,209 patients with HF (Oreopoulos et al. 2008b). All cause mortality was 16 % lower in overweight patients with HF and 33 % lower in obese subjects with HF than in normal weight patients with HF. Similarly, CV mortality was 19 % lower in overweight patients with HF and 40 % lower in obese subjects with HF than in normal weight patients with HF. In virtually all studies, underweight patients had the highest mortality risk. Overweight and class I obese patients consistently had the lowest mortality rates. Class II obesity was associated in low mortality rates in some studies and increased mortality risk in others. Limited information suggests that class III obesity is generally associated with higher mortality rates than normal weight, overweight, and class I obese patients (Lavie et al. 2013a). The obesity paradox in the context of HF has been described in men and women, patients with preserved and a reduced LV systolic function, patients with acute and chronic HF, and in those with peripheral and central obesity with HF (Clark et al. 2011, 2012; Lavie et al. 2009c; Padwal et al. 2014; Nicklas et al. 2006; Fonarow et al. 2007). Possible mechanisms of the obesity paradox in HF patients are similar to those discussed previously in the section on obesity and CVD. A higher degree of cardiopulmonary fitness in lean patients with HF may attenuate the obesity paradox (Lavie et al. 2013b).

17 Effect of Weight Loss on Cardiac Hemodynamics, LV Morphology, LV Function, and Clinical Manifestations of HF

The abnormalities of cardiac structure and function are most pronounced in severely obese patients. Substantial purposeful weight loss is capable of reversing many of the adverse hemodynamic alterations and changes in LV morphology and function in such individuals (Ashrafian et al. 2008; Rider et al. 2009; Alexander and Peterson 1992; Alaud-din et al. 1982; Backman et al. 1979; Grapsa et al. 2013; Jhaveri et al. 2009; Reisin et al. 1983). Because bariatric surgery

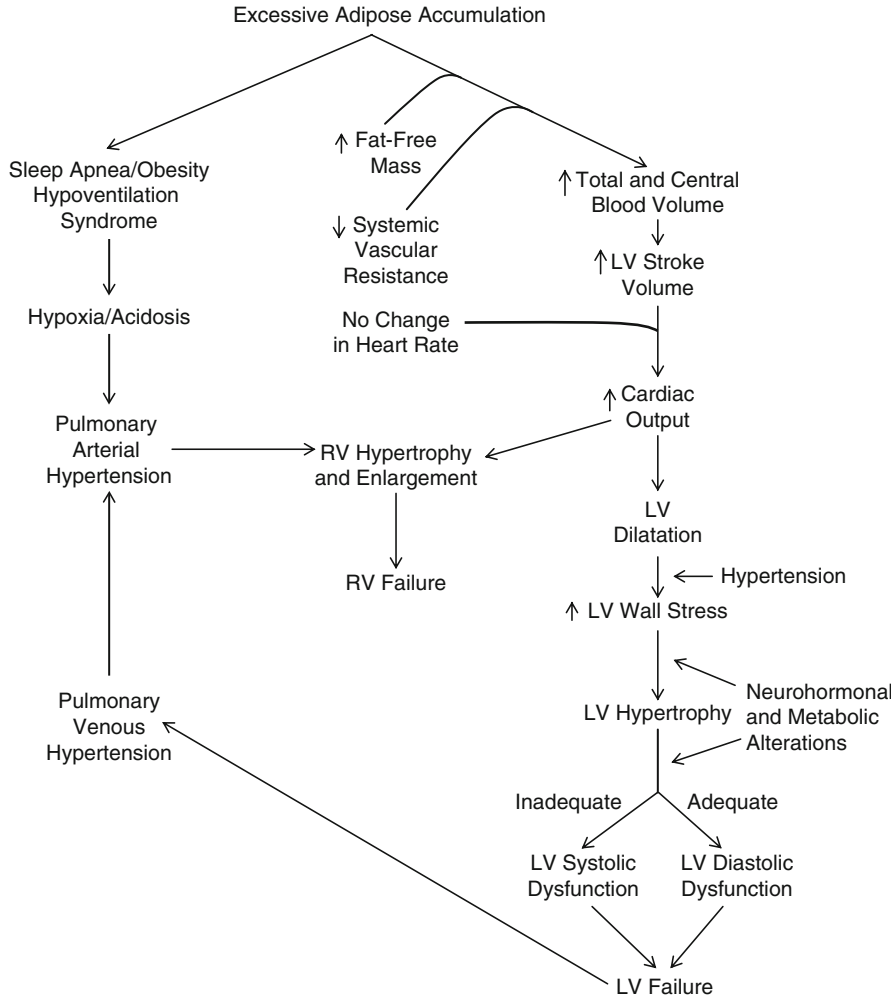

Fig. 1 Pathophysiology of obesity cardiomyopathy. This diagram shows central hemodynamic alterations that result from excessive adipose accumulation in severely obese patients and their subsequent effects on cardiac morphology and ventricular function. Left ventricular (LV) hypertrophy in severe obesity may be eccentric or concentric. Factors influencing LV remodeling and geometry include severity and duration of obesity, duration and severity of adverse LV loading conditions (particularly hypertension), and possibly, neurohormonal and metabolic abnormalities such as increased sympathetic nervous system tone, activation of the renin-angiotensin-aldosterone system, insulin resistance with hyperinsulinemia, leptin resistance with hyperleptinemia, adiponectin deficiency, lipotoxicity, and lipoapoptosis. These alterations may contribute to the development of LV failure. LV failure, facilitated by pulmonary arterial hypertension from sleep apnea/obesity hypoventilation, may subsequently lead to right ventricular (RV) failure (Adapted from reference Lavie et al. 2013a)

produces greater weight loss than diet and exercise, the most pronounced changes in cardiac structure and function occur with surgical weight reduction.

Substantial purposeful weight loss in severely obese persons is associated with decreases in total and central blood volume, cardiac output, oxygen consumption, arteriovenous oxygen difference, LV stroke volume, cardiac work, and LV stroke work (Alaud-din et al. 1982; Alexander et al. 1972; Backman et al. 1973). Systemic vascular resistance generally rises following weight loss in normotensive individuals. The reported response of LV end-diastolic pressure and pulmonary capillary wedge

pressure to weight loss is more variable, declining in some and remaining unchanged in others. Right heart pressures often decrease with substantial weight loss, in part due to improvement in sleep apnea and obesity hypoventilation.

Most studies assessing the effect of purposeful weight loss in cardiac morphology have reported substantial reduction in LV mass and chamber size (Ashrafian et al. 2008; Rider et al. 2009; Grapsa et al. 2013; Jhaveri et al. 2009). Weight loss has also been associated in reverse remodeling in severely obese patients with abnormal LV geometry (Luaces et al. 2012). These favorable alterations in LV morphology are attributable in part to improvement in LV loading conditions. However, weight loss-related improvements in insulin resistance and hyperleptinemia may also contribute to regression of LV hypertrophy.

In moderately to severely obese patients, substantial purposeful weight loss has produced improvement in LV diastolic filling in most studies employing noninvasive diagnostic techniques (Ashrafian et al. 2008; de las Fuentes et al. 2009; Haufe et al. 2012; McCloskey et al. 2007). Such changes have been attributed in part to favorable alterations in LV loading conditions. One study reported improvement in LV diastolic filling with weight loss only in those with LV hypertrophy (Alpert et al. 1997).

Most obese patients including those who are severely obese have normal or supernormal LV systolic function. Weight loss in such patients produces either no change or normalization of LV ejection phase indices (Alpert and Alexander 1998b; Alpert et al. 2014a). In those with depressed LV systolic function, weight reduction produces improvement in LV ejection phase indices (Alpert et al. 1993). Improvements in mitral annular systolic velocities detected using tissue Doppler imaging and reduction in myocardial deformation using speckle track imaging have been reported following weight loss in obese subjects (Alpert et al. 2014a).

Limited information exists concerning the effects of weight loss on symptom and signs of HF in obese subjects. One early study by Estes et al. reported reversal of somnolence periodic breathing, polycythemia, and dyspnea in five of six severely obese patients who lost 38–143 lb (Estes et al. 1957). In a study of 14 severely obese patients with substantial purposeful weight loss following bariatric surgery, Alpert and colleagues reported improvement in the New York Heart Association functional class in 12 of 14 patients (Alpert et al. 1997). Miranda and colleagues noted improvement in the quality of life, dyspnea, and lower extremity edema in seven severely obese patients undergoing bariatric surgery, but no change in six patients with dietary weight loss. Substantial weight loss in capable of reversing many of the abnormalities of cardiac performance and morphology in severely obese patients with HF just as it is in severely obese persons without HF (Miranda et al. 2013). Ramani et al. reported similar findings in 12 severely obese patients treated with bariatric surgery (Ramani et al. 2008).

18 Conclusions

Hemodynamic alterations in obesity include increased total and central blood volume, LV stroke volume, and cardiac output. Systemic vascular resistance is reduced. LV end-diastolic pressure is often increased in long-standing severe obesity. Right heart pressures are frequently elevated in severe obesity. LV mass is increased in all classes of obesity relative to LV mass in lean patients. LV dilatation is frequently, but not invariably, present in severe obesity. Impairment of LV diastolic filling occurs commonly in obese persons, particular when LV hypertrophy is present. LV systolic function is usually normal in obese persons. Hypertension promotes the development of eccentric-concentric hypertrophy in the presence of long-standing severe obesity. The clinical presentation of HF in patients with obesity cardiomyopathy is characterized by several unique clinical manifestations due to sleep apnea and obesity hypoventilation. An obesity paradox exists with respect to mortality in obese persons with HF. Many of the abnormalities of cardiac structure and function as well as clinical manifestations of HF are reversible with substantial purposeful weight loss.

19 Cross-References

- Dyslipidemia in Obesity
- Genetics of Cardiovascular Risk in Obesity
- Insulin Resistance in Obesity
- Obstructive Sleep Apnea and Other Respiratory Disorders in Obesity

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Nonalcoholic Fatty Liver Disease

34

Elisabeth Smolle, Sonja M. Kessler, Nicole Golob, and Johannes Haybaeck

Contents

Abstract

The metabolic syndrome (MetS), also known as syndrome X or insulin resistance syndrome, is defined by the combination of insulin resistance, abdominal fat distribution, high blood pressure, and dyslipidemia. The coexistence of these risk factors leads to an excess cardiovascular disease morbidity. MetS is an emerging public health and clinical challenge worldwide, caused by the hypercaloric diet and sedentary lifestyle of today's population.

MetS means a proinflammatory or prothrombic condition, comprising, for example, elevated C-reactive protein (CRP) levels, elevated levels of uric acid, and a shift toward small, dense low-density lipoprotein (LDL) cholesterol particles. An association between the occurrence of MetS and the polycystic ovary syndrome, as well as with nonalcoholic steatohepatitis (NASH), has been described.

In this article, we review current data about the MetS and related diseases. We focus especially on the hepatic damage that is caused by MetS, and thus we describe animal models of nonalcoholic fatty liver disease (NAFLD) giving insights into the mechanisms of NAFLD, and we also provide information about the neoplastic final common path, namely, hepatocellular carcinoma (HCC).

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Keywords

Metabolic syndrome (MetS) • Nonalcoholic fatty liver disease (NAFLD) • Nonalcoholic steatohepatitis (NASH) • Hepatocellular carcinoma (HCC) • Obesity

Abbreviations

AACE	American Association of Clinic Endocrinologists
ALD	Alcoholic liver disease
ATF6	Activating transcription factor-6
BMI	Body mass index
CARDIA	Coronary Artery Risk Development in Young Adults
CBS	Cystathionine beta-synthetase
CCC	Cholangiocellular carcinoma
CEA	Carcinoembryonic antigen
CRP	C-reactive protein
CVD	Cardiovascular disease
DDC	3,5-diethoxycarbonyl-1,4-dihydrocollidine
EBV	Epstein-Barr virus
EGIR	European Group for the Study of Insulin Resistance
ER	Endoplasmic reticulum
FATP	Fatty acid transporter protein
FLC	Fibrolamellar carcinoma
FLS mice	Fatty liver Shionogi mice
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HepPar1	Carbamoyl phosphate synthetase-1
HFDs	High-fat diets
IDF	International Diabetes Federation
IGF2	Insulin-like growth factor 2
IR	Insulin resistance
JNC 7	Seventh Report of the Joint National Committee on Prevention Detection, Evaluation, and Treatment of High Blood Pressure
LDL	Low-density lipoprotein
LpL	Lipoprotein lipase
MAT1A	Methionine adenosyltransferase 1 alpha
MCD	Methionine- and choline-deficient diet
MCR4	Melanocortin 4 receptor
MDBs	Mallory-Denk bodies
MetS	Metabolic syndrome
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NCEO/ATP	National Cholesterol Education Program-Adult Treatment Panel
PERK	PKR-like ER kinase
PTEN	Phosphatase and tensin homolog
SH-HCC	Steatohepatitic HCC
SREBP	Sterol regulatory element-binding protein
T2DM	Type 2 diabetes mellitus
VLDL	Very low-density lipoprotein
WHO	World Health Organization

1 Introduction

The metabolic syndrome (MetS), also known as syndrome X or insulin resistance syndrome, is defined by the combination of insulin resistance, abdominal fat distribution, high blood pressure, and dyslipidemia, as defined by the World Health Organization (WHO) (Deen 2004; Vega 2001; Alberti and Zimmet 1998). The coexistence of these risk factors in an individual leads to an excess cardiovascular disease (CVD) morbidity (Vega 2001). As a result of the populations' increasing energy intake and sedentary lifestyle, MetS becomes a major escalating public health and clinical challenge worldwide (Kaur 2014). According to a report from the National Cholesterol Education Program-Adult Treatment Panel (NCEO/ATP III), MetS is an independent risk factor for CVD, indicating the necessity of a profound lifestyle modification (National Institutes of Health 2004). The NCEO/ATP has edited a new, operational definition of MetS, different from the initial definition by the WHO: The co-occurrence of any three of the four risk factors (insulin resistance, abdominal fat distribution, high blood pressure, and dyslipidemia) (Alberti and Zimmet 1998; National Institutes of Health 2004). MetS means a proinflammatory or prothrombic condition, comprising elevated C-reactive protein (CRP) levels, endothelial dysfunction, elevated fibrinogen levels, elevated platelet aggregation,

high levels of plasminogen activator inhibitor 1, elevated levels of uric acid, microalbuminuria, and a shift toward small, dense low-density lipoprotein (LDL) cholesterol particles (Deen 2004). An association between the occurrence of MetS and the polycystic ovary syndrome, as well as with nonalcoholic steatohepatitis (NASH), has been described (Deen 2004). Several attempts of exactly defining the diagnostic criteria for MetS have been made (Eckel et al. 2005). First, the WHO diabetes group came up with a definition of MetS in 1998 (Alberti and Zimmet 1998). In 1999 the European Group for the Study of Insulin Resistance (EGIR) provided a second definition, which was a modification of the original WHO definition, and in 2001 the National Cholesterol Education Program-Adult Treatment Panel (NCEO/ATP) came up with a third definition (Balkau and Charles 1999; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001). In 2003, the American Association of Clinic Endocrinologists (AACE) offered a revised definition of MetS, and in the hope of unifying all these definitions, the International Diabetes Federation (IDF) proposed a novel diagnostic definition in April 2005 (Einhorn et al. 2003; International Diabetes Federation n.d.).

2 Epidemiology

Dependent on what definition is used and what population is studied, the prevalence of MetS varies (Ford and Giles 2003). The Third National Health and Nutrition Examination Survey (1988–1994) has provided data, showing that the prevalence of MetS ranges from only 16 % in black males to 37 % in Hispanic females (Ford et al. 2002). The prevalence is directly associated with age and with body weight. People are constantly becoming older in most industrialized countries, and the average body weight increases continuously. Thus, it is estimated that MetS will soon outrun cigarette smoking as the major risk factor for CVD (Eckel and Krauss 1998). Notably, MetS is a very strong predictor of type 2 diabetes (T2DM), meaning that MetS confers fivefold the risk of T2DM (Grundy et al. 2004; Alberti et al. 2009). Moreover, MetS twofold increases the risk of developing CVD within the next 5–10 years (Alberti et al. 2009). Moreover, MetS leads to a two- to fourfold increased risk of stroke, a three- to fourfold increased risk of myocardial infarction, and a twofold risk of dying from a cardiovascular event, in comparison to those who do not suffer from MetS, independent of the previous history of cardiovascular events (Alberti et al. 2005; Olijhoek et al. 2004). MetS is considered a first-order risk factor for atherothrombotic complications, and thus it must be considered as an indicator of long-term risk for atherosclerosis and the related events (Kaur 2014; Grundy 2006).

3 Etiology and Pathogenesis

An exact definition of the etiology of MetS has not been established. Insulin resistance has been hypothesized to be the primary condition in the development of MetS, since insulin resistance correlates with abdominal fat storage, also called android fat distribution, as measured using the waist-to-hip ratio (Deen 2004). Presumably, oxidative stress is the link between insulin resistance and CVD, as it causes endothelial cell dysfunction, vascular damage, and plaque formation (Lopez-Candales 2001). Another hypothesis indicates hormonal changes as being the cause of abdominal obesity. Patients with elevated serum cortisol levels due to chronic stress are also more likely to develop abdominal obesity, as well as insulin resistance and dyslipidemia (Bjorntorp 2001). Dysregulation of the hypothalamic-pituitary-adrenal axis due to chronic stress has been assumed to be responsible for the link between psychosocial problems and the increased incidence of myocardial infarction (Bjorntorp 2001).

4 Diagnosis

For the diagnosis of MetS, it is mandatory to assess the patient's medical history and family history with respect to CVD or T2DM. Recent

weight changes and a diet and physical activity history must be evaluated (Hark and Deen 1999). Further clinical examination shall comprise the assessment of the patient's height, weight, body mass index (BMI; body weight in kilogram divided by the squared body height in meter), blood pressure, waist circumference, and hip circumference (waist-to-hip-ratio; waist circumference divided by hip circumference). Interestingly, waist circumference alone appears to be a better predictor of a patient's cardiovascular risk than waist-to-hip-ratio (Pouliot et al. 1994). Furthermore, fasting glucose levels and a fasting lipid profile must be obtained for the diagnosis of MetS (Deen 2004). Novel tests are now available that measure LDL particle size, in order to evaluate the amount of small dense LDLs. However, these tests are expensive and unnecessary because low levels of high-density lipoprotein (HDL) and high levels of LDL have been shown to predict an abundance of small dense LDL particles. As recommended by the American Heart Association, measuring CRP for risk stratification in patients at high risk of CVD is mandatory (Pearson et al. 2003). Uric acid levels and liver function tests or liver ultrasonography will screen for NASH. Using ultrasonography, liver steatosis can be diagnosed even before liver function turns pathologic (Deen 2004).

5 Treatment

For the prevention or at least delay of the onset of T2DM, hypertension, and CVD, it is essential to treat the components of MetS aggressively (National Institutes of Health 2004; Chobanian et al. 2003; Knowler et al. 2002). Primary treatment consists of a diet change and change of physical activity habits. Weight loss has been proven to improve all aspects of MetS and to reduce all-cause as well as cardiovascular mortality (Gregg et al. 2003). If weight loss is not achieved, an increase in physical exercise and a change toward healthy diet habits can lower blood pressure, improve lipid levels, and increase insulin sensitivity, even in the absence of weight loss (Duncan et al. 2003). Skeletal muscle is the most insulin-sensitive tissue of the human body. Thus, building up muscle tissue through physical exercise is essential to improve insulin sensitivity. Independent of BMI, physical exercise reduces skeletal muscle lipid levels and insulin resistance (Goodpaster et al. 2001). Notably, exercise increases insulin sensitivity temporarily, namely, for 3–5 days, and disappears after that. Thence, patients must work out regularly to effectively reverse insulin resistance (Deen 2004). Regular low-intensity exercise has a significant impact on patients' health, but investigations show that patients tend not to participate in exercise programs any longer as the frequency of workouts is increased (Keller and Trevino 2001). Thus, patients must be supported in finding an exercise regimen which they can accomplish over a long period of time (McInnis et al. 2003). The optimal exercise regimen consists of a combination of cardio/endurance exercise and strength or resistance training. Sedentary patients need to start with walking and should gradually raise the intensity and frequency of their workouts (Slentz et al. 2004). According to a study by Ross et al. in 2000, walking or light jogging for 1 h per day leads to significant loss of abdominal fat in men without caloric restriction (Ross et al. 2000).

Diet is, alongside physical exercise, the most important issue with regard to lifestyle modification in patients with MetS. So far, no clear dietary recommendations for patients with MetS have been made, and thus, physicians need to attune diet recommendations to a patient's metabolic alterations specifically (Szapary et al. 2002). Patients may be referred to registered dietitians for implementation of a sustainable dietary regimen, ensuring the adequate intake of vitamins and mineral nutrients in order to reduce total carolic intake. Regarding macronutrients (protein, fat, and carbohydrates), there is still a debate which proportion of these may lead to the best outcome in patients with MetS. Low-fat diet, low-carbohydrate diet, and the so-called Mediterranean diet are discussed. However, one must take into account that patients lose weight only if their caloric intake is lower than their caloric requirement – and if a patient consumes fewer calories than he or she expends, the exact proportion of protein, fat, and carbohydrates is

probably of little importance. That is to say, that weight loss as such is of great benefit in MetS (Deen 2004). Dietary intervention in MetS has been shown to reduce cardiovascular risk, as per two Cochrane Database of Systematic Reviews. Notably, a diet low in sodium helps to maintain a low blood pressure, even if antihypertensive medication is withdrawn (Hooper et al. 2004). A low-fat diet has been proven to reduce the incidence of cardiovascular events, as demonstrated by a clinical trial where participants consumed a low-fat diet over >2 years (Hooper et al. 2001). A beneficial effect on overall mortality was also described (Hooper et al. 2001). According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), systolic values between 120 and 139 mmHg and/or diastolic values between 80 and 89 mmHg are considered prehypertensive and indicate the need for a lifestyle modification in order to prevent CVD (Chobanian et al. 2003b). A diet low in saturated fat and high in carbohydrates has been shown to effectively reduce blood pressure, even if the patients did not lose weight (Vollmer et al. 2001). In this study by Vollmer et al., patients consumed fruits, vegetables, low-fat dairy products, whole grain products, poultry, fish, and nuts but cut back on saturated fats, red meat, sweets, and sugary beverages (Vollmer et al. 2001). The Coronary Artery Risk Development in Young Adults (CARDIA) study reported dairy product consumption as being associated with a significantly reduced risk for developing MetS (Pereira et al. 2002). Notably, low-fat-high-carbohydrate diets are controversially discussed, because they may lead to elevated triglyceride levels and low HDL cholesterol, thus promoting dyslipidemia in patients with MetS. If HDL cholesterol levels decline in a patient consuming a low-fat diet, it is mandatory to slowly decrease carbohydrate consumption and replace them either with unsaturated fats or with low-glycemic-index/complex carbohydrates. Thereby the diet is adjusted according to a Mediterranean diet, which also evidently reduces the mortality from CVD (Trichopoulou et al. 2003, 2004). An association between CVD and consumption of refined, non-whole grain, grain products, and potatoes has been found in a study by Liu et al. (Liu and Manson 2001). Thus, it is recommended by the authors of this study to consume minimally processed products, predominantly fruits, vegetables, and wholegrain products. Notably, a cohort study also found an increased consumption of dietary fiber, e.g., vegetables and fruits, to correlate with a risk reduction for CVD (Jenkins et al. 2002). Although low-carbohydrate diets evidently improve blood lipid levels in short term, lowering triglycerides and elevating HDL cholesterol, this diet is still controversially discussed since long-term data is not available yet (Foster et al. 2003). As an alternative to a low-carbohydrate diet, high-glycemic-index foods, i.e., refined carbohydrates, shall be replaced by complex/wholegrain carbohydrates, as these do not produce postprandial insulin and glucose peaks. Since fiber intake is currently below the recommended amount in most countries, cutting back on grains will worsen this condition additionally and lead to constipation and decelerated gut passage which may even be a risk factor for colorectal cancer in the long term (Durko and Malecka-Panas 2014). Moderate intake of alcohol, meaning one drink per day for females and two drinks per day for males, may be beneficial for patients with MetS, as this amount reduces insulin resistance and even the risk for CVD (Bell 2002). However, this recommendation does not apply to patients with liver steatosis (Bell 2002).

Family doctors can deliver significant support when it comes to lifestyle modification in patients suffering from MetS. Family physicians have recognized that there is the need for lifestyle counseling in many patients (Petrella and Wight 2000) and they can effectively support their patients by assessing their knowledge about a healthy lifestyle and by giving advice for diet and exercise.

5.1 Pharmacotherapy

Pharmacotherapy is needed in patients whose risk factors are not sufficiently reduced by lifestyle changes. Thereby the patients' blood pressure and blood lipid levels can be controlled (Ginsberg 2003). The use of aspirin and statins was shown to lower CRP levels and so does weight loss. It is

recommended to treat patients with T2DM aggressively regarding their risk factors, in order to prevent CVD (Gaede et al. 2003). The US Preventive Services Task Force recommends behavioral dietary counseling in the first place, for adults with known cardiovascular risk factors (US Preventive Services Task Force 2003). The role of physical activity still needs to be studied in depth, and due to a lack of evidence, no recommendations exist yet (US Preventive Services Task Force 2002).

6 Insulin Resistance

The prevalence of NAFLD increases due to the rising incidence of metabolic disorders, such as T2DM (Cohen et al. 2011; Takamatsu et al. 2008). Savage et al. proposed insulin resistance (IR) in skeletal muscle as the earliest event in the pathogenesis of T2DM in most patients (Savage et al. 2007) and can precede to hepatic IR (Petersen et al. 2004). In skeletal muscle, decreased insulin signaling is responsible for IR (Griffin et al. 1999). Furthermore, impaired GLUT4 translocation contributes to IR (Ciaraldi et al. 1995). Muscle IR is associated with peripheral and portal vein hyperinsulinemia, which promotes hepatic steatosis, at least in part by inducing sterol regulatory element-binding protein (SREBP)-1c-mediated de novo lipogenesis and inhibiting fatty acid oxidation.

Although steatohepatitis is frequently associated with the MetS involving IR, 40–67 % of patients with steatosis do not exhibit signs of decreased glucose tolerance (Kimura et al. 2011; Manchanayake et al. 2011), while other studies showed a clear dissociation between hepatic steatosis and IR (Postic and Girard 2008). Furthermore, hepatic IR can occur without the development of peripheral IR (Kim et al. 2001; Kraegen et al. 1991). In a rodent model, fat transplantation could resolve hepatic IR (Kim et al. 2000). The same is true for the reversion of steatosis in humans by leptin therapy (Petersen et al. 2002). Concordantly, a relationship of hepatic IR and hepatic lipids but not visceral fat was described (Fabbrini et al. 2009).

Genetic mouse models give insight to the association of lipid accumulation and hepatic IR on a molecular level. Lipoprotein lipase (LpL), a key enzyme of fatty acid uptake into tissues, promotes both muscle lipid uptake and muscle IR when being overexpressed (Kim et al. 2001). A liver-specific overexpression of LpL results in hepatic steatosis and hepatic IR (Merkel et al. 1998). Also other proteins involved in fat transport, such as CD36, fatty acid transporter protein (FATP) 2, and FATP5, play a role in steatosis and hepatic glucose sensitivity (Doege et al. 2008; Falcon et al. 2010; Goudriaan et al. 2003). Fat-induced hepatic IR may result from activation of PKC-ϵ and its target JNK1 (Samuel et al. 2004). JNK1 can drive hepatic IR via tyrosine phosphorylation of IRS-1 (Lee et al. 2003; Hirosumi et al. 2002), which impairs the ability of insulin to activate glycogen synthase.

One major common mechanism underlying NAFLD and hepatic IR seems to be endoplasmic reticulum (ER) stress. Modulation of key players in ER stress, i.e., PKR-like ER kinase (PERK) and activating transcription factor-6 (ATF6), alters hepatic lipid export (Yamamoto et al. 2010). In addition, ER stress can lead to increased de novo lipogenesis due to activation of lipogenic transcription factors, i.e., SREBP1c and ChREBP. In parallel XBP1 as a component of ER stress is able to mediate insulin resistance (Ozcan et al. 2004). To close the circle, insulin signaling can again induce ER stress by itself.

7 Animal Models of NAFLD

The human disease of NAFLD develops over years or even decades. The ideal animal model should reflect all steps of disease progression and combine histological abnormalities and metabolic disorders, which are associated with the human disease spectrum. Currently, however, there is no ideal model available fully matching the complex situation in human NAFLD. Therefore, one has to choose the best fitting model depending on the underlying research hypothesis. More weight has to be given to certain aspects of the disease. The following section will discuss available animal

models based on their potential of reflecting the spectrum of human NAFLD pathogenesis.

Two major groups of animal models for NAFLD exist: dietary and genetic models (Table 1 and Fig. 1). Dietary models are of high relevance since in most cases the human disease bases on overnutrition and the modern sedentary lifestyle. In contrast to that, the most commonly used animal model, the methionine- and choline-deficient diet (MCD), displays a nutrient-deficient model. The hepatic lipid accumulation results from an increased hepatic fatty acid uptake and decreased very low-density lipoprotein (VLDL) secretion (Rinella et al. 2008). Additionally, liver inflammation and oxidative stress contribute to liver injury (Schattenberg et al. 2006; Chowdhry et al. 2010). After prolonged feeding, fibrogenesis takes place. There are two major disadvantages of the MCD model: the lack of IR due to massive weight loss (Rinella et al. 2008) and the disturbances of DNA methylation caused by the methionine deficiency, which exclude studies on epigenetic changes in NAFLD using this model.

High-fat diets (HFDs), in which 45–75 % of calories are derived from fat, are used in analogy to human Western diets (Schattenberg and Galle 2010). HFD combines characteristics of the MetS and hepatic steatosis, to some extent inflammation and fibrosis, depending on the mouse strain and the source of dietary fat. However, hepatic injury is less severe than in the MCD model (Varela-Rey et al. 2009). A variant of the classical HFD, the high medium-chain trans-fat, high-carbohydrate model, comprises fibrogenesis (Kohli et al. 2010), in contrast to the ALIOS diet, which consists of long-chain trans-fats (Tetri et al. 2008). Both of these diets include application of a fructose syrup in addition to the HFD mimicking "fast-food" nutrition. Diets with increased cholesterol were originally used in arteriosclerosis research but show also signs of hepatic disorders, i.e., steatohepatitis and fibrosis (Matsuzawa et al. 2007).

Intoxication with 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) serves as a NAFLD model lacking fibrosis, but leading to hepatic inflammation with specific histological features of the human disease, i.e., formation of Mallory-Denk bodies (MDBs) (Bardag-Gorce et al. 2004).

In general, different genetic backgrounds cause significant variations in NAFLD development and progression using dietary models. These differences are most likely related to different susceptibilities of certain animal strains to different aspects of the clinical picture of NAFLD. Some phenotypic variability can be explained by genetic variations due to single nucleotide polymorphisms (Merriman et al. 2006).

Genetic models of NAFLD are high in number, but most of them fail to cover the full spectrum of NAFLD as complete as possible (Table 1). Simple steatosis without any other features, such as obesity, IR, inflammation, and fibrosis, is modeled by JVS, ADK, PITPa, and ApoE knockout mice. In addition to steatosis, some models comprise rather metabolic features. Rodents with impaired leptin signaling (db/db mice, ob/ob mice, LRbS1138/1138 knockin mice, Zucker rats) develop pronounced obesity and massive hepatic lipid accumulation. However, due to the absence of inflammatory events, disease progression is inhibited. Increased appetite is also the cause of the phenotype of KKAγ mice, which closely resembles human MetS (Okumura et al. 2006). Models, in which factors of lipid or glucose metabolism are affected (ChREBP knockout, PPARg hypomorphic, A-ZIP/F-1, diphtheria toxin transgenic, SREBP1c and nSREBPα transgenic mice), do not develop obesity but IR. Interestingly, disease in SREBP1α mice progresses to steatohepatitis (Takahashi et al. 2005), and SREBP1c transgenic mice show almost the full spectrum of the disease lacking an obese phenotype (Shimomura et al. 1998).

Transgenic overexpression of insulin-like growth factor 2 (IGF2) is associated with obesity and IR (Rossetti et al. 1996). Mice liver, specifically overexpressing the *IGF2* mRNA-binding protein p62, display neither obesity nor IR (Laggai et al. 2014), but mild inflammation (Kessler et al. 2014). A further progression to fibrotic changes is inducible (Simon et al. 2014). Inflammation can also be observed in OLEFT rats, CD36 knockout mice, RARα dominant-negative transgenic mice, PEMT, and IKKγ/NEMO knockout mice. Still, up to now, not much emphasis has been given on the quality of the respective

Table 1 Animal models of NAFLD

Model	Obesity	Insulin resistance	Inflammation	Fibrosis	Reference
Feeding models					
MCD	No	No (hepatic)	Yes	Yes	Weltman et al. 1996
HFD	Yes	Yes	Yes/no	Yes (mild)	Buettner et al. 2007
High-fat (medium chain trans fat) high-carbohydrate	Yes	Yes	Yes	Yes	Kohli et al. 2010
ALIOS diet (long chain saturated trans fats)	Yes	Yes	Yes	No	Tetri et al. 2008
Fructose-rich diet	Yes	Yes	Yes	No	Kawasaki et al. 2009; Botezelli et al. 2010
Cholesterol and cholate	No	No (hepatic)	Yes	Yes	Matsuzawa et al. 2007
DDC	No	Yes	Yes	No	Haybaeck et al. 2012; Zatloukal et al. 2014
Genetic models					
JVS mice	No	No	No	No	Kuwajima et al. 1991
ADK mice	No	No	No	No	Boison et al. 2002
PITPα ko mice	No	No	No	No	Alb et al. 2003
ApoE ko mice	No	nd	No	No	Ma et al. 2008
Leptin deficiency (ob/ob)	Yes	Yes	No	No	Trak-Smayra et al. 2011
Db/db	Yes	Yes	No	No	Trak-Smayra et al. 2011
LRbS1138/1138 ki mice	Yes	Yes	No	No	Jiang et al. 2008
Zucker (fa/fa) rats	Yes	Yes	No	No	Kava et al. 1990
KK-A^{γ} mice	Yes	Yes	No	No	Okumura et al. 2006
ChREBP ko mice	No	Yes	No	No	Iizuka et al. 2004
PPARγ hypomorphic mice	No	Yes	No	No	Koutnikova et al. 2003
A-ZIP/F-1 tg mice	No	Yes	No	No	Moitra et al. 1998
Diphteria toxin tg mice	No	Yes	No	No	Ross et al. 1993
SREBP-1c tg mice	No	Yes	Yes	Yes	Shimomura et al. 1998
nSREPB1α tg mice	No	Yes	Yes	No	Takahashi et al. 2005
Nestin-Cre STAT3 ko mice	Yes	Yes	No	No	Piper et al. 2008
11β-HSD1 tg mice	Yes	Yes	No	No	Morton and Seckl 2008
7B2 ko mice	Yes	Yes	Yes	No	Laurent et al. 2002
STAT5b ko mice	Yes	Yes	No	No	Zhou et al. 2002
IDPc tg mice	Yes	Yes	No	No	Koh et al. 2004
Aromatase ko mice	Yes	Yes	No	No	Nemoto et al. 2000
Alms1 ko mice	Yes	Yes	No	No	Arsov et al. 2006
MTP ko mice	No	Yes	No	No	Raabe et al. 1999
IGF2 tg mice	Yes	Yes	No	No	Rossetti et al. 1996
IMP2-2/p62 transgenic mice	No	No	Yes	No (diet-inducible)	Laggai et al. 2014; Kessler et al. 2014; Simon et al. 2014; Tybl et al. 2011
OLEFT rats	Yes	Yes	Yes	No	Kawano et al. 1992

(*continued*)

Table 1 (continued)

Model	Obesity	Insulin resistance	Inflammation	Fibrosis	Reference
CD36 ko mice	No	No (hepatic)	Yes	No	Coburn et al. 2000
RARα dominant negative tg mice	No	No	Yes	No	Yanagitani et al. 2004
PEMT ko mice	No	No	Yes	Nd	Zhu et al. 2003
IKKγ/NEMO ko mice	Nd	Nd	Yes	Yes	Luedde et al. 2007
AOX ko mice	No	No	Yes	Yes/no	Cook et al. 2001; Fan et al. 1998
MAT1A ko mice	No	No	Yes	Yes	Lu et al. 2001
PTEN ko mice	No	Yes	Yes	Yes	Horie et al. 2004; Stiles et al. 2004
CBS ko mice	Yes	Nd	Yes	Yes	Hamelet et al. 2007
MC4R ko mice	Yes	Yes	Yes	Yes	Itoh et al. 2011
FLS-ob mice	Yes	Yes	Yes	Yes	Soga et al. 2010

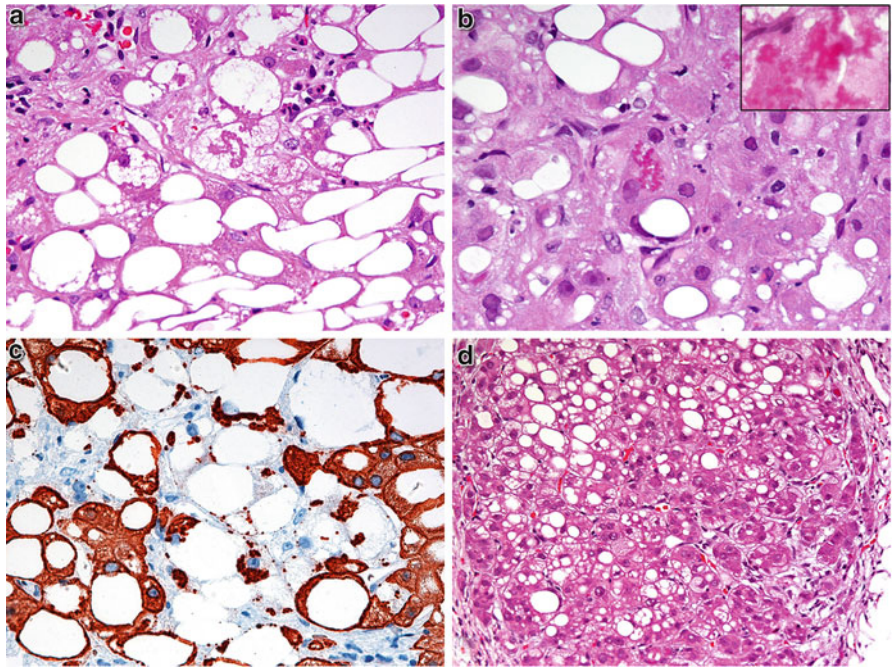

Fig. 1 (**a**, **b**, **c**) Nonneoplastic steatohepatitic liver tissue with multiple eosinophilic irregular intracytoplasmic protein aggregates, positively stained for K8/18 (MDBs) (**a**, **c** magnification 20×, **b** magnification 40×, insert magnification 60×). (**c**) Immunohistochemistry with K8/18 antibody cocktail highlights MDBs. (**d**) Steatohepatitis-associated hepatocellular carcinoma with steatohepatitic features (**d** magnification 10×)

inflammation. Further progression of inflammatory events toward liver fibrosis can be studied in mice, in which an enzyme of the β-oxidation of very-long-chain fatty acids AOX is knocked out. Fibrogenesis is also a morphological feature of methionine adenosyltransferase 1 alpha (MAT1A) knockout mice, in which VLDL secretion is disturbed (Cano et al. 2011).

Only few genetic models combine metabolic disorders with both inflammation and fibrosis. Phosphatase and tensin homolog (PTEN) downregulates phosphatidylinositol 3-kinase

(PI3K), thereby acting as tumor suppressor. PTEN knockout mice develop all steps of NAFLD and can even serve as a model for NASH-associated hepatocellular carcinoma (HCC), since 80-week-old animals bear hepatic adenomas and HCCs (Horie et al. 2004). Cystathionine beta-synthetase (CBS) is involved within the transsulfuration pathway, which builds cystathionine. CBS knockout mice develop not only steatosis but also obesity, inflammation, and fibrosis (Hamelet et al. 2007). Mice with deleted melanocortin 4 receptor (MCR4), which was reported to be mutated in human NAFLD (Vaisse et al. 2000), exhibit inflammation and liver fibrosis. Since MCR4 regulates food intake and lipid metabolism (Balthasar et al. 2005), MCR4 knockout mice show obesity and IR. Crossing fatty liver Shionogi (FLS) mice and ob/ob mice results in FLS-ob mice which become obese and develop distinct clinical signs of diabetes. Furthermore, a progression of steatosis toward steatohepatitis including fibrotic changes is assured (Soga et al. 2010).

8 Hepatocellular Carcinoma

HCC is the fifth most common malignancy worldwide and the third most common cause of cancer-related death (Mann et al. 2007; Salomao et al. 2012). Over the last two decades, the incidence of HCC has increased by 80 %. A related evaluation has been observed in many developed countries including Australia, Canada, Japan, and Western European nations (Bosch et al. 2004; El-Serag and Mason 1999). The distribution of HCC is similar for males and females, although males have a precise higher risk of developing HCC. A geographical shift in HCC incidence and mortality can be traced back to different levels of exposure to HCC-associated risk factors (Bosman et al. 2010). Established risk factors for HCC are chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), hemochromatosis, exposure to aflatoxin, smoking, and alcoholic liver disease (ALD) in developed countries (Salomao et al. 2012; Bosman et al. 2010). The most important causes of HCC are chronic viral infections (HBV, HCV, or coinfection), accounting for approximately 85 % of cases, and the alcohol-induced liver injury extinguishes the most important nonviral risk factor. NAFLD also leads to end-stage liver disease and often belongs to the metabolic syndrome, with NASH. The characteristics for NASH are inflammation, steatosis, and hepatocyte injury, morphologically expressed by ballooning, Mallory-Denk body (MDB) formation, hepatocyte death, and the endpoint cirrhosis (Zhou et al. 2005; Harada et al. 2008; Brunt et al. 2004). In addition, there are signs that NASH describes an important etiology of HCC, at times even in the absence of cirrhosis (Salomao et al. 2012; Guzman et al. 2008). Another variant of HCC in patients' experienced liver transplantation for HCV is referred to as steatohepatitic HCC (SH-HCC). SH-HCC reveals histopathologic features reminiscent of steatohepatitis in nonneoplastic liver, in fact, hepatocyte ballooning, MDBs, inflammation, and pericellular fibrosis (Salomao et al. 2010, 2012). The central clinical issue for HCC is liver cirrhosis, largely independently of its etiology, though cirrhosis itself is now not considered premalignant transformation in the setting of chronic liver disease (Bosman et al. 2010).

The symptoms of HCC include abdominal pain, general malaise, anorexia or weight loss, and nausea or vomiting. In many cases, clinical signs include ascites, fever, hepatomegaly, jaundice, and splenomegaly. HCC may spread by lymphatic and hematogenous routes. The lungs are the most common site of extrahepatic metastasis with 47 %, followed by the lymph nodes with 45 %, bone with 37 %, and the adrenal glands with 12 % (Uka et al. 2007).

8.1 Macroscopy and Histopathology

Most HCCs are nodular lesions and typically softer than the background liver. The macroscopic characteristics diversify to tumor size and the presence or absence of liver cirrhosis. In livers

without cirrhosis, HCC leans to be unencapsulated, while in cirrhosis, HCC often has a fibrous pseudocapsule. HCCs may be unifocal or multifocal; unifocal tumors can grow as single nodules or as clusters of closely approximated and adjacent individual nodules. Multifocality is specified as tumor nodules clearly separated by invasive nonneoplastic liver. Multifocal tumors show either independent HCCs developing simultaneously or intrahepatic metastases from a primary tumor. The macroscopic features of HCC can be further altered by varying degrees of necrosis and tumor participation of portal and hepatic veins (Bosman et al. 2010; Uka et al. 2007).

The classical HCC consists of tumor cells that typically resemble hepatocytes. The stroma consists of sinusoid-like blood spaces lined by a single layer of endothelial cells and shows changes of capillarization. They resemble normal capillaries, including immunohistochemically verifiably factor VIII-related antigen, CD34, Type IV collagen, and subendothelial lamina. In HCC, the portal tracts are not existent; though, at the tumor periphery, entrapped portal tracts may be seen underneath invasive neoplastic cells. HCC is characterized by immunohistochemical staining with antibodies against carbamoyl phosphate synthetase-1 (HepPar1), and the canalicular patterns may be seen with polyclonal antibodies to carcinoembryonic antigen (CEA) or antibodies to CD10 or ABCB1/MDR1. AFP, fibrinogen, and Keratin 8 and 18 are also often positive in HCC but typically negative for epithelial membrane antigen and keratins 19 and 20 (Chu et al. 2002; Enzan et al. 1994; Kimura et al. 1998).

There are different architectural patterns in HCC, the trabecular (platelike) pattern, pseudoglandular or acinar pattern, and the compact pattern. The trabecular (platelike) pattern is the most usual in well- and moderately differentiated HCCs. The pseudoglandular or acinar pattern is usually admixed with the trabecular pattern; the gland-like structure is referred to as pseudoglands or pseudoacini by reason that they are not true glands but modified, between tumor cells abnormal bile canaliculi formed. The compact pattern is common in poorly differentiated tumors. HCC show different cytological variants, such as pleomorphic cells, clear cells, spindle cells, fatty change, bile production, hyaline bodies, pale bodies, and ground glass inclusions (Bosman et al. 2010).

HCCs include special types of carcinomas, the fibrolamellar carcinoma (FLC), scirrhous HCC, undifferentiated carcinoma, lymphoepithelioma-like carcinoma, and sarcomatoid hepatocellular carcinoma. FLC are prominent liver cancers of children and young adults and differ from classical HCC at clinical, histological, and molecular levels (Torbenson 2007). FLC arises in non-cirrhotic livers; etiology and risk factors are not known, and there is no strong gender predilection. The prognosis for FLC is better than for typical HCC that occurs in cirrhotic livers, but the same to typical HCC that occurs in non-cirrhotic livers (Bosman et al. 2010). The scirrhous type of HCC should not be mixed up with cholangiocellular carcinoma (CCC) or FLC. These HCCs show a scirrhous growth pattern characterized by clearly fibrosis along the sinusoid-like blood spaces with different extent of atrophy of tumor trabeculae (Kurogi et al. 2006). Most of these tumors occur directly underneath the liver capsule. Undifferentiated carcinoma is predominant in male, and localization, signs, and symptoms represent no differences compared with hepatocellular carcinoma. Compared with HCC, undifferentiated carcinoma has a worse prognosis (Nemolato et al. 2008; Ishak et al. 1999; Craig et al. 1989). The lymphoepithelioma-like carcinoma is a rare type of HCC, in which the tumor cells tend to be small with focal syncytial growth (Nemolato et al. 2008). In most of the cases, the tumor cells are positive for Epstein-Barr virus (EBV). The histological findings, clinical features, and prognosis are limited because of the rarity of this tumor (Bosman et al. 2010). Frequently, HCC is partly or fully contained of malignant spindle cells and difficult to differentiate from various sarcomas. If this attributes are prominent, the tumor is called sarcomatoid HCC (Kojiro et al. 1989).

8.2 Grading and Prognosis

Four histological grades of HCC are established, based on the tumor differentiation: well differentiated, moderately differentiated, poorly differentiated, and undifferentiated types. The well-differentiated HCC is rare in advanced tumors but common in small, early-stage tumors of <2 cm. The lesions consist of cells with mild atypia and increased nucleus-to-cytoplasm ratio in a thin trabecular pattern, with pseudoglandular structures and fatty change. Moderately differentiated HCC is usual in tumors of >3 cm and has a trabecular growth of three or more cells in thickness. The tumor cells have round nuclei with distinct nucleoli and abundant eosinophilic cytoplasm. In moderately differentiated HCC, you can see a pseudoglandular pattern, and pseudoglands often include proteinaceous fluid or bile. Poorly differentiated HCC grows in a solid pattern without clear sinusoid-like blood spaces. This HCC is extremely rare in small, early-stage tumors. The undifferentiated tumor cells include small cytoplasm, are spindle or round-shaped, and show solid growth (Bosman et al. 2010).

The prognosis for patients with classical HCC is generally very poor (Allgaier et al. 1998; Sugo et al. 1999). In cases of morphologically pure HCC, demonstrating significant immunostaining for keratin 19 has been found to be associated with a poorer prognosis and higher recurrence rates and lymph node metastasis than keratin 19-negative HCC (Uenishi et al. 2003). Many studies report a 5-year survival rate of >5 % in patients with symptomatic HCC. A main problem in established HCCs is that it is widely resistant to radio- and chemotherapy. Established HCCs are mostly resistant to radio- and chemotherapy, though patients have shown in studies response to new agent that inhibits several tyrosine kinases (Boucher et al. 2009). A long-term survival is only present in patients with small asymptomatic HCCs that can be treated by resection, including liver transplantation. The nonsurgical methods for HCC treatment include percutaneous ethanol or acetic acid injection and percutaneous radiofrequency thermal ablation (Bosman et al. 2010).

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Metabolic Syndrome, GERD, Barrett's Esophagus

35

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Contents

Abstract

Gastroesophageal reflux disease (GERD) is on the rise with more than 20 % of the Western population reporting symptoms. GERD is the most common gastrointestinal disorder in the United States. This increase in GERD is not exactly clear but has been attributed to the increasing prevalence of obesity, changing diet, and perhaps the decreasing prevalence of *Helicobacter pylori* infection. Complications of GERD could be either benign or malignant. Benign complications include erosive esophagitis, bleeding, and peptic strictures. Premalignant and malignant lesions include Barrett's metaplasia (BE), and esophageal cancer (EA). Metabolic syndrome is considered a state of chronic inflammation and is strongly associated with circulating levels of C-reactive protein (CRP) and fibrinogen. Chronic subclinical inflammation may be one pathophysiological mechanism explaining the increased risk of GERD and complications of GERD associated with metabolic syndrome. Moreover, among patients with BE, increased levels of leptin and insulin resistance are associated with increased risk for EA. A structured weight loss program can lead to resolution of GERD symptoms in the majority of patients.

Keywords

Obesity • Metabolic syndrome • Esophagus • Cancer

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1 Introduction

1.1 GERD Is a Common Chronic Disorder of the Gastrointestinal Tract

Gastroesophageal reflux disease (GERD) is a highly prevalent disease in Western populations (El-Serag et al. 2014) associated with a decreased health-related quality of life and an increased risk of esophageal adenocarcinoma (Hoyo et al. 2012). The Montreal definition and classification of GERD states that: "GERD is a condition which develops when the reflux of stomach contents cause troublesome symptoms and/or complications," and the definition recognizes that heartburn and acid regurgitation are characteristic symptoms of GERD. Surveys have found that approximately 20 % of all adults in the United States (US) experience GERD symptoms such as heartburn and acid regurgitation at least once each week, and it has been estimated that Americans spend more than $9 billion each year for the evaluation and treatment of this prevalent disorder (El-Serag et al. 2014). Over the past two decades, the incidence of GERD increased in the Western population with the overall prevalence in the general population ranging from 10 % to 20 % (El-Serag 2007; Dent et al. 2005; Locke et al. 1997).

The exact etiology for the rising prevalence of GERD is not clear. While there are no gender or racial predispositions for GERD development (El-Serag et al. 2004; Sharma et al. 2008), various lifestyle factors including increased consumption of dietary fats, smoking, and alcohol and change in body mass index (BMI) are potential risk factors that can lead to GERD (Wang et al. 2004; Nilsson et al. 2004; Becker et al. 1989; El-Serag et al. 2005a). Numerous studies also support a positive association between obesity and GERD (El-Serag et al. 2005b; El-Serag and Johanson 2002; Gunji et al. 2011; Kang et al. 2007; Lee et al. 2006, 2009; Singh et al. 2013a; Tai et al. 2010). In a meta-analysis of 9 reports, an association between BMI and erosive esophagitis was reported in 6 of 7 studies (Singh et al. 2013a). The evidence that supports the link between obesity and reflux symptoms remains significant after adjusting for other previously known risk factors such as the presence of hiatus hernia, smoking, race, gender, family history of GERD, or dietary fat intake.

1.2 Increasing Prevalence of Obesity Has Paralleled Increasing Rates of GERD Worldwide

It is estimated that relative to period before 1995, the rate ratio for GERD prevalence was 1.45 from 1995 to 1999, 1.46 from 2000 to 2004, and 1.51 from 2005 to 2009 (El-Serag et al. 2014). A study done by Jacobsen and his colleagues, where they used a supplemental GERD questionnaire to the Nurses Health Study, showed that a near linear increase in the adjusted odds ratio (aOR) for reflux symptoms was associated within each BMI strata (Jacobson et al. 2006a). Similar results were noted in a study from the Kaiser Permanente Multiphasic Health checkup cohort, in which BMI and GERD were associated with OR of 1.58 among whites, and after adjusting for abdominal circumference, the OR was 1.39 (Corley et al. 2007). Multiple studies from the United States (US) and Europe examined an increase in the prevalence rate of GERD in parallel with overweight and obesity. The German National Health Interview and Examination Survey estimated the OR for GERD to be 1.8 for overweight patients and 2.6 for obese individuals (Chang and Friedenberg 2014). Similarly the results from the Bristol Helicobacter Project showed that obese patients have odds ratio (OR) of 2.91 for presence of heartburn (Murray et al. 2003a). In Spain, a telephone survey showed obese individuals to be at 1.74 higher odds for developing GERD symptoms (Nilsson et al. 2003a). Kang and colleagues studied 2457 patients who underwent upper endoscopy in Korea and noted a positive relationship between higher strata of BMI and the presence of erosive esophagitis (Kang et al. 2007). In summary, several population-based studies support the association between obesity and GERD reflux. Such an association has been noted in the

United States where obesity rates are the highest but also noted in Europe and Asia.

1.3 Dose–Response Relationship Between Increasing BMI and Central Obesity with GERD

In a telephone survey based in Spain, it was shown that patients with GERD symptoms for more than 10 years were 1.92 times more likely to be obese (Nilsson et al. 2003a). Moreover this study showed that a weight gain of more than 5 kg in the past year was associated with a 2.7 times higher risk of new onset GERD symptoms. In a survey performed in Norway, the prevalence of GERD in morbidly obese men and women was noted to be 3.3 and 6.3, respectively (Nilsson et al. 2003a).

1.4 Clinical Correlation Between Complications of GERD and Metabolic Syndrome

The well-known complications of GERD include erosive esophagitis (EE), Barrett's esophagus (BE), and esophageal adenocarcinoma. A previous large endoscopic study by El-Serag et al. showed that compared to those with no esophageal erosions, those with EE were more likely to be overweight or obese (El-Serag et al. 2005b). Based on an endoscopic study in Korea studying 3,000 participants, obese individuals compared to normal weight subjects had an OR of 3.3 for EE (Lee et al. 2009). A meta-analysis by Hampel et al. confirmed the association with increasing levels of obesity and esophageal mucosal injury (Hampel et al. 2005a).

From 1975 to 2001, the incidence of esophageal adenocarcinoma rose approximately sixfold. Obesity was associated with an OR of 16.2 for the development of adenocarcinoma compared with the leanest individuals (BMI <22 kg/m^2) (Hoyo et al. 2012; Chow et al. 1998). A recently pooled analysis (Atherfold and Jankowski 2006; DeMeester 2001) from 12 worldwide epidemiological studies showed that patients with a BMI of ≥ 40 compared to non-overweight patients had an OR of 4.76 for esophageal adenocarcinoma (Chow et al. 1998).

2 Metabolic Syndrome and Barrett's Esophagus

Barrett's esophagus (BE) is a precancerous condition that is considered to arise as a complication of gastroesophageal reflux disease (GERD). BE is associated with a 30–40-fold increased risk of developing esophageal adenocarcinoma (Atherfold and Jankowski 2006; DeMeester 2001; Festa et al. 2001). The incidence and mortality from esophageal adenocarcinoma have increased by more than fivefold in the Western populations in the past three decades, and these trends have paralleled the increasing prevalence of obesity in many countries. Epidemiological evidence strongly links obesity with esophageal adenocarcinoma.

2.1 Pathophysiology

There is evidence that the prevalence of GERD is increasing in the United States, a phenomenon that may be related to the increasing prevalence of obesity in this country (El-Serag et al. 2004; Sharma et al. 2008). Several studies have suggested that weight gain and/or obesity can play a major role in the development of GERD (El-Serag et al. 2005a; Delgado-Aros et al. 2004; Nilsson et al. 2003b; Jacobson et al. 2006b; Kulig et al. 2004; Murray et al. 2003b; Hampel et al. 2005b; Locke et al. 1999) through mechanical changes in the gastroesophageal junction and/or altered metabolic milieu from visceral fat (lower adiponectin and increase in interleukin-1β, tumor necrosis factor-α) (Festi et al. 2009).

The mechanical effect of obesity is a widely accepted mechanism by which adiposity amplifies intragastric pressure and disturbs normal sphincter function and promotes GERD. However, it has to be noted that in addition to the mechanical effect, metabolic syndrome also confers a systemic inflammatory state which could increase the risk of BE and represent a potential indirect mechanism

by which increasing adiposity is associated with BE. Acid reflux in the lower esophagus induces secretion of various pro-inflammatory cytokines including IL-8, IL-6, IL-1, NF-Kappa, and TNF-alpha. This systemic inflammatory state consequent on the altered metabolism in obese patients and the associated impact of adipokines, cytokines, and procoagulant factors released by the adipocytes, particularly central fat, manifests in the metabolic syndrome. Moreover, the chronic acid and inflammation induced by GERD damage the native stratified squamous epithelium, and without repair, cells become necrotic and are replaced with metaplastic BE. Recent data from a case control study recruited from primary care clinics compared to colonoscopy and endoscopy controls suggests that obesity, as part of the metabolic syndrome, increases the risk of BE, independent of GERD (Thrift et al. 2015).

3 Weight Loss and GERD Symptoms

The Nord-Trøndelag Health Study (HUNT 3) surveyed 44,997 people from 2006 to 2009 and found that weight loss was dose dependently associated with a reduction of symptoms (Ness-Jensen et al. 2013). A prospective cohort study of 332 obese adults enrolled in a structured weight loss program was performed by Singh and others, and the mean weight loss was 13 kg and the prevalence of GERD decreased from 37 % to 15 %, with 81 % of subjects experiencing a reduction in symptom scores (Singh et al. 2013b).

4 Bariatric Surgery and GERD

Bariatric surgical procedures can be classified as restrictive, malabsorptive, or both. In the restrictive procedures, the gastric anatomy is altered to reduce gastric volume to induce early satiety which in turn leads to weight loss. De Groot et al. performed a systematic review on bariatric surgery and the effects on GERD. They identified eight studies that evaluated GERD symptoms after RYGB and three studies that compared RYGB to other weight loss techniques with respect to GERD symptoms (De Groot et al. 2009; Tutuian 2014). Few studies showed an improvement in GERD symptoms after RYGB. Most of the studies included in the systematic review used questionnaires, and only four of the eleven studies used objective measurements (i.e., endoscopy, 24-h pH monitoring) to define GERD (Merrouche et al. 2007; Pallati et al. 2014; Saber 2014; Tolonen et al. 2006).

In a recent systematic review by Chiu et al. which included 15 studies, four studies found a postoperative increase in GERD prevalence, seven showed reduced prevalence, and in four studies, the prevalence before and after surgery could not be determined. As with most studies examining the effects of bariatric surgery on GERD, there was significant heterogeneity between studies including differences in follow-up time ranging from 6 months to 5 years, differences in the case definition of GERD, and lack of control groups. As is the case with laparoscopic adjustable gastric banding (LAGB), it is difficult to conclusively determine the effects of sleeve gastrectomy on GERD (Chiu et al. 2011). Recent studies indicate that laparoscopic gastric banding and laparoscopic sleeve gastrectomy have little influence on preexisting GERD symptoms and findings, but some patients may develop GERD after laparoscopic sleeve gastrectomy (Altieri and Pryor 2015; El-Hadi et al. 2014; Laffin et al. 2013). A number of studies have documented that laparoscopic Roux-en-Y gastric bypass (RYGB) improves GERD symptoms and findings, making it the preferred procedure for morbid obese patients with concomitant GERD (Altieri and Pryor 2015; El-Hadi et al. 2014; Laffin et al. 2013).

5 Conclusions

The most important risk factor for the development of BE is the reflux of gastric contents into the esophagus. The precise mechanisms responsible for the transition of the normal squamous epithelium of the esophagus into columnar epithelium are unclear, but it is likely that stem cells and

tumorigenic mechanisms are involved in the progression from columnar metaplasia to esophageal adenocarcinoma. Central obesity is common in both GERD and BE. Studies indicate that mechanical and metabolic factors associated with central obesity are involved in the pathogenesis and progression of BE to esophageal adenocarcinoma. Mechanical effects of abdominal fat disrupt the gastroesophageal reflux barrier. Insulin resistance associated with central obesity, pro-inflammatory cytokines, and adipokines is likely to potentiate reflux-mediated inflammation and mediate the pathogenesis of BE and esophageal adenocarcinoma. A better understanding of the mechanisms linking obesity and metabolic syndrome to GERD and BE would lead to effective preventive and treatment strategies.

6 Cross-References

- Adipokines and Metabolism
- Bariatric Surgery
- Body Composition Assessment
- Carbohydrate, Fat, and Protein Metabolism in Obesity
- Diet and Obesity (Macronutrients, Micronutrients, Nutritional Biochemistry)
- Diet, Exercise, and Behavior Therapy in the Treatment of Obesity and Metabolic Syndrome
- Gut Hormones and Obesity
- Insulin Resistance in Obesity
- Overview of Metabolic Syndrome
- Pharmacotherapy of Obesity and Metabolic Syndrome

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Sarcopenic Obesity

36

John A. Batsis

Contents

Abstract

An aging population in conjunction with a worsening obesity epidemic worldwide is leading to a public health epidemic of older adults with considerable mobility limitations. Loss of muscle mass and function with age is termed sarcopenia and is a natural phenomenon of the aging process, which is aggravated with coexistent obesity. These persons with sarcopenic obesity are thought to be at higher risk of adverse outcomes than of people with either sarcopenia or obesity alone. Emerging consensus in identifying patients will provide a standardized manner in developing clinical trials that will lead to modification of body composition and improvement of physical function. Recommended multicomponent management strategies consisting of dietary and exercise modifications are safely recommended for weight loss and mitigation of worsening of sarcopenia. Promising and emerging therapies have potential to alter body composition and muscle physiology with a goal of improving primary and secondary outcomes in this subgroup of patients.

Keywords

Sarcopenia • Obesity • Physical function • Elderly

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Abbreviations

BMI	Body mass index
FNIH	Foundation for the National Institutes of Health
NHANES	National Health and Nutrition Examination Survey
SarcO	Sarcopenic obesity

1 Introduction: An Aging Population

While the population in the United States and other countries is increasing (Census Bureau Statistics 2012), the proportion of those aged 65 years and older are the fastest rising group. Two major reasons have contributed to these trends. First, the baby boomer population, those born between 1946 and 1964, are now in the "geriatric" age-group (Census Bureau Statistics 2012). Second, there has been an increase in life expectancy in all countries; in particular, this has been observed in developed countries (Lubitz et al. 2003; Katz et al. 1983). Life expectancy at birth of a person born in the year 1900 was 47 years, while a person born in the year 2010 is predicted to live to 76 and 81 years in males and females, respectively. Put differently, a 65-year-old was predicted to live another 13.9 years in year 1900, as opposed to a 65-year-old in the year 2010 believed to live another 17.9 years (Centers for Disease Control Vital Statistics 2012). Improvements in primary and secondary cardiovascular disease prevention are the predominant reasons for these changes (Ford et al. 2007).

As one ages, the number of chronic medical illnesses rises. In one study of Medicare beneficiaries, 82 % had >1 chronic medical conditions and 65 % had multiple problems (Wolff et al. 2002). An aging multi-morbid older adult is at higher risk for incident disability (Dunlop et al. 1997). Impaired function (Table 1) is a primary geriatric syndrome which leads to functional decline, frailty (Fried et al. 2001), and death (American Geriatrics Society 2012), all of which increase healthcare utilization and result in loss of independence. Secondary outcomes of interest that are patient-specific include quality of life, which drops with higher rates of comorbidity (Chambers et al. 2002) and disability (Rosemann et al. 2008). The rise in the number of older adults, and in particular those oldest old (>age 80 years) who are the fastest growing subset (Census Bureau Statistics 2012), results in comorbidity and disability which will impact health in a significant manner.

Table 1 Functional status – activities of daily living (Katz et al. 1963; Lawton and Brody 1969)

Basic	Instrumental
Bathing	Shopping
Dressing	Housekeeping
Transferring from bed to chair	Preparing meals
Toileting	Taking medications
Eating	Finances
Walking	Using transportation
	Making phone calls

2 Obesity

Obesity is a known public health concern that has drawn considerable attention in the adult and pediatric populations. According to recent epidemiologic surveys, prevalence of obesity measured by body mass index is 34.9 % (Ogden et al. 2014), rising from 14.1 % in 1971–1974 (Flegal et al. 1998). While the rate of change has dropped (Lopez-Jimenez et al. 2009), overall prevalence is still increasing with over 65 % of the US population classified as having obesity or overweight (BMI of 25–29.9 kg/m^2). Changes in body composition occur with age (Baumgartner 2000). Loss of skeletal muscle mass and increases in visceral adiposity with age make BMI a relatively inaccurate index in older subjects as compared to younger populations (Okorodudu et al. 2010; Romero-Corral et al. 2008). However, little attention has been paid to the impact of obesity in older adults although prevalence rates are thought to parallel those of the general population. The rise in the number of older adults aged 65 years and older will lead to larger numbers of persons with obesity.

The relationships between obesity and hypertension, hyperlipidemia, diabetes, sleep apnea (Gregg et al. 2005), and other disorders including osteoarthritis (Ambrose et al. 2010) and cancer have been well established epidemiologically (Reeves et al. 2007). Obesity is also associated with cognitive dysfunction (Hassing et al. 2009). These relationships exist even in older adults. The risk of cardiovascular disease is heightened in older adults (Lopez-Jimenez et al. 2009). Yet, people with obesity often die prematurely. In one study, having obesity is associated with approximately 112,000 excess death in the United States as compared to not having obesity (Flegal et al. 2005).

It has been hypothesized that there are likely subtypes of obesity, including those with and without "metabolic abnormalities" (Kramer et al. 2013). There likely is a component of genetic predisposition to surviving, and further research is needed to better identify patients at lower risk. Both duration of obesity during the life span (Houston et al. 2009) and obesity at the age of 65 years are associated with increased risk of physical impairments, disability (Houston et al. 2009), and nursing home placement (Zizza et al. 2002). Using 7-year follow-up data from the Health, Aging, and Body Composition Study, in 2,845 community-dwelling US adults, men and women who were overweight or obese at all three designated time points had increased risk of mobility limitations compared to normal weight (HR 1.61 [1.25–2.06] and 2.85 [2.15–3.78]) (Houston et al. 2009). Whether functional impairment is due to increased load on joints or metabolic changes is currently under study of investigation. One subject of controversy is the manner in which obesity is ascertained, whether it be by anthropometric measures (and which ones) or by radiological means. Irrespective of its assessment, it is well accepted that obesity is detrimental to overall function in older adults (Schaap et al. 2012). A recent systematic review by Schaap et al. noted a risk ratio of 1.60 [1.43, 1.80] of impaired function in those with a BMI $\geq$ 30 kg/m^2. In addition, body fat assessed by bioelectrical impedance is associated with a risk of impaired function (Batsis et al. 2014b).

We caution that the majority of studies use BMI as a surrogate for obesity. While this anthropometric measure is practical and easy to measure clinically, it does have a number of limitations. First, patients lose height as they age (Sorkin et al. 1999). Second, with changes in body composition, weight does change (Williamson 1993). Third, a BMI cutoff of 30 kg/m^2 is classified as obesity and this cutoff was based on older epidemiological studies (Physical status: the use and interpretation of anthropometry. Report of a WHO expert committee 1995). In fact, in older adults, a BMI of 26–27 kg/m^2 is associated with the lowest mortality (Kuk and Ardern 2009). Lastly, BMI accounts for both fat mass and muscle mass and may poorly reflect specific differences in body composition. For instance, a 30-year-old male who is a body builder has very little fat mass with considerable proportion of muscle mass; however, this patient may inadvertently be classified as having obesity. As will be discussed below, BMI fails to account for the changes in muscle mass and quality with aging. Other measures of assessing obesity and fat can be considered including waist circumference and body fat. While a discussion on these measures is outside the scope of this chapter, solely using BMI can be problematic in that there is a subset of persons with elevated central adiposity that are at higher risk of disability (Batsis et al. 2014b) and mortality (Batsis et al. 2013b), both in cross-sectional and longitudinal studies (Batsis et al. 2015).

3 Sarcopenia

An under-recognized and under-characterized phenomenon in clinical medicine is that of sarcopenia. This term was initially coined in 1989 by Rosenberg to characterize the natural reduction of muscle mass with aging. The word sarcopenia is derived from the Greek word "sarcos" meaning flesh and "penia" meaning lack of. The concept of sarcopenia is located on the spectrum of frailty and disability (Cruz-Jentoft et al. 2010). Muscle mass increases with age until 30–40 years of age and then starts decreasing in the fourth decade of life (Fig. 1). Below a given

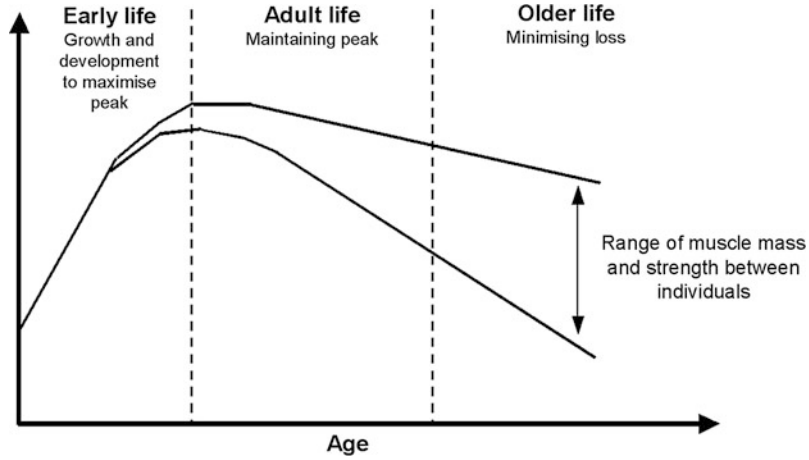

Fig. 1 Muscle mass and function during the life cycle. Muscle mass and function increases in early in life, peaks in the third and fourth decades, and then decreases in later life

threshold of muscle mass, it is believed that patients are at risk for disability (Sayer et al. 2008). The trajectory of muscle loss can be altered with physical exercise and/or environment changes. This age-related decline parallels that observed with bone mass (Warming et al. 2002), whereby, once bone mass reaches a critical level, one's risk of a fracture is increased (Kanis et al. 2008). While sarcopenia is primarily a disease of the elderly, it may be associated with other chronic health conditions seen in younger patients, including disuse, malnutrition, and cachexia (Morley et al. 2009).

The definition of sarcopenia has evolved considerably over the years and has led to considerable confusion in identifying the natural history and course of this geriatric syndrome. The European Working Group for the Study of Sarcopenia in Older People (Cruz-Jentoft et al. 2010) developed a clinical algorithm to identify those with sarcopenia. This group included muscle quality/strength in their definition of sarcopenia. Definitions of sarcopenia in the past were primarily based on muscle mass. However, such definitions accounted for both total-body skeletal muscle mass and appendicular skeletal muscle mass, often adjusted for height in meters squared. Many of the threshold definitions were based on epidemiological studies of a healthier population, based on two standard deviations below the population mean, or based on the bottom two quintiles of a given target population (Batsis et al. 2013a). Basing threshold definitions on mathematical definitions and distributions and not proven clinical outcomes led in part to such disparate definitions. A recent analysis noted that the prevalence of sarcopenia (and sarcopenic obesity) ranged markedly depending on the definition used (Batsis et al. 2013a). Many advocated the need to create thresholds and cutoffs that corresponded to validated clinical outcomes such as disability, mortality, and institutionalization (Cruz-Jentoft et al. 2010). This consortium recommended incorporating muscle mass and function (strength or performance) into the definition of sarcopenia for its diagnosis.

In 2013–2014, the Foundation for the National Institutes of Health Sarcopenia (FNIH) project (Studenski et al. 2014) formed a consensus group to develop clinically appropriate threshold measures to predicted incident disability and adverse outcomes. Based on epidemiological studies (McLean et al. 2014; Dam et al. 2014; Cawthon et al. 2014; Alley et al. 2014), muscle strength is more predictive of impaired function than muscle mass. Muscle mass, in fact, was believed to indirectly impact function in community-dwelling older adults. Low muscle mass is associated with weakness or dynapenia, which itself is strongly associated with reduced function. However, low muscle mass is less likely to be associated with impaired function, as muscle strength is (Schaap et al. 2012). Hence, the causal pathway between muscle mass and strength to

Table 2 Cut points for weakness and low lean mass (Studenski et al. 2014)

Cut point	Males	Women
Weakness		
Grip strength	<26 kg	<16 kg
Grip strength adjusted for body mass index	<1.0	<0.56
Appendicular lean body mass (ALM)		
ALM adjusted for BMI	<0.789	<0.512
ALM	<19.75 kg	<15.02 kg

Table adapted from the Foundation for the National Institutes of Health Sarcopenic Project. Grip strength measured using a dynamometer
BMI body mass index, *ALM* appendicular lean mass

function is now being challenged. In fact, there are likely two patient phenotypes: those with weakness but with preserved muscle mass and those with low muscle mass leading to weakness. This consortium identified a number of large-scale epidemiological studies to ascertain these relationships and selected mobility impairment as a primary outcome (gait speed <0.8 m/s) as such a measure predicts mortality and disability (Studenski et al. 2011). Table 2 outlines the current thresholds and cutoffs that have been proposed for use in clinical and research practice.

Prevalence estimates range depending on the definition used. One author has estimated that a conservative estimate is that it may affect >50 million persons today and >200 million in the next 40 years (Santilli et al. 2014), and that its estimated direct health cost in 2000 was $18.5 billion (Janssen et al. 2004).

4 Sarcopenic Obesity

The confluence of sarcopenia and obesity in an aging population has the potential to lead to synergistic impairment of function. Individuals with sarcopenic obesity (SarcO) constitute a combination of fulfilling criteria for both sarcopenia and obesity. It is expected that the prevalence of sarcopenic obesity will rise with the concomitant risk in older adults. Recent estimates suggest that the prevalence of SarcO ranges 18-fold (Batsis et al. 2013a). There are no recent prevalence studies that incorporate the new FNIH guidelines for SarcO at this time.

Importantly, while the definition of sarcopenia has been debated, the definition of obesity used also is a matter of debate. BMI is used clinically; however, it has poor specificity in identifying older adults with obesity, missing obesity in over 50 % of patients (Okorodudu et al. 2010). Waist circumference is another proposed anthropometric measure used in cohort studies examining prevalence and outcomes of SarcO (Stenholm et al. 2008). Traditional metabolic syndrome cutoffs of 88 cm in females and 102 cm in males can be used (Batsis et al. 2007). Percent body fat can also classify subjects with obesity. However, as with muscle mass, measurement with CT scanning, MRI scanning, bioelectrical impedance, or dual-energy X-ray absorptiometry scanning is needed to quantify these values. As with differing thresholds, combining two measures with variable thresholds increases the variability in the estimates obtained (Batsis and Lopez-Jimenez 2010). For SarcO, to avoid the controversies in using BMI as a measure for obesity, one can consider using more sophisticated methods to ascertain body fat and use cutoffs proposed by professional recommendations as a guideline.

4.1 Common Underlying Mechanisms + Theoretical Framework

The underlying pathophysiology and mechanisms to explain the development of SarcO are unclear. While common inflammatory pathways have linked sarcopenia and obesity, the interplay is still poorly understood. Studies now demonstrate that the alterations observed in body composition are likely due to fat infiltration of the muscle leading to lower muscle quality and work performance (Villareal et al. 2004). There may indeed be some potentiation of each entity on each other. Fat and muscle are both metabolically active. For instance, excess energy intake, physical inactivity, low-grade inflammation, and insulin resistance due to losses of skeletal muscle result in

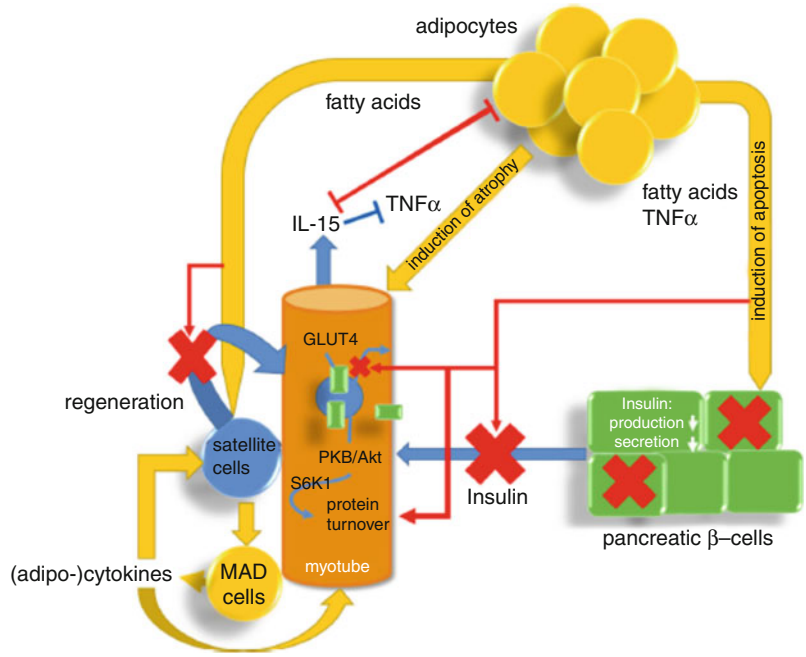

Fig. 2 Possible pathways involved in sarcopenic obesity are presented. Pathways which favor proper functionality of the skeletal muscle are depicted in *blue*, blocking of these pathways by obesity is shown in *red*. An excess of fatty acids in the organism leads to apoptosis of pancreatic β-cells (*green*) and consequently to reduced secretion of insulin. This results in deregulation of the muscular PKB/Akt pathway and a decreased translocation of GLUT4 transporters leading to insulin insensitivity. Moreover, protein turnover is altered due to changes in S6K1 activity. Secretion of IL-15, a paracrine anabolic myokine, is suppressed by adipose tissue. Hence, TNF-α induces muscle atrophy by stimulation of apoptosis as well as by upregulation of the proteasomal decay of filament proteins. Satellite cells dedifferentiate to an adipocyte-like phenotype stunting regeneration of muscle fibers. With multimorbidity: an approach for 2012

alterations of hormonal homeostasis in the development of SarcO (Santilli et al. 2014). Production of adipokines and pro-inflammatory cytokines (IL-6, TNF-a) by adipocytes or infiltrating macrophages in adipose tissue can induce C-reactive protein in the liver. Additionally, the association of C-reactive protein with low handgrip strength and high body fat suggests underlying inflammation as a causative factor (Stenholm et al. 2008). Leptin and low adiponectin concentrations negatively impact muscle mass leading to reductions in muscle quality (Hamrick et al. 2010). In fact, leptin resistance has been hypothesized as an underlying mechanism linking atherosclerosis and metabolic syndrome (Sweeney 2010) and in one study has demonstrated that it is negatively related to appendicular skeletal muscle mass adjusted for fat mass (Waters et al. 2008). Further data from the InCHIANTI study has demonstrated that global and central obesity negatively affect muscle strength leading to the development and progression of sarcopenic obesity (Schrager et al. 2007). All these findings suggest that there may be a higher risk of cardiovascular disease in those patients with SarcO. Additionally, high levels of circulating free fatty acids appear to play a role in the development of SarcO (Stenholm et al. 2008). The pathogenesis is undoubtedly complex which has been nicely summarized by Kob et al. (2015) (Fig. 2). With the increase in fat occurring with aging and the drop in muscle mass, excess fatty acids deposit in extra-adipose tissues, possibly leading to lipotoxicity and thus to insulin resistance. Deposition of fat into muscle alters their morphology, size, and function, and protein turnover occurs.

5 Consequences and Implications on Function in Older Adults

Irrespective of the challenges in defining SarcO, most past studies used a combination of muscle mass and BMI to define this entity. The impact of sarcopenia and obesity on physical performance has been increasingly studied. Using bioelectrical impedance, sarcopenic obesity subjects in a Taiwanese cohort were worse than their counterparts in physical performance (Chang et al. 2014). Initial epidemiologic studies, however, demonstrated inconsistent results on impairment of function (Bouchard et al. 2009; Davison et al. 2002). SarcO is related to subjective impairment in physical performance (Auyeung et al. 2013), including falls (Baumgartner et al. 1998). Baumgartner et al., using the New Mexico Aging Process Health Study, noted that the risk of incident disability was a HR 2.63 [1.19, 5.85] over the course of an 8-year follow-up (Baumgartner et al. 2004). The EPIDOS study in Europe noted that SarcO had a 2.60 higher odds of having difficulty climbing stairs and 2.35 higher odds of difficulty going down stairs than those without any of these entities (Rolland et al. 2009). A study using the Quebec Longitudinal Study (Nutrition as a Determinant of Successful Aging) compared four groups of high/low muscle mass and high/low obesity and examined their physical function characteristics (Bouchard et al. 2009). Interestingly, their results did not demonstrate that SarcO had lower physical capacity as compared to nonsarcopenic/obese individuals in this cohort. What was clear from this study was the impact of obesity on function. Inflammatory markers, including C-reactive protein, and homeostasis model assessment (IR_{HOMA}) were higher in subjects with SarcO in NHANES 1999–2004 (Levine and Crimmins 2012) and also in the InCHIANTI study (Schrager et al. 2007), suggesting that pro-inflammatory cytokines may be critical in both the development and progression of SarcO. Certain studies have demonstrated important associations between SarcO and important functional measures. For instance, using a sample from a community-based cohort of 1,655 older adults suggested that fat mass negatively impacts domains of physical performance and overall functioning and that its interrelation with lean mass importantly impacts these estimates (Sternfeld et al. 2002).

The Korean National Health and Nutrition Examination Survey (NHANES) had considerable data on older adults. These authors observed, in a cross-sectional analysis, that SarcO was associated with radiographic knee osteoarthritis (OR 3.51 [2.15–5.75]) as opposed to those with sarcopenia and obesity (OR 2.38 [1.80–3.15]) (Lee et al. 2012). A specific SarcO study performed in South Korea has been instrumental in better characterizing the associations between this entity and important geriatric outcomes. While there are inherent ethnic differences in body composition, their population focused predominantly on an Asian population. Applying the National Cholesterol Education Program-Adult Treatment Panel III guidelines to the Korean NHANES cohort, those with SarcO had a higher risk for dyslipidemia (OR 2.82 [1.76–4.51]) than the other groups (Baek et al. 2014). The risk of metabolic syndrome was elevated in those with SarcO (OR 3.24 [1.21, 8.66] in both females and 5.13 [0.90–29.30] in males) (Kim et al. 2009). This was confirmed in a longitudinal study noting that SarcO was at higher risk for metabolic syndrome (OR 8.28 [4.45–15.40]) than either obesity or sarcopenia alone (Lim et al. 2010). This same cohort demonstrated that over a period of 28 months, visceral fat was associated with future loss of skeletal muscle mass in Korean adults (Kim et al. 2014).

5.1 Mortality

The relationship between sarcopenia and obesity and mortality has been investigated with emerging new data. The prospective Cardiovascular Health Study of 3,336 community-dwelling older adults free of cardiovascular disease at baseline classified subjects having SarcO based on measures of muscle mass or strength and waist circumference (Stephen and Janssen 2009). After

a mean follow-up of 8 years, there was a 23 % increased risk of death [95 % CI: 0.99–1.54; $p = 0.06$] within the SarcO group. Using the British Regional Heart Study of men aged 60–79 years ($n = 4{,}252$), SarcO patients, classified using WC and mid-arm muscle circumference, were found to have markedly higher mortality rates (HR 1.72 [1.35, 2.18]) than in those with sarcopenia or obesity alone (Atkins et al. 2014). Interestingly, this group also used fat-free mass index and fat mass index to define SarcO but found no significant relationships using these measures. Using data from the NHANES III, SarcO defined using body fat and total skeletal muscle mass adjusted for height^2 cutoffs had a higher mortality risk in woman (HR 1.35 [1.05–1.74]) than in males (0.98 [0.77–1.25]). The data thus far suggests that SarcO likely is associated with an increased risk of mortality. Further evaluation with recent recommended thresholds and cutoffs are needed, and sex-specific analyses would be helpful in identifying whether differences indeed are present.

6 Management of Sarcopenic Obesity

To date there have been no formal guidelines for the management of SarcO. Due to disparities in defining this entity, there have been few clinical trials examining possible interventions in reducing fat and preserving muscle. In addition, there lack a number of primary outcomes for the design of such trials. Recently, the European Working Group (Cruz-Jentoft et al. 2010) identified three primary outcome variables in sarcopenia, including muscle mass, muscle strength, and physical performance. A number of additional secondary outcomes have been proposed as well (Table 3).

Table 3 Proposed outcomes from the European Working Group for the study of sarcopenia in older adults (Cruz-Jentoft et al. 2010)

Primary outcome domains	Physical performance
	Muscle strength
	Muscle mass
Secondary outcome domains	Activities of daily living
	Quality of life
	Metabolic and biochemical markers
	Markers of inflammation
	Global impression of change by subject or physician
	Falls
	Admission to the hospital or nursing home
	Social support
	Mortality

6.1 Nutritional Recommendations

The Society for Sarcopenia, Cachexia, and Wasting Disease convened an expert panel for nutritional management of sarcopenia and based on a literature review drafted recommendations (Morley et al. 2010). As aging is associated with physiological anorexia, a high risk of inadequate protein intake occurs. Their report found that no older persons ingest protein to account for 35 % of the total macronutrient distribution. A positive relationship between protein ingestion and muscle mass has been observed (Abellan van Kan et al. 2008; Heath and Stuart 2002). Additionally, older persons synthesize less protein. This task force recommended that a balanced protein and energy supplement may be useful in preventing and reversing sarcopenia and that total protein amounts to 1–1.5 g/kg/day. Additionally, leucine-enriched essential amino acids should be considered. Some reported studies in their report suggest the addition of creatine to enhance the effects of exercise in patients with sarcopenia, although long-term studies are needed.

Vitamin D levels are known to decline with age, and deficiencies are associated with reduced muscle strength, statin myopathy, reduced function, falls, and fractures (Holick et al. 2011; Wicherts et al. 2007). Vitamin D replacement is associated with reduced mortality (Zittermann et al. 2012) and hence should be considered as part of the multimodal approach to care. Doses of 50,000 units can be considered in older adults in the form of vitamin D2 or vitamin D3 (American Geriatrics Society Workgroup on Vitamin 2014).

7 Lifestyle Modifications

Weight loss is the cornerstone of management in older adults with SarcO yet still remains controversial in clinical practice due to the loss in muscle mass that can occur leading to worsening sarcopenia (Villareal et al. 2004). A limited number of clinical trials focusing exclusively on older adults have been published (Beavers et al. 2014; Messier et al. 2013; Shea et al. 2010; Villareal et al. 2011). As with any lifestyle modification program, the cornerstones of management include dietary (caloric) restriction, behavioral counseling, and physical activity. Weight reduction of 5–10 % can lead to comorbidity resolution. A recent benefit available to Medicare beneficiaries has led to reimbursable models for primary care clinicians to counsel older adults with obesity (Batsis et al. 2014a).

The mean age of participants in the Look AHEAD trial, a major randomized trial focusing on weight, was 59 years (Look 2014). This trial examined the effectiveness of an intensive lifestyle modification program, tailoring meetings to reduced calorie intake and physical activity. The intervention group demonstrated improved functional status, more physical activity, improved cardiovascular risk profile, and higher metabolic equivalents. The ADAPT (Arthritis, Diet, and Activity Promotion Trial) (Messier et al. 2013) observed reduced mortality in the subset of older adults at 18 months. An important randomized trial by Villareal (Villareal et al. 2011) highlighted the differences between individual diet or physical activity therapy, combination therapy, and standard care in older frail individuals. Weight loss led to improvements in physical function and quality of life. Importantly, though, lean mass was mitigated with the resistance training and frailty prevalence was reduced. While lean mass was modestly reduced, there were continued improvements in objective physical performance, suggesting that weight loss may be a suitable intervention for the treatment of SarcO.

A multidisciplinary program is important with any type of lifestyle intervention, not only to reduce fat mass and increase lean mass but to improve cardiovascular fitness. The American College of Sports Medicine has presented recommendations for physical activity(Garber et al. 2011) consisting of both aerobic and resistance, flexibility, balance, and vestibular exercises. Exercise results in improved muscle protein synthesis (Atherton and Smith 2012), increased intramuscular IGF-1 (Burke et al. 2008), improved skeletal muscle sensitivity to insulin (Rabol et al. 2011), and reduced inflammatory gene expression (Linden et al. 2014). The recent multicenter, randomized LIFE study (Pahor et al. 2014) demonstrated that in 1,635 older adults aged 70–89 years with physical limitations, the risk of persistent mobility disability was lower in the intervention care group than the standard care (HR 0.72 [0.57–0.91]), with no significant differences in serious adverse events in a 2.6-year follow-up. Their results suggested the benefit and potential for structured physical activity programs in older adults at risk and vulnerable, despite incident functional decline. While this cohort was not specific to those with SarcO, it provides a reasonable foundation for future studies in this subgroup. Additionally, the mean BMI was 30 kg/m^2.

7.1 Emerging Pharmacotherapy

While a number of therapies are being currently tested in the phase I trials and in rodent models, therapies that have been trialed in the past but have been unsuccessful or fraught with challenges. Testosterone concentrations drop with aging and parallel the changes observed in body composition with aging. While hypogonadal males appear to have some benefit with therapy (Behre et al. 2012), disparate results have been seen with healthy older males (Emmelot-Vonk et al. 2008). For instance, testosterone therapy with exercise altered body composition favorably by reducing fat mass and increasing skeletal muscle but did not alter physical performance. Other studies have observed similar findings. However, the Food and Drug Administration has placed a warning on supplementation with testosterone and adverse events (Fernandez-Balsells et al. 2010) including erythrocytosis, prostate cancer,

blood clots, stroke, myocardial infarction, and heart failure (Xu et al. 2013).

A potential contributing factor to the development of SarcO is a decline in growth hormone and IGF-1 synthesis. While supplementation appears physiologically plausible, clinical studies have again been fraught with disappointment and adverse events (Nair et al. 2006). Emerging analogs are being studied that potentially can alter body composition, and future studies should examine their effects on physical function. A systematic review of DHEA therapy demonstrated changes in body composition (Baker et al. 2011), but future studies are needed to determine whether it impacts physical function.

8 Future Directions

The phenotype of sarcopenic obesity is gaining traction in both the research and clinical realms. The "fat frail" older adult is at high risk for adverse events and utilization. Standardized definitions related to outcomes are needed for both sarcopenia and obesity. Understanding the basic biological mechanisms will assist in drug targeting and development in the future. By identifying such subjects in clinical practice, practitioners could prescribe lifestyle modifications consisting of weight loss and exercise programs to lose weight and preserve/augment muscle mass and quality. Clinical trials are desperately needed to test both known and experimental interventions that potentially prevent or reverse the inevitable functional decline these patients endure.

9 Cross-References

- Body Composition Assessment
- Diet, Exercise, and Behavior Therapy in the Treatment of Obesity and Metabolic Syndrome
- Insulin Resistance in Obesity
- Obesity and Cardiac Disease
- Epidemiology of Obesity in the United States
- Overview of Metabolic Syndrome

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Obstructive Sleep Apnea and Other Respiratory Disorders in Obesity

37

Silke Ryan and Walter T. McNicholas

Contents

Abstract

Obesity represents a major risk factor for sleep-disordered breathing, which can be manifested by sleep apnea or hypoventilation, both of which may occur together. Sleep apnea may be central or obstructive, depending on the relative contribution of different pathophysiological factors such as upper airway narrowing and disordered respiratory control. The prevalence of sleep apnea has greatly increased over the past two decades, and the rising prevalence of obesity is likely the most important factor to account for this rise. Obese patients with obstructive sleep apnea (OSA) and/or hypoventilation can develop profound oxygen desaturation during sleep and are particularly likely to develop cardiovascular and metabolic comorbidities. Systemic inflammation appears to be an important basic mechanism in the development of these comorbidities, and both intermittent hypoxia and visceral adipose tissue represent important factors in this inflammatory response. Management of these patients typically includes noninvasive nocturnal pressure support, either continuous positive airway pressure (CPAP) in those with predominant OSA or bi-level pressure support in those with predominant hypoventilation. Obesity represents an aggravating factor for asthma, particularly in women, and there is evidence that weight loss benefits asthma control. Furthermore, recent evidence indicates that

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patients with asthma are predisposed to OSA, although the clinical significance of this association is not yet clear.

Keywords
Obesity • Metabolic Syndrome • Sleep apnea • Asthma • Hypoventilation • Diabetes • Cardiovascular Disease

1 Introduction

Obesity represents an important risk factor for sleep-disordered breathing (SDB), especially obstructive sleep apnea (OSA) and obesity-hypoventilation syndrome (OHS). These disorders are independently associated with cardiovascular and metabolic diseases, and in combination with obesity, this association is further increased. The present review provides an overview of OSA and OHS with particular reference to the association with obesity and discusses the mechanisms leading to cardiometabolic comorbidities. Furthermore, recent evidence has also linked asthma with sleep-disordered breathing, which represents a topical subject of respiratory sleep research.

2 Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is characterized by instability of the upper airway during sleep, resulting in markedly reduced (hypopnea) or absent (apnea) airflow at the nose/mouth. These episodes are usually accompanied by loud snoring and oxyhemoglobin desaturation and are typically terminated by brief arousals, which result in marked sleep fragmentation and diminished amounts of slow-wave and rapid eye movement (REM) sleep. Patients with OSA are usually unaware of this sleep disruption, but the changes in sleep architecture contribute significantly to the prominent symptom of chronic daytime sleepiness found in these patients. The prevalence of OSA among the adult population is high. In 1993, data collected from the community-based Wisconsin Sleep Cohort Study estimated that 4 % of men and 2 % of women were suffering from obstructive sleep apnea syndrome (OSAS), i.e., the combination of sleep-disordered breathing and daytime sleepiness (Young et al. 1993). Remarkably, follow-up data from the same cohort study, published 20 years later, indicated a substantial increase in these figures with prevalence of OSAS now reaching 14 % of men and 5 % of women. Numerous factors may account for this increase, but the rapidly rising incidence of obesity which is the most important risk factor of OSA plays clearly an important role (Peppard et al. 2013).

OSA is associated with significant morbidity and mortality. The excessive daytime sleepiness leads to impairments in quality of life, cognitive performance, and social functioning (Engleman and Douglas 2004). Furthermore, the disorder is associated with a three- to sevenfold increase in the rate of road traffic accidents (Stoohs et al. 1994). The major health burden in OSA patients, however, is the strong risk of cardiovascular diseases, such as systemic arterial hypertension, coronary artery disease, heart failure, and stroke (McNicholas and Bonsignore 2007). Furthermore, there is increasing evidence of an independent association of OSA with metabolic dysfunction and in particular with alterations in glucose metabolism such as type 2 diabetes mellitus (Aurora and Punjabi 2013; Levy et al. 2009).

Nasal continuous positive airway pressure (CPAP) is the treatment of choice, particularly in severe cases. CPAP splints the upper airway (UA) open during sleep and thus counteracts the negative suction pressure during inspiration that promotes UA collapse in these patients (Sullivan et al. 1981). Nasal CPAP completely controls the condition and has a dramatic effect on the patient's awake performance because of the normalized sleep pattern. It improves quality of life, neurocognitive function, and driving performance (Jenkinson et al. 1999; Montserrat et al. 2001; Engleman et al. 1994; Krieger et al. 1997). Moreover, it has significant benefit in reducing cardiovascular mortality and morbidity (Doherty et al. 2005; Marin et al. 2005).

Obesity is strongly associated with OSA – the prevalence of OSA in obese subjects exceeds 30 % and at least 60 % of OSA patients are obese (Peppard et al. 2000). Obesity contributes

to the pathophysiology of OSA, but there is also emerging evidence of a role of OSA in obesity pathogenesis and obesity-mediated inflammation as the culprit of associated cardiovascular and metabolic disorders.

2.1 Pathogenesis of OSA and Effects of Obesity

The pathophysiology underlying OSA is complex and not fully understood (Deegan and McNicholas 1995). Most subjects with OSA have an anatomical predisposition to airway collapse. A narrowed upper airway (UA) is very common among OSA patients due to either increased soft tissue surrounding the airway or bony abnormalities such as reduction in the length of the mandible, an inferiorly positioned hyoid bone, or a retroposition of the maxilla (Lowe et al. 1995; Schwab et al. 1995). Furthermore, increasing length of the UA is predictive of pharyngeal collapse (Malhotra et al. 2002). The observed variability in airway size might be determined by genetic influences (Mathur and Douglas 1995) or acquired factors, particularly obesity (see below).

The UA patency is mainly dependent on the activity of the pharyngeal dilator muscles. During "wakefulness," this activity is tightly controlled by various mechanisms. Negative intrapharyngeal pressure seems to be the most important stimulus to these muscles and allows the muscles to adapt to any threat to airway patency with active contraction, thereby dilating and protecting the airway (White 2006). This mechanism is particularly active in OSA patients while awake as the anatomically small airway leads to increased negative pressure augmenting the activity of dilator muscles (Fogel et al. 2001). Due to this augmented reflex, OSA patients breathe normally during "wakefulness." With the onset of sleep, the control of these muscles changes significantly. The response to negative pressure is reduced during sleep leading to increased UA resistance (Shea et al. 1999; Wheatley et al. 1993). In patients with OSA, sleep induces a substantially larger decrement in contraction, thus contributing to the development of obstructive apneas (Mezzanotte et al. 1996). However, OSA patients show at least as forceful pharyngeal dilator muscle contraction during sleep as normal subjects which reinforces the fact that an imbalance between pharyngeal collapsing forces and dilator muscle contraction is responsible for the obstruction rather than a primary deficiency in muscle contraction.

The collapse of the UA leads to hypoxia and hypercapnia which drive increasing respiratory effort, leading ultimately to an arousal (Fogel et al. 2004). Arousal is one important mechanism to terminate an apnea. It usually causes lightening of sleep rather than complete awakening. However, this response leads to sleep fragmentation in OSA which is the major cause for daytime sleepiness in these patients (Deegan and McNicholas 1995). Relief of the UA obstruction is typically followed by a short period of hyperventilation with a fall in partial pressure of carbon dioxide (pCO_2) and respiratory drive, thus predisposing to further apnea, promoting a vicious cycle (Deegan and McNicholas 1995; Fogel et al. 2004).

Obesity contributes to the pathogenesis of OSA in a number of ways. It narrows the cross-sectional area of the UA by increased fat deposition in the pharyngeal walls and possibly also by external compression from superficially located fat masses (Shelton et al. 1993). This pattern of fat deposition may alter the shape of the pharyngeal airway from an elliptical shape with the long axis oriented in the coronal plane seen in normal subjects toward a more circular pharynx in obese individuals. These alterations also increase extraluminal tissue pressure which in combination with the anatomical changes promotes UA collapsibility (Schwartz et al. 2010). Obesity through increased levels of abdominal fat is also associated with a reduction in lung volumes, particularly functional residual capacity (FRC). This leads to a reduction in the longitudinal traction of the pharynx, and it can also indirectly contribute to UA instability by disruption of reflex mechanisms of the respiratory control (Gifford et al. 2010). Furthermore, hormonal changes associated with obesity may affect the pathogenesis of OSA. Leptin is an adipose-derived hormone which reduces appetite. It is also a powerful ventilatory stimulant, and in human obesity, which is characterized by

central leptin resistance, there is a blunted response to hypercapnia, leading to impairment of the arousal response (Campo et al. 2007).

Despite these multiple effects of obesity on OSA pathogenesis, the impact of weight loss is still poorly investigated. It is clearly beneficial and patients with greater severity of OSA derive more benefit from weight loss than those with moderate disease (Strobel and Rosen 1996). Imaging studies have confirmed an increase in pharyngeal cross-sectional area with weight loss (Sutherland et al. 2011). However, the relationship between weight loss and OSA is not simply curative. Pre- and post-bariatric surgery measurements of OSA have shown that although there is an improvement in OSA severity postweight loss, the majority of patients had residual OSA and some patients with improvements in snoring or daytime somnolence may be inclined to inappropriately discontinue CPAP therapy, increasing the risk of worsening OSA and weight gain (Greenburg et al. 2009). This aspect underlines the important role of the genetically influenced narrowing of the oropharyngeal airway in the pathogenesis of OSA, which would not be reversed by weight reduction (Kent et al. 2010).

2.2 The Impact of OSA on Obesity Pathogenesis

Besides the well-defined effects of obesity on the pathogenesis of OSA, there is also increasing interest on the potential impact of OSA on obesity. This subject is mainly driven by the frequent observation that weight gain follows the onset of OSA symptoms and is often reported prior to the diagnosis (Phillips et al. 1999). This area of research is still in its infancy but several potential mechanisms support an adverse effect of OSA on obesity. Firstly, sleep deprivation is increasingly linked to obesity. Although this is poorly investigated directly in OSA cohorts, sleep deprivation is a well-recognized feature of OSA, and therefore, one could extrapolate data on sleep restriction in other settings. There is a stream of epidemiological data mainly in pediatric and adolescent populations showing an association between chronic sleep restriction and incidence of obesity (Gozal and Kheirandish-Gozal 2012). Moreover, short sleep also seems to lead to adverse metabolic outcomes including insulin resistance or dyslipidemia. Partially explaining this relationship, current data support the assumption that short sleep alters the hormonal regulation of food intake by increasing levels of the appetite-stimulant hormone ghrelin and reducing levels of the suppressor leptin with the anticipated effect of the subjective feeling of hunger with subsequent increased food intake (Spiegel et al. 2004).

Secondly, ample evidence points to a direct effect of OSA on obesity through increased leptin resistance, a typical feature of human obesity. Several studies reported increased leptin levels in OSA cohorts compared to weight-matched controls correlating with OSA severity and improvement with CPAP therapy (Ong et al. 2013). Beyond the indirect effects of sleep deprivation as mentioned above, a direct effect of OSA through intermittent hypoxia and redistribution of adipose tissue with promotion of visceral fat have been suggested as playing a role in the mechanisms, but the definitive pathophysiology is still far from understood.

Thirdly, there is a reduction in energy expenditure in OSA patients, likely mediated by daytime sleepiness and fatigue with a consequent reduction in physical activity (O'Driscoll et al. 2013). Furthermore, evidence of higher calorie intake in OSA subjects than in obese controls exists. It is suggested that this may at least in part be explained by the frequent association of OSA with mood disorders (Harris et al. 2009).

In summary, while there is increasing evidence pointing to a causal relationship of OSA on the pathogenesis of obesity, the exact mechanisms are still unknown, and there is a distinct lack of well-designed studies investigating this relationship. Furthermore, treatment of OSA with CPAP therapy does not generally result in weight reduction. Although there is evidence of a beneficial impact of CPAP therapy on metabolic parameters, lifestyle habits are usually not modified by this treatment which may explain the failure in weight management within this patient cohort (West et al. 2009).

2.3 Interaction of OSA and Obesity in Systemic Inflammation

OSA is strongly associated with significant cardiovascular morbidity and mortality, and long-term follow-up studies have demonstrated a significant benefit in cardiovascular outcome measures with effective CPAP therapy. There is also increasing evidence for a link between OSA and metabolic dysfunction, in particular insulin resistance and metabolic syndrome. OSA comprises various pathophysiological triggers for cardiovascular diseases, which include sleep fragmentation, intrathoracic pressure swings, and recurrent hypercapnia (Levy et al. 2013). However, there is now strong evidence that the particular form of intermittent hypoxia (IH) observed in OSA, with repetitive short cycles of desaturation followed by rapid reoxygenation, plays a pivotal role in the development of cardiovascular comorbidities. The pathogenesis is likely multifactorial, and our current concept involves sympathetic nervous system overactivity, systemic inflammation, and oxidative stress leading to endothelial dysfunction and, possibly, metabolic dysfunction as the most important pathways (McNicholas and Bonsignore 2007). Inflammatory processes are central in this pathogenesis and there is ample evidence – arising from both cell culture and in vivo models – that IH selectively activates the transcription factor nuclear factor-kappa B (NF-κB) (Ryan et al. 2005, 2009). NF-κB is a key player in inflammatory and innate immune responses and when chronically activated contributes to atherosclerosis through driving production of inflammatory mediators such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-8, and IL-6 (Cummins and Taylor 2005). Moreover, these mediators have been found to be upregulated in OSA patients versus matched controls, and effective CPAP therapy significantly lowers these levels supporting the key role of NF-κB as driver of inflammation in OSA (Ryan et al. 2006).

The main source organ of the IH-dependent release of inflammatory mediators in OSA is still unknown; however, white adipose tissue (WAT) is a very attractive candidate given the close link between OSA and obesity. Moreover, obesity itself represents a low-grade inflammatory condition through the secretion of pro-inflammatory mediators from WAT (termed adipokines) (Trayhurn and Beattie 2001). This includes a variety of pro-inflammatory mediators such as TNF-α and IL-6 that may be a critical link between obesity and obesity-induced cardiovascular diseases. There is emerging evidence that hypoxia is a key factor in modulating the production of inflammatory adipokines in obesity (Trayhurn et al. 2008). As IH represents a stronger inflammatory stimulus than sustained hypoxia, this process may be potentiated in diseases associated with IH such as OSA. Support for this hypothesis comes from animal studies demonstrating exacerbation of insulin resistance by IH in obese versus lean mice associated with increased liver inflammation (Drager et al. 2011). Furthermore, atherosclerotic-prone apolipoprotein E-deficient mice treated with IH demonstrated remodeling of the adipose tissue associated with higher secretion of IL-6 and TNF-α and also more severe atherosclerotic lesions than mice treated with control protocol (Poulain et al. 2014). We reported, using a cell culture model, that human primary adipocytes bear greater sensitivity to the stimulus of IH toward pro-inflammatory pathway activation than primary cells of non-adipose linkage (Taylor et al. 2013).

Despite the growing body of evidence, the topic of the interaction between OSA and obesity in driving inflammatory processes and subsequent cardiovascular and metabolic diseases is still far from understood. There is a clear need for large, multicenter well-designed studies investigating this subject in humans accompanied by detailed cell culture and in vivo mechanistic studies exploring the effect of IH on the adipose tissue.

3 Asthma

Asthma is a heterogeneous disease characterized by chronic diffuse airway inflammation. In susceptible individuals, this inflammation causes recurrent episodes of dyspnea, chest tightness, coughing, and wheezing. These symptoms are usually associated with widespread but variable

airflow obstruction. Typical triggering factors for asthma symptoms include exercise, allergen or irritant exposure, change in weather, or respiratory infections. Symptoms and airflow limitation are often reversible, either spontaneously or with treatment (From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2015). Asthma is among the most common chronic diseases worldwide, and it is estimated that over 300 million people are currently suffering from the disease. A growing body of literature suggests that obesity has a significant impact on asthma prevalence, phenotype, and prognosis, but the pathophysiology underlying this association remains incompletely understood, and further elucidation of the mechanism is essential for the formulation of effective treatments for this difficult category of patients.

3.1 The Epidemiology of Asthma and Obesity

Concurrent with the rising prevalence of obesity, many countries have seen a large increase in the occurrence of asthma which has raised the possibility that these two conditions might be connected. Cross-sectional studies investigating the association of asthma with obesity have not been consistent, but most suggest a modest association between these two conditions, with odd ratios of 1.5–3.5 (Ford 2005). Most of these studies used self-reported physician diagnosis of asthma and determined obesity by the crude anthropometric measure of the body mass index (BMI). Various prospective analyses support the notion that increased body weight precedes the development of asthma and hence promote a causal relationship (Camargo et al. 1999; Kronander et al. 2004; Romieu et al. 2003). However, while there are consistent data on the relationship of obesity and asthma incidence in women, studies have drawn a different conclusion of this association in men (Beckett et al. 2001; Chen et al. 2005; Hancox et al. 2005). Differences in obesity prevalence and levels of anthropometric measures defining obesity may account for the apparent sex difference, and in a meta-analysis of seven prospective studies, no difference between men and women was observed, and overall, there was a dose–response effect of increasing BMI and asthma development (Beuther and Sutherland 2007).

If excess weight contributes to asthma pathophysiology, weight loss would be expected to improve the clinical status of asthma in this patient group. Indeed, observational studies in patients undergoing bariatric surgery support this hypothesis, showing impressive improvements with up to 50 % of patients seeing their condition resolved (Dhabuwala et al. 2000; Macgregor and Greenberg 1993). However, asthma was often not assessed by rigorous criteria, and as cough and dyspnea are common among morbidly obese patients, diagnosis of asthma may have been falsely made. Some studies have examined the effect of weight loss achieved by dietary modifications and, although numbers were small, benefits in asthma status were shown with these interventions (Hakala et al. 2000; Stenius-Aarniala et al. 2000).

Support of a relationship between obesity and asthma comes from animal studies. Obese mice exhibit innate airway hyperresponsiveness (AHR), the cardinal feature of asthma, and this is observed in mice with various forms of genetic obesity and in mice in which obesity is induced by a high-fat diet (Johnston et al. 2008; Shore et al. 2003). The magnitude of the AHR increases with the degree of obesity. In addition, in comparison to lean mice, obese mice also have greater AHR to various asthma triggers, including viral infections and ozone (Johnston et al. 2008, 2007; Shore et al. 2003). The latter has been reproduced in humans with AHR being enhanced in response to this trigger in obese in comparison to lean subjects (Bennett et al. 2007).

3.2 The Phenotype of Obese Asthma

There is accumulating data suggesting that asthma in obese patients differs to that in nonobese subjects in relation to asthma control and response to treatment. These differences led to the introduction of this separate phenotype.

In comparison to nonobese asthmatics, obese patients have more severe symptoms, decreased asthma-specific quality of life, and increased medication use adjusted for various potential confounding factors (Taylor et al. 2008; Vortmann and Eisner 2008). Some studies suggested that asthma severity is only significantly correlated with increasing BMI in women, particularly among women in their early menarche; this gender difference, however, will require further evaluation (Varraso et al. 2005). In addition, obese individuals have a 4.6-fold increased risk of hospitalization for asthma compared with nonobese subjects (Mosen et al. 2008).

Interestingly, despite worse asthma controls, airways of obese asthmatics do not usually exhibit eosinophilic or neutrophilic inflammation and sputum/blood eosinophil counts, and IgE concentrations are commonly unaffected (Sutherland et al. 2008; Tantisira et al. 2003). Instead, oxidative stress determined by increased levels of 8-isoprostane has been implemented to play a role in the pathophysiology, but further studies are required to better understand the pathways involved (Komakula et al. 2007).

Clinically of important relevance is the fact that obesity impinges a relative refractoriness to asthma treatment and hence, asthma control is more difficult to achieve in this patient group. In particular, response to inhaled corticosteroid (ICS) medication is diminished in comparison to nonobese asthmatics measured by spirometry and symptoms (Boulet and Franssen 2007). The decreased airway inflammation in obese subjects has been proposed to be responsible for this finding. This results in greater usage of rescue medication, such as short-acting β2-agonists, and increased need for oral glucocorticosteroids among these patients. Interestingly, the response to leukotriene modifiers such as montelukast seems independent of body mass index; however, this is based on a retrospective analysis and prospective studies are required to investigate these altered responses to pharmacotherapy (Peters-Golden et al. 2006).

The most obvious therapeutic intervention to improve asthma control is weight loss and many studies employing bariatric surgery or dietary intervention have shown to improve asthma symptoms and quality of life and to reduce hospital admissions and asthma medication and even to induce full remission (Stenius-Aarniala et al. 2000; Dixon et al. 1999; Spivak et al. 2005). The impact of weight loss on airway inflammation and AHR, however, remains unknown, and there is a clear need for large studies assessing the combined treatment of pharmacotherapy and weight loss in this difficult-to-treat category of patients.

3.3 Pathogenesis of Asthma in the Obese

The pathogenesis of asthma in obesity still remains to be fully elucidated, but mechanical factors leading to lung restriction, chronic inflammation, hormonal influences, and additional comorbidities, such as gastroesophageal reflux disease, obstructive sleep apnea, and hypertension, may contribute.

Thoracoabdominal adiposity is associated with a decrease in functional residual capacity (FRC) and expiratory reserve volume (ERV), reflecting decreased respiratory system compliance (Bedell et al. 1958; Watson and Pride 2005). These reductions are associated with increased airway resistance in peripheral small airways, such as the noncartilaginous small membranes, terminal bronchioles, and alveolar ducts (Nicolacakis et al. 2008; Rubinstein et al. 1990). During tidal breathing, these small airways may collapse, leading to a cyclical opening and closing of the airway which is known to trigger local inflammation and subsequent structural damage (D'Angelo et al. 2002; Hakala et al. 1995). As a consequence, asthma symptoms worsen and may become refractory to treatment. Furthermore, the low FRC in obesity has also been postulated to result in an increase of the airway smooth muscle contractility either by plastic adaptation to a shorter length or alterations in actin/myosin cross-bridge cycling with the net consequence of an increase in airway responsiveness (Gump et al. 2001; Pankow et al. 1998; Seow 2005).

Besides these mechanical factors, obesity also represents a low-grade inflammatory state which

may promote asthma pathogenesis. The adipose tissue in obesity undergoes significant changes toward a pro-inflammatory phenotype. Macrophages infiltrating the adipose tissue play an important role in this process and in obesity are polarized to an M1 or "classically activated" phenotype, and these M1 macrophages produce pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α which is in contrast to lean adipose tissue where macrophages predominantly show an alternative, M2 pattern of expression with upregulation of anti-inflammatory factors such as IL-10 or adiponectin and downregulation of pro-inflammatory cytokines (Ouchi et al. 2011). In addition, obese adipose tissue is also characterized by necrotic adipocytes surrounded by macrophages called "crown-like structures" and infiltration of cytotoxic T-cells. Pro-inflammatory cytokines, chemokines, and complement factors produced by the adipose tissue in obesity have also been associated with asthma and therefore could play a role in the relationship between obesity and asthma (Shore 2007; Sideleva et al. 2012).

Adipose tissue is also the source of the satiety hormone leptin, and serum concentrations are markedly increased in obesity. Leptin has pro-inflammatory effects, and therefore, it has been proposed to contribute to the obesity–asthma relationship. In mice, leptin is causally associated with asthma development (Shore et al. 2005). In humans, leptin has been linked to more severe asthma symptoms, AHR, and greater impairment in lung function (Baek et al. 2011; Leao da Silva et al. 2012).

Adiponectin is another adipose tissue-derived protein, but in contrast to leptin, adiponectin levels are decreased in obesity. Adiponectin has anti-inflammatory effects and promotes insulin sensitivity. In mice, adiponectin infusion decreases airway inflammation and adiponectin-deficient mice demonstrate enhanced allergic airway inflammation and greater accumulation of eosinophils and macrophages in the airway (Shore et al. 2006).

Most human studies show a positive relationship between serum levels of leptin and an inverse association of serum adiponectin with asthma risk (Guler et al. 2004; Sood et al. 2006). The associations are modest and differ in different patient groups. Relationships are strongest in prepubertal boys, peripubertal girls, and premenopausal women and suggest that other factors such as age and sex may modify the adipokine–asthma affect.

In summary, the pathogenesis of asthma in obesity is complex and requires further detailed translational studies. An improved understanding of these mechanisms will facilitate the design and conduct of clinical trials to identify the best therapeutic interventions for this important and growing subset of asthma patients.

3.3.1 Obesity-Hypoventilation Syndrome

Hypoventilation indicates a level of alveolar ventilation that is inadequate to maintain normal gas exchange, which results in both hypoxemia and hypercapnia and is typically most pronounced during sleep. Different pathophysiological mechanisms contribute to hypoventilation, which may occur alone or in combination (Simonds 2013). These mechanisms include neuromuscular disorders, thoracic cage disorders, and other mechanical factors, in addition to obesity. Obesity is the most prevalent cause of hypoventilation, often referred to as the obesity-hypoventilation syndrome (OHS), and the present review will concentrate on this form of hypoventilation. Patients typically experience an increased mechanical load to breathing and frequently have a decreased ventilatory drive/response. This combination interacts to produce hypoventilation. Sleep-related hypoventilation is separate but may coexist with sleep apnea as both share common pathophysiological factors such as obesity and central respiratory insufficiency (McNicholas 1997). Sleep apnea in patients with OHS may be central or obstructive. The exact prevalence of OHS is unknown but is estimated to be present in between 10 % and 20 % of subjects referred to sleep laboratories and rises to about 50 % in hospitalized patients with a BMI greater than 50 (Mokhlesi et al. 2007; Nowbar et al. 2004).

Pathophysiology of OHS

Obesity-hypoventilation syndrome (OHS) is defined by daytime hypercapnia ($Pa_{CO2} > 6$ kPa) in the presence of obesity (BMI ≥ 30 kg/m^2) and in the absence of other reasons for alveolar hypoventilation such as coexisting respiratory or neuromuscular disease. Obese subjects have an increased demand for ventilation and elevated work of breathing, in addition to respiratory muscle inefficiency and diminished respiratory compliance. Thus, obese individuals have an increased central respiratory drive compared with normal-weight patients to compensate for the increased ventilatory requirements.

The pathophysiology of OHS is complex and not yet fully understood. Although the likelihood of developing OHS increases with rising BMI, weight alone does not explain the presence of hypercapnia. In comparison to eucapnic obese subjects, OHS patients are characterized by a greater decrease in lung volumes, particularly functional residual capacity (FRC), associated with decreased respiratory system compliance and expiratory flow limitation (Resta et al. 2000). As a consequence, respiratory muscle work is significantly increased even at rest. Possible mechanisms include direct mechanical effects on respiratory function by central fat distribution and low-grade inflammation generated by visceral adipose tissue promoting the metabolic syndrome and associated muscle impairment (Piper and Grunstein 2011). UA obstruction leading to OSA is common in OHS, and even patients diagnosed initially with sleep hypoventilation alone may later exhibit OSA. The pattern of breathing in OSA has a major influence on the likelihood of hypercapnia in OHS, and an inadequate post-apneic ventilatory compensation has been described as one such factor (Ayappa et al. 2002).

Clinical Manifestations

The two most common presentations of OHS are an acute-on-chronic exacerbation leading to admission to an intensive care unit or during a routine evaluation by a sleep specialist for suspected OSA (Priou et al. 2010; Chau et al. 2013). The numbers of hospitalizations prior to diagnosis as well as the numbers of admissions in intensive care unit are higher in newly diagnosed OHS patients than in eucapnic obese patients. Subjects with OHS share many characteristics with pure OSA patients but are more likely to suffer from congestive cardiac failure and pulmonary hypertension, resulting in significant additional morbidity and mortality (Nowbar et al. 2004). Accordingly, in contrast to eucapnic OSA, patients with stable OHS frequently complain of dyspnea and may have signs of cor pulmonale including lower extremity edema.

Patients with OHS are often morbidly obese and the great majority have associated OSA, frequently in the severe range of AHI, and the combination typically results in profound oxygen desaturation during sleep. As a consequence the majority of OHS patients exhibit classic symptoms of OSA, including loud snoring and excessive daytime sleepiness. There are more quantitative rather than qualitative differences to OSA patients such as higher BMI, higher AHI, and greater impairment in pulmonary function (Balachandran et al. 2014). The severity of objectively measured daytime sleepiness is associated with the proportion of REM sleep hypoventilation which is another classical feature of OHS. Daytime hypercapnia is the distinguishing feature of OHS that separates it from simple obesity and OSA. SDB, although not currently included in the basic definition of OHS, is a typical finding and encompasses frank OSA or obstructive hypoventilation, with a small percentage also presenting with nonobstructive hypoventilation which is most pronounced in rapid eye movement (REM) sleep (Simonds 2013).

Morbidity

OHS is typically characterized by chronic systemic low-grade inflammation and associated inflammatory changes in the adipose tissue. OHS patients have a higher level of high-sensitivity C-reactive protein, a higher level of the pro-atherogenic chemokines, and lower adiponectin levels compared with age- and BMI-matched eucapnic control subjects (Borel et al. 2009). Accordingly, OHS patients exhibited higher insulin resistance and impaired glucose tolerance. Endothelial dysfunction, a key early

feature in the pathogenesis of atherosclerosis and a strong predictor of incident cardiovascular events, was also more impaired in OHS patients compared with eucapnic obese patients (Borel et al. 2009). Taken together, these results support a particular cardiovascular and metabolic risk associated with OHS and strengthen the results of observational cohort data that demonstrate a higher prevalence of cardiovascular and metabolic diseases in OHS (Jennum and Kjellberg 2011). These cardiometabolic comorbidities also represent the main factor predicting mortality in patients with OHS treated by NIV (Borel et al. 2013).

There is emerging evidence of an important role for leptin in the pathogenesis of OHS, and leptin deficient ob/ob mice exhibit OHS with replacement of leptin in these mice, restoring ventilatory function (Tankersley et al. 1998). Obesity in humans is characterized by high leptin levels but with central leptin resistance. Circulating levels of leptin are higher in OHS than in weight-matched controls and have been reported as a better predictor of hypercapnia than the degree of adiposity (Phipps et al. 2002).

Mortality

Beyond the additional burden of comorbidities compared with eucapnic obese individuals, OHS patients have a higher mortality risk, particularly when not treated with NIV (Chau et al. 2013). Nowbar and coauthors reported a mortality rate of 23 % in OHS patients 18 months after hospital discharge, compared with 9 % in eucapnic obese patients (Nowbar et al. 2004). OHS patients had a hazard ratio for mortality of 4.0 after adjustment for age, gender, BMI, and other confounders. In observational cohorts, mortality rate was reduced when OHS patients were treated with NIV (Pépin et al. 2012) but may still be higher than long-term mortality rates observed in large cohorts of obese patients without OHS.

Treatment

Since the majority of patients with OHS also demonstrate OSA, continuous positive airway pressure (CPAP) is a suitable first-line therapy for many such patients. CPAP is effective in reversing nocturnal hypoventilation in most patients with mainly OSA-related hypoventilation, although some exhibit continuing hypoventilation despite CPAP and thus require noninvasive positive pressure ventilation (NIV). Furthermore, NIV is the treatment modality of first choice for patients with nonobstructive hypoventilation (Carrillo et al. 2012; Piper and Grunstein 2011). Weight loss in conjunction with increased physical activity should be promoted in all patients. However, this process takes time, even with bariatric surgery, and there should not be a delay in initiating positive airway pressure therapy. Failure to recognize OHS and to initiate effective treatment is associated with increased hospitalization rates and reduced survival. Untreated OHS patients have an 18-month mortality of 23 % which falls to 3 % in NIV-treated patients (Pérez de Llano et al. 2005). OHS has become the major indication for home ventilator support in many countries and is most effective when delivered with a mandatory backup frequency (Priou et al. 2010).

4 Cross-References

- ▶ Body Composition Assessment
- ▶ Endocrine Disorders Associated with Obesity
- ▶ Kidney Disease in Obesity and Metabolic Syndrome
- ▶ Linking Obesity, Metabolism, and Cancer
- ▶ Metabolic Syndrome, GERD, Barrett's Esophagus
- ▶ Nonalcoholic Fatty Liver Disease
- ▶ Obesity and Cardiac Disease
- ▶ Obesity, Metabolic Dysfunction, and Dementia
- ▶ Obstructive Sleep Apnea and Other Respiratory Disorders in Obesity
- ▶ Overview of Metabolic Syndrome
- ▶ Reproductive Disorders and Obesity in Males and Females and Focus on the Polycystic Ovary Syndrome
- ▶ Sarcopenic Obesity
- ▶ Type 2 Diabetes: Etiology, Epidemiology, Pathogenesis, Treatment

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Reproductive Disorders and Obesity in Males and Females and Focus on the Polycystic Ovary Syndrome

38

Andrea Repaci and Renato Pasquali

Contents

Abstract

Obesity can disrupt the fertility processes in both men and women by various mechanisms, chiefly including hormonal derangements on sex steroids and a dysmetabolic milieu characterized by an insulin-resistant state. In addition, low-grade inflammation and a consequent lipotoxic state may impair structural and functional mitochondrial physiology, thereby oocyte function and sperm quality in women and men, respectively. In women, obesity may also impair endometrial receptivity that became an important factor explaining the failure of assisted reproductive technologies in these women. The polycystic ovary syndrome (PCOS) is the commonest cause of anovulatory infertility in women. Obesity tends to favor the development of PCOS in adolescent girls and worsens the phenotype of adult affected women, by increasing the hyperandrogenic state and ovarian dysfunction. Moreover, it plays a major role in the development of a dysmetabolic profile. In turn, obesity reduces the potential efficacy of medical treatments of infertility in most of these women. Weight loss may conversely favor ovulation rates and pregnancy rates in these women. This short review summarizes the most important aspects of obesity-related infertility in both men and women, including those affected by PCOS.

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Sex differences • Obesity • Androgens • Infertility • Polycystic ovary syndrome

1 Introduction

Obesity is a multifactorial disorder that results from a combination of physiological, genetic, and environmental inputs. Obesity is associated with adverse health consequences, including type 2 diabetes mellitus (T2DM), cardiovascular diseases, musculoskeletal disorders, obstructive sleep apnea, different types of cancer, and infertility. Body mass index and waist circumference are two key measures of total body fat and its distribution. Worldwide, the prevalence of subjects with a body mass index (BMI) $\geq$ 30 kg/m^2 is around 20–30 %, with some difference according to geographical area, and much more high rates are expected to develop in the next decades (Ogden et al. 2012).

Infertility, defined by the WHO as the inability to achieve a clinical pregnancy despite 12 months of regular unprotected intercourse, is estimated to affect 48.5 million couples worldwide (Mascarenhas et al. 2012). The prevalence of infertility in the USA is estimated between 12 % and 15 % and the male factor contributes in 20–50 % of couples (Louis et al. 2013). In this chapter, we analyzed the role of obesity on infertility in both sexes.

2 Obesity and Altered Testosterone Balance in Males

With increasing age in normal individuals, there is a progressive decrease of both total and free testosterone but an increase in SHBG blood levels (Feldman et al. 2002; Harman et al. 2001). Starting from the third decade, aging is associated with a 1–2 % per annum decrease on testosterone. Notably, the impact of age per se in the decline of testosterone seems to be more evident when obesity is present. In fact, obesity in males is often associated with a proportional decrease of testosterone with increasing BMI (Zumoff et al. 1990). Therefore, obesity is considered to be an important predictor of low testosterone in middle-aged and aging men (Mohr et al. 2006). The association between obesity and low testosterone blood levels has been confirmed by cross-sectional studies (Allan and McLachlan 2010). Longitudinal studies have also confirmed these findings, showing an inverse relationship between total testosterone, sex hormone-binding globulin (SHBG) levels, and free testosterone [calculated by the Vermeulen formula, using the ratio between testosterone and SHBG (Vermeulen et al. 1971)] with BMI and waist circumference (Derby et al. 2006).

The abdominal phenotype of obesity is specifically prone to develop metabolic alterations associated with low testosterone levels, emphasizing the phenotype of the dysmetabolic hypotestosteronemia as a potential target for prevention treatments (Ding et al. 2007). It is worthy of mentioning for the purposes of this chapter that low testosterone and low SHBG blood levels in obese males have been found in many studies and meta-analyses as significantly important predictive risk factors in the development of T2DM (Ding et al. 2006, 2007, 2009). Notably, this risk is shared by the combination of multiple systems including, other than obesity and particularly the abdominal/visceral phenotype, all other components of the metabolic syndrome (Corona et al. 2011). The strong association between low testosterone and T2DM is further emphasized by the following: (i) there is evidence that weight loss and lifestyle modification in otherwise overweight or obese individual reverts obesity-associated altered glucose tolerance states and hypotestosteronemia (Corona et al. 2013); (ii) available data clearly support the concept that testosterone treatment may significantly improve glycometabolic control as well as fat mass in patients with altered glucose tolerance states including T2DM (Allan 2014).

Different mechanisms can be considered to be responsible for the association between obesity and infertility, specifically including low testosterone levels, altered spermatogenesis, and erectile dysfunction. Notably, it is worth mentioning that plasma androgen or estrogen levels are strong

correlates of adipose tissue steroid content both in the omental and subcutaneous fat depots; however, regional differences may be observed. Androgen concentration differences in omental versus subcutaneous adipose tissue suggest a depot-specific impact of these hormones on adipocyte function and metabolism (Bélanger et al. 2006). Moreover enlarged subcutaneous and visceral fat increases the peripheral conversion of testosterone to estradiol by an increased aromatase activity that is promoted by insulin and leptin excess (Hammoud et al. 2008). The increase of estrogen levels may in turn inhibit the hypothalamic-pituitary-gonadal axis causing hypogonadotropic hypogonadism. Indirect evidence comes from studies showing that clomiphene citrate (CC) and aromatase inhibitor treatment may restore normal testosterone levels in dysmetabolic hypotestosteronemic obese men (Chua et al. 2013; Wiehle et al. 2014; Raman and Schlegel 2002). In addition, there are studies showing that insulin and leptin excess per se may contribute to reduce the amplitude and pulsatility of the gonadotropin-releasing hormone (GnRH) leading in turn to a decrease of both the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) release from the pituitary, with the participation of the inhibiting action of Kiss neurons (Vermeulen et al. 1993; George et al. 2010). Another factor responsible for low testosterone in obese men is represented by low hepatic synthesis and circulating blood levels of the carrier protein of major androgens SHBG, that is, largely due to the inhibiting activity of high circulating insulin, the product of a whole body insulin resistance state (Ramlau-Hansen et al. 2010). In fact, low SHBG in obese men directly correlates with low testosterone levels (Cooper et al. 2015). A potential role of increased generation of cortisol due to an increased activity of 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) activity and/or a reduced activity of 5α and 5β reductase in the visceral fat has been found to contribute to the decrease of circulating testosterone (Bélanger et al. 2006). High leptin levels, which characterize obesity, may also negatively affect testosterone production in the testis (Isidori et al. 1999). Finally, recent findings support a potential role of low insulin-like peptide-3 (INSL3) levels, a peptide representing a functional biomarker of gonadal androgen production (Foresta et al. 2009).

3 Testosterone Supplementation Improves Obesity and the Metabolic Syndrome in Men

Since hypotestosteronemia has been implicated in the pathogenesis of the metabolic syndrome, it is tempting to speculate that affected men may benefit from testosterone supplementation therapy. Many studies support the efficacy of testosterone replacement therapy in dysmetabolic obese men. It is important to outline that this treatment should be considered only for men with a clear evaluation of hypotestosteronemia (possibly measured by very sensitive assays) associated with chronic disorders (obesity and the metabolic syndrome) and that benefits as well as risks potentially related to overtreatment should be taken into consideration (Lin et al. 2008; Bhasin et al. 2010). Available randomized controlled trials (RCTs) assessing the effect of testosterone therapy on insulin resistance yielded mixed findings (Kelly and Jones 2014), with some studies reporting consistent metabolically favorable changes in body composition (reduced visceral fat and increased muscle mass) and decreasing measures (surrogate markers) of insulin resistance, although these findings have been found to achieve significant evidence only in trials longer than 6 months (Dandona and Dhindsa 2011). A recent systematic review assessed the metabolic effects of testosterone replacement therapy on hypotestosteronemic men with T2DM and found that this treatment improved glycemic control and decreased triglyceride levels in most of these patients (Dandona and Dhindsa 2011; Allan 2014). Overall, testosterone-induced metabolic changes appear less pronounced than would be expected from successful lifestyle programs and metformin or glitazone treatment, although large trials that directly compared testosterone therapy to lifestyle intervention and/or insulin sensitizers are still lacking (Cai et al. 2014). This obviously

emphasizes the need for long-term RCTs in well-selected patients. In addition, a prerequisite for appropriate analyses of the data would be the availability of age-related reference values, measured by appropriate methodology, such as liquid chromatography coupled with mass spectrometry (LC-MS/MS).

The consequences of male hypogonadism are routinely attributed solely to androgen deficiency, and the potential role of the concomitant alteration in the estrogen balance is often ignored. However, it is known that estrogen deficiency may have important effects on body composition and metabolism as documented by a seminal recent study (Finkelstein et al. 2013). In fact, it found that the amount of testosterone required to maintain lean mass, fat mass, and strength varied widely in men and that androgen deficiency accounted for decreases in lean mass, muscle size, and strength, whereas estrogen deficiency primarily accounted for increases in body fat. These findings may support the need for and individualized approach in evaluating and managing long-term treatment not only in classical hypogonadic states but specifically in obese dysmetabolic men with low testosterone blood levels.

4 Altered Sperm Count and Function and Erectile Dysfunction (ER) in Obese Men

Apart from low testosterone levels, other factors should be considered to explain the association between obesity and infertility, such as altered sperm count and function and erectile dysfunction. Data from three epidemiologic studies [the Agricultural Health Study (Sallmén et al. 2006), the Danish National Birth Cohort (Olsen et al. 2001), and the Norwegian Mother and Child Cohort Study (Nguyen et al. 2007)] indicate that BMI rates of infertility in males tend to increase too. The negative effect of obesity on infertility has been also found in male patients undergoing assisted reproductive technologies (ART). In fact, some study found a decrease in sperm concentration in overweight/obese men that was associated with a decreased rate of pregnancy with increasing paternal BMI (Bakos et al. 2011). However, not all studies confirmed these findings (Colaci et al. 2012). Notably, it should be considered that low testosterone blood levels in obese dysmetabolic men can be associated with altered sperm count. In the last two decades, different studies have documented a decline in sperm parameters over time (Carlsen et al. 1992). Recent data have shown an inverse relationship between male BMI and waist circumference with low sperm concentration and count (Eisenberg et al. 2014). These findings have been also confirmed in a recent meta-analysis (Sermondade et al. 2013). In addition, obesity has been found to be negatively associated with other sperm parameters, specifically sperm mobility, morphology, and DNA fragmentation (Chavarro et al. 2010). These alterations have been suggested to be related to an increased oxidative stress. In fact, enlarged visceral fat has been found to be characterized by the presence of macrophages and other inflammatory cells, secreting inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukins (IL-1, IL-6, IL-18). These factors may locally favor low testosterone levels by paracrine and autocrine mechanisms. In addition, they may act distantly (by blood circulation) by increasing oxidative stress and reactive oxygen species (ROS), leading to increased DNA damage of spermatozoa and reducing their ova-penetrating ability (Aitken and Baker 2006). Insulin resistance has also been negatively associated with sperm quantity and quality, and metformin treatment has been shown to improve sperm parameters (Morgante et al. 2011). A role of altered lipid profile has also been associated with low semen volume (Schisterman et al. 2014). A potential explanation comes from studies showing that excess cholesterol can precipitate into the sperm membrane, thereby altering the head morphology and inhibiting acrosomal reaction (Yamamoto et al. 1999). In addition, it has been found that excess ROS production may induce fragmentation of spermatozoa nuclear and mitochondrial DNA, thereby favoring aberrant recombination and/or defective packing (Shukla et al. 2011). The altered spermatogenesis process could also depend on raised intratesticular temperature, favored by the enlarged fat (in the suprapubic

region and in the medial thighs) around testicles and the spermatic cord. This is supported by the findings of autoptic studies demonstrating the presence of scrotal lipomatosis in the majority of men with idiopathic infertility (Shafik and Olfat 1981a). The potential role of local fat excess has been confirmed by the efficacy of scrotal lipectomy and suprapubic lipectomy in improving semen quality and pregnancy rate of the couple in a group of 102 infertile men with lipomatosis (Shafik and Olfat 1981b). Finally, it should be considered that low inhibin B production rate (Chavarro et al. 2010), a marker of Sertoli cell function, may partly explain the impaired spermatogenesis in the presence of obesity (Pauli et al. 2008).

Erectile dysfunction (ED) should be considered another potential factor associated with male infertility, particularly in dysmetabolic obese men. In fact, the risk of erectile dysfunction tends to increase with increasing BMI (Corona et al. 2010). Causative factor responsible for ED in obese men may be related not only to the presence of low testosterone but also to the negative effects of proinflammatory cytokines (particularly IL-6, TNF-α), which are able to increase endothelium ROS and reduce nitric oxide and their vasodilatory effects (Sullivan et al. 1999; Tamler 2009). Several recent review articles published in the last years may help the reader in understanding the pathophysiological aspects and psychological correlates of ED in obese men (Esposito and Giugliano 2011; Kolotkin et al. 2012; Shamloul and Ghanem 2013).

5 Obesity and Infertility in Women

The association between obesity and infertility was first described by Hippocrates in the essay to Scythians: "...The girls get amazingly flabby and podgy....and fatness and flabbiness are to blame. The womb is unable to receive the semen and they menstruate infrequently and little..." (Lloyd 1978). The adverse effects of obesity on reproductive function begin early in life. Childhood and adolescent obesity may modulate timing of puberty and reproductive maturation and is linked to earlier puberty onset in girls (Burt Solorzano and McCartney 2010). Obese women are three times more likely to present with infertility compared to women of normal BMI (Moran et al. 2011a). Young obese women are less likely to conceive within 1 year of unprotected intercourse compared with nonobese women with a linear relationship between BMI and prolonged time to conception (Hassan and Killick 2004). In particular, visceral abdominal fat has a significant association with infertility with a reduction in the probability conception by 30 % per cycle for increased waist/hip ratio (WHR) (Zaadstra et al. 1993). The obesity contributes to infertility via several mechanism altering hormone secretion, ovulation, menstrual cycles, oocyte development, endometrial receptivity, and embryo development (Pasquali et al. 2007). Obesity causes important alteration on sex hormone secretion and metabolism. In fact, it was associated with reduced SHBG levels that were inversely related to BMI (Pasquali et al. 1990). In addition, the amount of visceral adipose tissue is significantly and inversely related to SHBG (Pasquali et al. 1990). The decrease of SHBG levels may in turn promote an increase in free sex hormone levels in particular testosterone, dihydrotestosterone, and androstenediol that have been found to be higher than normal in women with visceral adiposity and high WHR (Pasquali and Vicennati 2001). Moreover, obesity is associated with increased peripheral androgen aromatization (Kirschner et al. 1990), and pituitary hypersecretion of LH that, in turn, may favor ovarian androgen overproduction. In female obesity, it has also been observed that a relative overactivity of the hypothalamic-pituitary-adrenal (HPA) axis (Pasquali and Vicennati 2000) and a higher number of glucocorticoid receptors are present in abdominal adipocytes than subcutaneous adipocytes, thereby promoting an increased intracellular cortisol action (Rebuffé-Scrive et al. 1985). Besides this, in the visceral adipose tissue, an impaired activity of 11βHSD-1 that converts cortisol in cortisone and enhanced activity of 5α-reductase that metabolizes cortisol into its inactive tetrahydroderivates has been described (Tomlinson et al. 2004). By these ways insulin

resistance can be amplified (Masuzaki et al. 2001). The compensatory hyperinsulinemia associated with the insulin-resistant state has also a primary role in decreasing hepatic synthesis of SHBG and in increasing the availability of free androgens. High circulating insulin levels may also synergize with LH in the ovaries to promote thecal androgen synthesis and to reduce folliculogenesis (Pasquali and Gambineri 2013). This insulin-dependent ovarian derangement is additionally amplified by the increased activity of the insulin growth factor(s) (IGFs) through a decrease of the IGF-binding protein 1 (IGFBP1). In women with simple obesity, these hormonal alterations may therefore lead to a condition of relative functional hyperandrogenism (Pasquali 2006).

In the visceral adipose tissue, hyperinsulinemia promotes the differentiation of preadipocytes into adipocytes, therefore favoring its hypertrophic development (Ali et al. 2013). Hypertrophic adipocytes are in turn susceptible to inflammation, apoptosis, fibrosis, and release of FFA and become more resistant to the antilipolytic effects of insulin (Wajchenberg 2000). This process is mediated by infiltrated macrophages that are able to recruit inflammatory chemokines secreted via paracrine and autocrine functions from hypertrophic adipocytes (Suganami et al. 2012). In fact, the hypertrophic adipocyte-macrophage complex releases a greater amount of inflammatory markers such as free fatty acids (FFA), IL-6, and TNF-α, all factors involved in the local worsening of insulin resistance (Fain et al. 2008). Furthermore, hypertrophic adipocytes secrete higher amounts of leptin, resistin, visfatin, retinol binding protein-4 (RBP4), and decrease adiponectin, all factors additionally contributing to insulin resistance (Comninos et al. 2014).

The reproductive axis of obese women can be deeply disrupted in the presence of this dysmetabolic milieu. For example, even an increase of ghrelin levels has been found to disrupt the reproductive processes (Repaci et al. 2011). The low-grade inflammation state may play a major role in altering oocyte physiology. In fact, it is responsible for increased reactive oxygen species (ROS) which may impair structural and functional mitochondrial not only of hepatocytes, β cells, and muscular fibers but also of oocytes (Grindler and Moley 2013). In fact, they favor lipotoxic state, which is characterized by the fact that non-adipose cells may accumulate triglyceride droplets and FFA intracellularly, causing in turn important damages to mitochondria and endoplasmic reticulum (ER). Specifically, high levels of FFA in the mitochondria cause the release of ROS that in turn may destroy cell membrane and disrupt the energy production machinery. High ROS amounts into the oocytes impact the function of ER by preventing the transport and secretion of proteins which accumulate within the ER, thereby worsening the membrane stress. Oocytes that have matured in high dose palmitic acid environment have been found to be characterized by significantly altered mitochondrial function (Wu et al. 2011), impaired cumulus expansion, impaired nuclear maturation and fertilization, and blastocyst development (Aardema et al. 2011). In obese women, the follicle fluid bathing the cumulus-oocyte complex contains high levels of triglycerides and FFA (Robker et al. 2009) and high expression of ER stress marker genes (Robker et al. 2011) that are associated with poor cumulus cell morphology and with a trend poorer IVF outcomes (Jungheim et al. 2011). Very recently, it has been reported that abdominal obesity can induce local and systemic oxidative stress in both women with the polycystic ovary syndrome (PCOS) and non-PCOS women, as documented by increased levels of lipid peroxide in serum and follicular fluid (Nasiri et al. 2015). Studies inherent in the effects of obesity and ART outcomes reported a significant increase in the dose of gonadotropin required for ovarian stimulation of obese women, lower peak estradiol levels, reduced number of large follicles, and increased cancelation rates. Moreover, overweight women have significantly fewer oocytes and these were significantly smaller than oocytes from nonobese women (Zhang et al. 2015).

Obesity also affects women's fertility by impairing endometrial receptivity, which defines the ability of the endometrium to undergo changes that will allow the blastocyst to attach, penetrate, and induce changes in the stroma (Rashid

et al. 2011). Glucose metabolism has been shown to be important for the preparation of the endometrium for embryo implantation. In fact, the decidualization process is dependent on increasing expression of glucose transporters (GLUTs) (Frolova et al. 2009), in particular solute carrier family 2 (facilitated glucose transporter), member 2, an insulin-dependent SLC2A family member (Frolova and Moley 2011a). Insulin and IGF-1 receptor promote the translocation of SLC2A to the cell surface in insulin-sensitive tissues (Frolova and Moley 2011b). In addition to hyperinsulinemia, the presence of obesity negatively interplays with endometrial receptivity through androgen excess, as occurs in women with PCOS. In fact, androgen can interfere with endometrial receptivity by different mechanisms. High testosterone levels have been shown to reduce expression of homeobox A10 (HOXA10) that belongs to the homeobox genes essential for endometrial differentiation and receptivity (Cermik et al. 2003). Moreover, testosterone excess reduces the expression of Wilms tumor 1 (WT1), thereby affecting endometrial decidualization (Gonzalez et al. 2012). Finally, it has been also shown that high levels of dehydroepiandrosterone (DHEA) may reduce endometrial decidualization by inhibiting the glucose flux through the pentose phosphate pathway (Frolova et al. 2011). A clinical study involving more than 9500 ovum donation cycles from female donors with normal BMI has shown a significantly poorer outcome in terms of implantation, pregnancy, and clinical pregnancy rates in obese recipient women (Bellver et al. 2013). This indirectly supports the negative role of obesity on endometrial receptivity and, in general, on ART outcomes.

6 Obesity, Polycystic Ovary Syndrome, and Infertility

PCOS is a common reproductive and endocrinologic disorder characterized by hyperandrogenism, polycystic ovaries, and oligo-anovulation. The prevalence varies depending on which criteria are used to make diagnosis and could involve approximately 6–8 % of women in reproductive age when Rotterdam criteria were used (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004). Irregular menses commonly observed in PCOS include oligo-amenorrhea and prolonged erratic menstrual bleeding. However, 30 % of PCOS women have normal menses. More than 80 % of women presenting with symptoms of androgen excess have PCOS. Anovulatory infertility affects more than half of the women with PCOS.

A history of weight gain often precedes the development of clinical features of PCOS, particularly during the adolescent years. Obesity not only identifies the preexisting PCOS phenotypes but also can worsen the hyperandrogenic state and insulin resistance, therefore impairing the effectiveness of infertility treatments (Conway et al. 2014). The prevalence of obesity in PCOS women is relatively high, often exceeding that observed in the control non-affected population, although some recent studies have suggested that these findings may not reflect true prevalence, described by the few epidemiological studies available, rather a selection bias in evaluating clinical cohorts derived by populations attending specialized centers for treatment of this disorder. In women with PCOS, elevated levels of Antimülleran Hormone (AMH) appear to be an optimal clinical biomarker of ovarian dysfunction and low fertility (Pierre et al. 2013). Women with AMH >10 ng/ml show a significant correlation with the more severe phenotype of PCOS, including both hyperandrogenism and severe oligo-amenorrhea (Tal et al. 2014). Another typical feature of PCOS is an increased frequency and amplitude of LH pulsatile secretion that refers to an abnormal GnRH secretion. The increase hypothalamic and pituitary drive may in turn be responsible for overproduction of androgens by the ovarian theca cells (Blank et al. 2009). In addition, hyperandrogenemia induces a decrease in feedback sensitivity to both estradiol and progesterone in gonadotropic hypothalamic cells, reinforcing GnRH and LH hypersecretion (Burt Solorzano et al. 2012). This represents the first of many self-perpetuating pathophysiologic cycle in which hyperandrogenemia plays a pivotal role in the development and progression of PCOS, while

simultaneously warranting the presence of the clinical manifestations. The constant growth of follicles, along with nonselection of a dominant unit, leads to the hyperstimulation of several of these structures which maintains all the characteristic hormonal imbalances. Insulin resistance and compensatory hyperinsulinemia contribute to impaired ovarian folliculogenesis. The prevalence of this condition in PCOS ranges from 50 to 70 % and occurs independently to obesity; however, the effect of obesity on insulin resistance is additive to that of PCOS (Diamanti-Kandarakis and Dunaif 2012). A specific abnormal pattern of insulin receptor phosphorylation, namely, increased serine phosphorylation and reduced tyrosine phosphorylation, appears to be responsible for insulin resistance in PCOS (Dunaif et al. 1995). Insulin excess may also play a role in the development of the typical increased amplitude and frequency of GnRH and LH pulse secretion seen in PCOS (Kim et al. 2005). Interestingly, insulin excess may also indirectly enhance hypothalamic corticotropin-releasing hormone (CRH) secretion and appears to augment adrenal cortex sensitivity to adrenocorticotropic hormone (ACTH) stimulation with increased adrenal androgen secretion (Alesci et al. 2001). It has also been demonstrated that in the ovary insulin cooperates with LH to increase androgen synthesis through a specific activation of the steroidogenic pathways, chiefly the 17-hydroxylase/17,20-lyase (CYP17A1) activity (Jamnongjit and Hammes 2006). Studies on the role of insulin on ovarian steroidogenesis have also involved an alteration in inositol phosphoglycan signaling that seems to be able to potentiate the steroidogenic activity in thecal cells (Nestler et al. 1998). All the effects on ovarian steroidogenesis by insulin are clearly amplified in the presence of obesity, particularly the abdominal phenotype, due to the significantly higher insulin-resistant state that inversely parallels higher circulating insulin blood levels (Morales et al. 1996).

If insulin resistance may be responsible for the hyperandrogenic state, the opposite is also true. Hyperandrogenemia per se may in fact impair insulin sensitivity (Gambineri et al. 2002). This may be mediated by the upregulation of β3 adrenergic receptors and hormone-sensitive lipase expression in visceral adipose tissue (VAT) through testosterone and dehydroepiandrostenedione (DHEA) signaling (De Pergola 2000), which modify the lipolytic activity and favor the release of FFA. This increase in FFA availability causes functional and structural changes in hepatocytes and skeletal myocytes, with the accumulation of metabolites from the long-chain FFA re-esterification pathway, including acyl-CoA and diacylglycerol. In turn, these molecules can activate protein kinase C (PKC), a serine/threonine kinase which is widely accepted as pivotal for the mechanisms underlying insulin resistance, particularly through serine phosphorylation of IRS-1 (Boden 2011). In PCOS, androgen excess also appears to modify metabolic architecture and functionality in skeletal muscle, by decreasing the amount of type I muscle fibers, which are highly oxidative and insulin sensitive, and increasing the amount of type II fibers, which are glycolytic and less sensitive, as well as decreasing expression of glycogen synthase (Corbould 2007). Further mechanisms including androgen-driven proinflammatory cytokine secretion from VAT and androgen-induced interference of insulin signaling still remain poorly characterized. In the adipocytes, testosterone appears to induce serine phosphorylation of the insulin receptor substrate-1 (IRS-1), which reflects on inhibition of the metabolic effects of insulin accompanied by normal mitogenic signaling (Corbould 2007). A direct proof of the role of the adipose tissue is that an obesogenic diet with high lipid and low fiber intake can produce a hyperandrogenism by intake-induced hyperinsulinemia. Recently, advanced glycation end products (AGEs) which are cytotoxic metabolites derived from disrupted carbohydrate metabolism that may be exogenously obtained from a myriad of food typical of Westernized diets (Diamanti-Kandarakis et al. 2007). AGE deposition in the ovarian tissue induces oxidative stress and aberrant structure modification due to molecule cross-linking, leading to damage of all ovarian cell types. Hyperandrogenemia appears to inhibit glyoxalase I activity, which is an important enzymatic scavenging system for 2-oxoaldehydes, including major precursors of AGEs, thereby exacerbating the deleterious effects of AGE deposition in the ovaries, which impair, in turn, the

reproductive function (Kandaraki et al. 2012). Finally, as reported above, the low chronic inflammation state promoted by the visceral adipose tissue hypertrophy has a pivotal role in determining insulin resistance and associated hyperandrogenemia in PCOS (Spritzer et al. 2015). Overall, these aspects are emphasized by the presence of obesity, supporting its role in infertility in affected women.

7 Obesity, Ovulation Induction, and ART's Outcomes in PCOS

Weight loss is recommended as first-line therapy for the management of infertility in overweight and obese women with PCOS. Observational studies indicate that weight loss of 5–10 % can increase ovulation and pregnancy rates (Homburg 2003). This has particular relevance because obese PCOS women are also characterized by an increased rate of miscarriages (Metwally et al. 2008) and the development of pregnancy complications, including, among others, gestational diabetes and hypertension/preeclampsia (Wolfe 1998). Changes in dietary behaviors have been found to be effective in improving fertility rates in overweight and obese women with PCOS (Chavarro et al. 2007; Moran et al. 2011). These advantages have been reported even when lifestyle changes are planned prior to ART treatment (Moran et al. 2011b; Sim et al. 2014; Awartani et al. 2012). In massively obese PCOS women, bariatric surgery could be an effective option, since it has been shown that it may restore ovulation and normal cycles in the short time (Escobar-Morreale et al. 2005), favor pregnancy rates, and additionally reduce pregnancy complications (Skull et al. 2004; Dixon et al. 2005; Patel et al. 2007; Merhi 2007; Sim et al. 2014).

Obese women with PCOS have also a reduced response to fertility treatments including clomiphene citrate (CC) (Imani et al. 1999), gonadotropins (Balen et al. 2006), and laparoscopic ovarian diathermy (Gjønnaess 1994). CC is the drug of first choice for ovulation induction in these women (Legro et al. 2013). CC is a partially selective estrogen receptor modulator, and its antiestrogenic activity at the hypothalamus induces a change in GnRH pulse frequency leading to increased release of follicle FSH from the pituitary gland. The ovulation rate with CC ranges from 70–85 % per cycle, while the cumulative live birth rate ranges from 50 to 60 % for treatment up to six cycles (Balen 2013). If ovulation cannot be induced at doses of 150 mg/day, the patient is considered to be CC resistant, and failure to achieve pregnancy after six ovulatory cycles is classified as a CC failure. In 2008, the ESHRE/ASRM consensus statement concluded that metformin is less effective than CC in inducing ovulation and that there was no advantage in adding metformin to CC (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2008). This recommendation has been recently supported by the Endocrine Society Guidelines on the diagnosis and treatment of PCOS (Legro et al. 2013). However, in adult women with PCOS, there are data supporting that in many cases pretreatment with metformin may favor ovulatory response to clomiphene citrate (Pasquali 2015). In fact, in a recent multicenter, randomized, double-blind, placebo-controlled study, metformin increased live birth rates compared to placebo (41.9 % versus 28.8 %, $P = 0.014$) with the most beneficial effect seen in obese women (Morin-Papunen et al. 2012). These results are consistent with another study that evaluated pretreatment with metformin for 3 months before in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) (Kjøtrød et al. 2011). Again, a recent meta-analysis showed that metformin administration in addition to gonadotropin treatment for ovulation induction in PCOS increases the live birth and pregnancy rate and reduces serum estrogen levels improving endometrial receptivity (Palomba et al. 2014).

Aromatase inhibitors have been advocated for their efficacy in women resistant to CC (Mitwally and Casper 2001). They act through an inhibition of aromatase activity, thereby reducing estrogen production rates from androgenic substrates. This releases the hypothalamus from negative feedback, allowing for an increase in the release of FSH (Casper and Mitwally 2011). Letrozole, the most commonly used aromatase inhibitor for ovulation induction, is characterized by putative

advantages including its lack of antiestrogenic effects on the endometrium, shorter half-life when compared to CC, and a higher rate of monofollicular ovulation (Pritts 2010). A recent systematic review of RCTs and meta-analysis, including nine studies and 1783 participants, concluded that letrozole is associated with significantly higher birth rates than CC is (OR 1.64, 95 % CI 1.32–2.04) (Franik et al. 2014). A more recent large study demonstrated the superiority of letrozole compared to CC as first-line treatment for anovulatory infertility in women with PCOS (most were overweight or obese) in achieving live birth (Legro et al. 2014). There is however still some concern about several aspects involving letrozole use in infertile PCOS women, which mainly relates to the following: (i) whether the efficacy is similar in obese versus normal-weight women, (ii) the opportunity to add a lifestyle intervention plan in obese PCOS women, (iii) its likely inefficacy on androgens, (iv) the lack of definition of a called letrozole resistance, and finally (v) the fetal risk. In fact, some potential teratogenic and embryotoxic or fetotoxic activity has been reported in animal models. Therefore, further research is undoubtedly warranted in this area (Palomba 2015).

Ovulation induction with gonadotropins and laparoscopic ovarian drilling (LOD) are considered to be second-line therapies for ovulation induction by the ESHRE/ASRM (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2008). The goal of FSH administration for ovulation induction is the development of a single follicle resulting in a singleton live birth. Risks associated with ovulation induction include ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. Because women with PCOS are very sensitive to the effects of FSH, a low-dose step-up protocol is recommended (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2008). A recent study showed the efficacy of low-dose step-up FSH protocol vs. CC in inducing a higher number of pregnancy rate in the first cycle, a higher cumulative pregnancy rate, and a higher cumulative live birth rate (Homburg et al. 2012). LOD is indicated for the treatment of infertility in CC-resistant PCOS (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2008). A study has shown that a single treatment results in the establishment of ovulatory menstrual cycles in 92 % of women and pregnancy in 58 % (Gjönnaess 1984). LOD helps to improve insulin resistance (Seow et al. 2007) and ovarian androgen production as well as increase the SHBG levels (Flyckt and Goldberg 2011). These improvements have been seen to last in long-term follow-ups in 54 % of women 8–12 years after the procedure (Nahuis et al. 2011). Predictors of a poor response to LOD include a body mass index of $\geq$35 kg/m^2, serum testosterone concentrations of $\geq$4.5 nmol/L, free androgen index $\geq$15, and a duration of infertility of 3 years. Serum LH concentrations $\geq$10 IU/L at baseline are associated with a significantly greater likelihood of pregnancy (Amer et al. 2004). Lower AMH levels (cutoff at 7.7 ng/ml) were found to predict a higher chance of ovulation in PCOS women after LOD (Amer et al. 2009).

The effect of female obesity on ART outcome has been controversial by a large number of confounding variables. Although some studies suggested that women with BMI >25 kg/m^2 require higher doses of gonadotropins to achieve an adequate ovarian response and have lower pregnancy rates and higher miscarriage rates after ART, the evidence regarding the effect of BMI on live birth was weak (Maheshwari et al. 2007). Two studies from SART CORS showed a reduction of embryos, of clinical intrauterine pregnancy, of live births, and of length of gestation with increasing BMI (Luke et al. 2011a). The negative effect of BMI on ART outcome was greater among women <35 years than in women >35 years using autologous oocytes (Luke et al. 2011b). Also, the obesity impacts negatively PCOS fertility in ART. A recent study compared outcomes of IVF between PCOS with BMI < 40 kg/m^2 vs. PCOS with BMI > 40 kg/m^2 that had significantly lower pregnancy rates (Jungheim et al. 2009). Obese PCOS women consume higher amounts of gonadotropins and have higher rates of miscarriage and ovarian hyperstimulation syndrome (OHSS).

In vitro fertilization (IVF) is recommended as third-line therapy for the management of infertility

by the 2008 Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2008). Ovarian stimulation in women with PCOS poses a particular challenge, as many of these women exhibit exaggerated response, resulting in an increased risk of ovarian hyperstimulation syndrome (OHSS) and multiple gestations. To reduce these PCOS-related complications, a recent study recommended the use of a GnRH antagonist protocol, which resulted in a decrease in the incidence of OHSS as compared with GnRH agonists in PCOS patients (Griesinger et al. 2006). As an alternative to conventional IVF, one potentially useful intervention involves immature oocyte retrieval with subsequent oocyte IVM. A recent meta-analysis showed that IVM is a feasible option for subfertile women with PCOS (Siristatidis et al. 2013). The implantation rate, miscarriage rate, and live birth rate in the IVM cycles were comparable to those in the GnRH agonist and GnRH antagonist cycles (Choi et al. 2012). Finally, metformin treatment before or during ART cycles has been found to increase clinical pregnancy rates and to decrease the risk of OHSS, particularly in obese PCOS women (Tso et al. 2014).

8 Conclusions

Obesity and infertility are two conditions, often associated with each other, involving a growing number of men and women. Search for pregnancy at least in some industrialized countries is increasingly moving after 35 years because of the desire for professional development, particularly in women. We support the concept that, before applying assisted reproductive technologies, it would be appropriate to try to eliminate other possible cofactors such as excess body weight and/or hypotestosteronemia in men or hyperandrogenism in women. Changes in lifestyle, insulin-sensitizing, and bariatric surgery may be an initial alternative to ART, because of their effects on weight loss and restoring fertility. Additional targeted treatments should also be performed according to individual needs, taking into consideration that by reducing body weight, their efficacy can be ameliorated in the short and particularly in the long term.

9 Cross-References

- ▶ Adipokines and Metabolism
- ▶ Insulin Resistance in Obesity
- ▶ Overview of Metabolic Syndrome
- ▶ Type 2 Diabetes: Etiology, Epidemiology, Pathogenesis, Treatment

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Obesity, Metabolic Dysfunction, and Dementia

39

Ashley A. Martin

Contents

Abstract

Evidence is accumulating which suggests that the current obesity epidemic may precede a second epidemic of accelerated cognitive decline, dementia, and Alzheimer's disease (AD). Obesity and the consumption of obesogenic "Western"-style diets (high in saturated fats and processed sugars) promote a variety of metabolic derangements that can have adverse effects on the brain and, subsequently, cognition. Here, we review evidence which suggests that obesity and the other components of the metabolic syndrome (i.e., hypertension, gluco-dysregulation, and dyslipidemia) promote cognitive decline and increase one's risk of developing dementia and AD. We also review recent insights regarding the role of blood-brain barrier dysfunction and neuroinflammation as a mediator of these relationships. Finally, we discuss the broader implications of living in a society that promotes cognitive impairment, highlighting two particularly concerning possibilities: (1) that Western diet-induced cognitive impairments may, themselves, be as a risk factor for future obesity and (2) that obesity in childhood may be a risk factor for dementia in adulthood.

Keywords

Inhibition • Cognition • High-fat diet • Dementia • Alzheimer's disease

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Dementia and obesity are global health issues in today's society. The current prevalence of Alzheimer's disease (AD) is estimated at 44 million and is predicted to double by 2030 (Prince 2014). This estimate increases by as much as 9–14 % when the predicted rise in obesity is taken into account (Loef and Walach 2013; Nepal et al. 2014). In this chapter, we review the evidence linking cognitive impairment with obesity and discuss the comorbid metabolic derangements which might mediate this relationship. We also discuss the implications of living in a society that promotes cognitive impairment, highlighting evidence which suggests that some cognitive impairments may serve as independent risk factors for obesity.

1 Dementia and Cognitive Impairment

Dementia and its most common cause, Alzheimer's disease, is associated with progressive memory loss and deficits in higher-order control processes important for planning and carrying out goal-directed behavior ("executive function") (Amieva et al. 2004). Patients with AD exhibit loss of neurons and synapses, in addition to the extracellular plaques and intracellular neurofibrillary tangles which are the hallmarks of AD. The plaques consist of aggregated amyloid beta-peptide (αβ) (alpha-beta), whereas the neurofibrillary tangles consist of insoluble tau aggregates. Both αβ (alpha-beta) and tau have been implicated in the etiology of AD-related cognitive impairment, though the precise nature of this relationship is not completely understood (Foley et al. 2015).

The cognitive deficits associated with AD can precede the onset of the disease by several years, often being diagnosed as mild cognitive impairment (MCI). MCI refers to modest but noticeable deficits in memory, attention, and problem solving. These deficits are not so extreme that they interfere with the activities of daily life. However, these deficits tend to worsen with age, often progressing to full-blown dementia and AD within 5 years of initial diagnosis (Gauthier et al. 2006). In this regard, MCI can be viewed as a state of pre-dementia, and risk factors for MCI can be considered to be risk factors for more severe cognitive decline in late life.

Cognitive function is assessed using screening batteries which comprise a variety of tests from different cognitive domains (i.e., "memory," "attention," "inhibition"). The relevance of particular tests to certain domains and the complications associated with interpreting their results (e.g., should poor performance on 3/7 tests be considered evidence of meaningful impairment?) are issues which have been discussed in detail elsewhere (Rabbitt 1997). For the purposes of this chapter, the terms *deficit*, *decline*, and *impairment* are used to refer to any observation of significantly lower performance on a test of cognitive ability. However, we will return to the issue of specificity later on in the chapter when we discuss whether obesity is related to certain types of cognitive deficits and the implications of those deficits for future obesity and dementia risk.

2 Diet-Induced Obesity and Cognitive Impairment

Longitudinal and cross-sectional studies indicate that obesity in early adulthood or in middle age can increase one's risk of later-life cognitive impairment (for recent reviews, see Smith et al. 2011; Elias et al. 2012b). Studies in non-demented adults suggest that these impairments are diverse, affecting performance across several cognitive domains (Elias et al. 2003, 2005; Nilsson and Nilsson 2009; Gunstad et al. 2010). For instance, a large prospective study examined whether participants' self-reported BMI in midlife (~50 years of age) was related to their performance on cognitive tests administered when subjects reached the age of 80+ years old. The authors found that individuals who reported higher BMIs in midlife exhibited deficits in a variety of cognitive domains, including long- and short-term memory, psychomotor speed, verbal ability, and

spatial ability (Hassing et al. 2010). Another study used a battery of 13 tests to derive a score of general cognitive performance – they found that having a higher BMI in midlife was associated with not only poorer overall cognitive performance but also with more rapid rates of cognitive decline (Dahl et al. 2010).

Others have shown that the magnitude of age-related cognitive decline can be predicted by the lifetime duration of that individuals' obesity. In a large UK cohort study that examined the relationship between lifetime obesity and cognitive decline, participants were grouped according to the number of times they had been classified as obese at diagnostic interviews conducted in young adulthood (25 years old), middle age (44 years old), and late life (61 years old) (Sabia et al. 2009). Results showed that people who had been obese on two to three occasions during the study performed than never-obese individuals and individuals who had been obese at only one time point. These data suggest that cognitive function is affected not only by being obese, but by the amount of time one remains obese, with more chronically obese individuals demonstrating more dramatic impairment.

In addition to predicting poorer cognitive ability among healthy adults, obesity also increases one's risk of dementia and AD (for recent reviews, see Luchsinger and Gustafson 2009; Elias et al. 2012b). Studies have shown that individuals who are obese at midlife are three times more likely to be diagnosed with AD compared to normal weight individuals (Whitmer et al. 2007, 2008). Indeed, a recent meta-analysis assessing the link between midlife obesity and dementia found that being either overweight or obese was a risk factor for developing any kind of dementia later in life (Anstey et al. 2011). After midlife, the association between obesity and cognition shifts such that excess weight appears to prevent or delay the onset of dementia (García-Ptacek et al. 2014). In late life (65+ years old), malnutrition, weight loss, and sarcopenia (the loss of muscle mass associated with aging) are not uncommon – these factors may, themselves, promote cognitive impairment. On this basis, having a higher body weight very late in life may provide a buffer against cognitive impairments that would otherwise be produced by being underweight or malnourished.

The effects of obesity on cognition appear to be at least partially due to consuming a "Western"-style diet (for a recent review, see Monti et al. 2014). Consuming higher proportions of saturated fats and refined sugars has been found to increase one's risk of MCI in late adulthood (Eskelinen et al. 2008) and is a factor which differentiates between elderly individuals who do/do not carry a diagnosis of AD (Gustaw-Rothenberg 2009). Preference for high-energy "junk" foods has also been found to predict weaker performance on tests of cognitive and inhibitory control (e.g., executive function) (Riggs et al. 2010a; Jasinska et al. 2012). In children, consuming higher amounts of saturated fats has been linked to impaired memory processing (Baym et al. 2014). Studies in rodents which have systematically examined the effects of diet-induced obesity on cognition have consistently shown that consuming a high-fat diet disrupts neuronal health in areas associated with learning and memory (e.g., hippocampus) and, thereby, disrupts cognitive performance (Stranahan and Mattson 2011; Hsu and Kanoski 2014). These findings provide converging evidence that the Western-style diets which promote obesity may also promote obesity-related cognitive impairment.

One of the likeliest ways in which Western-style diets disrupt cognition is by producing the comorbid metabolic derangements that are associated with obesity (e.g., Greenwood and Winocur 2005) (see Fig. 1). Indeed, controlling for these cardiovascular risk factors tends to reduce or eliminate the association between obesity and cognitive decline, whereas comorbidity among these factors positively predicts one's risk of dementia and the magnitude of overall cognitive impairment (Reis et al. 2013; Joosten et al. 2013; Crichton et al. 2014a). In the next section, we discuss the mechanisms by which these metabolic derangements can detrimentally affect the brain and, thus, cognition.

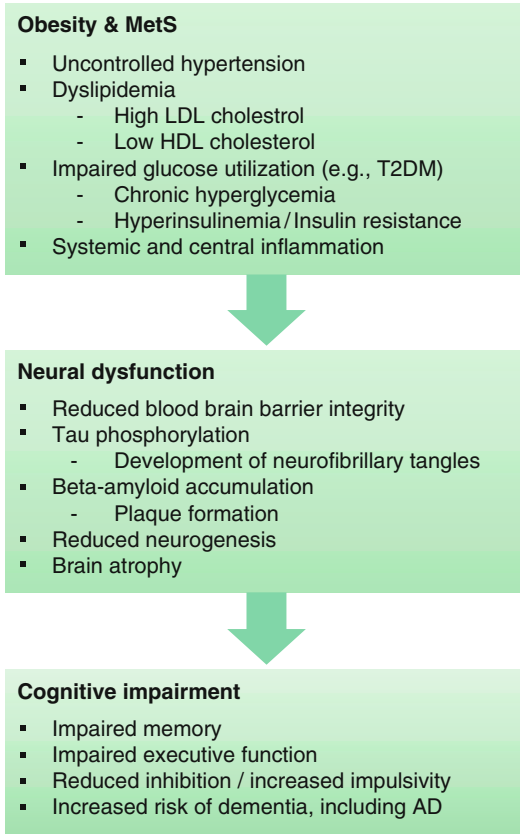

Fig. 1 Mechanisms by which obesity and obesogenic diets can promote cognitive impairment. The consumption of Western-style diets (high in saturated fats and processed sugars) leads to the development of obesity and comorbid metabolic disturbances (the metabolic syndrome, MetS). These metabolic symptoms can adversely affect brain health and, thereby, disrupt cognitive function. *AD* Alzheimer's disease

3 Mechanisms of Diet-Induced Cognitive Impairment

As has been discussed in detail in previous chapters, obesity is frequently accompanied by a host of adverse metabolic symptoms, including hyperlipidemia/high LDL ("bad") cholesterol, low HDL ("good") cholesterol, hypertension, and hyperglycemia/insulin resistance. These factors are collectively referred to as the metabolic syndrome (MetS). Here, we review the evidence linking these symptoms with cognitive decline and dementia.

3.1 Hypertension

It has long been known that hypertension increases one's risk of stroke and, consequently, increases one's risk of vascular dementia (for a historical review of the advances in this field, see Elias et al. 2012a). Chronic high blood pressure can cause hypertrophy of smooth muscle cells, alter arterial resistance, and impact the hemodynamic equilibrium of brain tissues which, together, may promote cardiovascular disease and AD (see Rios et al. 2014). Disruptions in the renin-angiotensin system (RAS), the hormonal system which regulates blood pressure, may also contribute to cognitive decline by influencing the aggregation and cytotoxic effects of αβ (alpha-beta) (Savaskan 2005; Kehoe and Wilcock 2007). Indeed, higher numbers of RAS precursor molecules and their receptors have been found in the brains of individuals with AD compared to age-matched controls, suggestive of a causal link between blood pressure dysregulation and cognitive impairment (Arregui et al. 1982; Savaskan et al. 2001). Studies from rodent models of hypertension suggest that high blood pressure disrupts blood-brain barrier (BBB) integrity and promotes the accumulation of αβ (alpha-beta)-like bodies in brain areas involved in decision making and memory (i.e., frontal cortex, hippocampus), thereby disrupting cognitive performance (Gentile et al. 2009; Carnevale and Lembo 2011). Notably, these effects appear to be preceded by the activation of microglia and proliferation of inflammatory cytokines (Carnevale et al. 2012), suggesting that neuroinflammation may mediate the effects of hypertension on cognition.

Supporting the idea that hypertension produces meaningful effects on brain pathology, several longitudinal studies have shown that individuals who exhibit higher blood pressure in midlife are at increased risk of developing dementia and cognitive impairment later in life (for a review of these relationships, see Tzourio et al. 2014). Compared to healthy individuals, elevated blood pressure has been observed in individuals with AD, often preceding the onset of the disease by several years (Skoog et al. 1996; Skoog and Gustafson 2006).

High blood pressure in midlife has also been linked with increased amyloid plaques and neurofibrillary tangles (Sparks et al. 1995; Petrovitch et al. 2000; Shah et al. 2012). Consistent with a causal link between hypertension and cognition, taking antihypertensive medications tends to reduce one's risk of developing dementia (Tzourio et al. 2014).

Hypertension also promotes cognitive impairment in non-demented individuals. Studies have shown that high blood pressure increases one's risk of being diagnosed with mild cognitive impairment (MCI) (Reitz et al. 2007) and predicts the level of impairment observed in these individuals (Goldstein et al. 2013). High blood pressure in midlife is inversely related to performance on a variety of cognitive tests, such as those assessing verbal memory and executive function (Launer et al. 1995; Elias et al. 2003). Indeed, high blood pressure was recently found to be the strongest MetS predictor of future cognitive performance (Levin et al. 2014). Fluctuations in blood pressure can also impact cognition and dementia risk (Alperovitch et al. 2014; Crichton et al. 2014b). This finding is novel in that is suggests that high blood pressure need not be chronic to detrimentally impact cognition.

3.2 Impaired Glucose Utilization

Type II diabetes mellitus (T2DM) is characterized by chronically high glucose levels (hyperglycemia), either as a result of reduced insulin levels (hypoinsulinemia) or reduced insulin effectiveness (insulin resistance). Insulin resistance can further result in hyperinsulinemia as the body attempts to compensate for reduced insulin effectiveness. These disruptions in gluco-regulation can have adverse effects on the brain and, consequently, cognitive functioning (for recent reviews, see Geijselaers et al. 2015).

One of the most direct ways that T2DM and insulin resistance can impact cognition is by altering brain insulin levels. Insulin plays a critical role in promoting neuronal health, neurogenesis, and plasticity, and evidence suggests these insulin pathways are disrupted in AD (Craft et al. 2013). In line with this idea, studies have shown that central insulin administration can be effective in improving cognitive performance in individuals with AD (Haj-ali et al. 2009; Freiherr et al. 2013; Holscher 2014; Claxton et al. 2015). Other evidence suggests that insulin could modulate the production of AD-related proteins (e.g., APP, tau) and thereby contribute to the development of AD pathology and cognitive impairment (De Felice et al. 2014; Umegaki 2014; Steculorum et al. 2014). T2DM appears to have a particularly deleterious effect on the hippocampus – an area of the brain important for a variety of memory and learning processes (den Heijer et al. 2003; Korf et al. 2006; Gold et al. 2007; Bruehl et al. 2009). The hippocampus contains a high proportion of insulin receptors and is highly vulnerable to metabolic insults; on this basis, it has been suggested that hippocampal-dependent memory deficits may be an early marker of diabetes-related cognitive impairment (e.g., Gold et al. 2007).

Consistent with a causal link between glucodysregulation and cognition, T2DM has been implicated as a risk factor for cognitive decline. A recent meta-analysis of 20 longitudinal studies concluded that diabetes was not only a risk factor for MCI and Alzheimer's disease but also for any other type of dementia (Cheng et al. 2012). Indeed, diabetic individuals are twice as likely to develop AD and other dementias compared to individuals without diabetes (Ott et al. 1999; Ahtiluoto et al. 2010; Mayeda et al. 2013). In non-demented individuals, diabetes (Gregg et al. 2000; Kanaya et al. 2004) and hyperinsulinemia/glucose intolerance (Kalmijn et al. 1995; Yaffe et al. 2004) are also predictive of cognitive impairment.

Midlife diagnosis of T2DM appears to be a particular concern, being linked to accelerated cognitive aging and worse cognitive performance. A recent prospective longitudinal study conducted in 13,351 US adults found that midlife diabetes was associated with a 19 % greater cognitive decline over 20 years, with greater impairments occurring in individuals with longer durations of diabetes (Rawlings et al. 2014).

One reason that early-to-midlife diagnosis of MetS may be so detrimental to later-life cognitive function is because earlier development of obesity and MetS confers a greater chance for long-term exposure to comorbid metabolic disturbances that, over time, can have cumulative effects on cognitive performance (i.e., midlife obesity may be a proxy for obesity duration and, consequently, duration of exposure to the MetS). In line with this possibility, studies have found more extensive cognitive impairments in individuals with longer durations of T2DM (Grodstein et al. 2001; Elias et al. 2005). These findings suggest that chronic exposure to diabetes in midlife proportionally impacts cognitive function in late life.

3.3 Dyslipidemia

The MetS is characterized by high blood triglycerides (hyperlipidemia) and high levels of LDL ("bad") cholesterol and low levels of HDL ("good") cholesterol. Aberrant lipid metabolism is implicated in AD pathogenesis because lipids regulate the transport and activity of several proteins implicated in AD. For instance, studies have shown that high LDL cholesterol can affect the aggregation of tau and αβ (alpha-beta) (for recent reviews, see Di Paolo and Kim 2011; Reitz 2012). In the brain, cholesterol is found mostly in the cellular membranes of glial cells and neurons (Dietschy and Turley 2001), and studies suggest that high membrane cholesterol may make hippocampal neurons more susceptible to tau neurotoxicity (Nicholson and Ferreira 2009).

Consistent with the idea that dyslipidemia can have adverse effects on brain health, studies have observed that low HDL levels can increase one's risk of AD (van Exel et al. 2002) and that high HDL levels reduces one's risk (Reitz et al. 2010). Other studies have shown that AD patients have been found to exhibit reduced HDL (Kuo et al. 1998), with the magnitude of the reduction predicting the severity of cognitive impairment in these individuals (Merched et al. 2000). AD brains also display greater numbers of "adipose inclusions" or "lipoid granules," suggestive of dyslipidemia (Foley 2010). High HDL cholesterol is also associated with cognitive impairment in non-demented individuals; notably, taking cholesterol-lowering medications (i.e., statins) appears to alleviate this impairment (Yaffe et al. 2002).

This relationship between dyslipidemia and cognition is at least partially mediated by allele 4 of the apolipoprotein E gene (ApoE4). ApoE is necessary for lipid metabolism and plays a fundamental role in regulating cholesterol metabolism in the brain (Di Paolo and Kim 2011). In addition to being a risk factor for the MetS, ApoE is a risk factor for AD (Mahley and Rall 2000; Liu et al. 2013). In fact, ApoE is the strongest genetic risk factor for sporadic AD, the most common form of AD (Corder et al. 1993; Bertram et al. 2010). In patients with AD, ApoE4 is positively associated with the presence of amyloid plaques (Saunders et al. 1993; Schmechel et al. 1993; Han et al. 1994). Although it has been debated whether amyloid plaques causally contribute to the symptomology of AD, these findings indicate that the same risk factors for obesity are also risk factors for cognitive decline.

3.4 Inflammation

One of the obvious consequences of obesity is excess adipose tissue. While adipose tissue was historically believed to be inert, it is now known that adipose tissue contributes to the proliferation of a number of cytokines and adipokines which can have adverse effects on brain health and function (Gregor and Hotamisligil 2011). Studies have shown that obesity and consuming a high-fat, Western diet lead to systemic low-grade inflammation and excess circulating free fatty acids. These circulating cytokines and fatty acids compromise the integrity of the blood-brain barrier (BBB), initiating a cascade of central inflammation that disrupts neural function in brain areas important for learning and memory (e.g., hippocampus) (see Fig. 2).

Supporting the idea that brain inflammation might contribute to cognitive impairment, studies in both rats and humans have shown that systemic

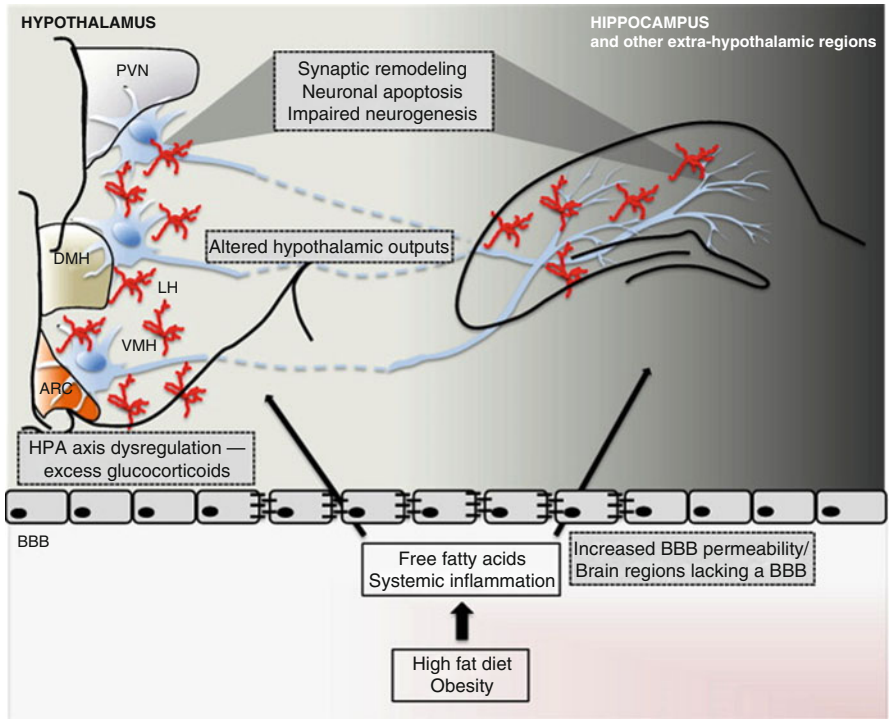

Fig. 2 Neuroinflammation as a potential mediator of high-fat diet/obesity and cognitive dysfunction. High-fat diets and/or obesity lead to increased levels of circulating free fatty acids and pro-inflammatory cytokines, which in turn gain access to the hypothalamus by increasing BBB permeability and/or via areas that lack an effective BBB (e.g., ARC). This initiates central inflammation, leading to synaptic remodeling, neuronal apoptosis, and impaired neurogenesis. These processes disrupt internal hypothalamic circuitry and potentially hypothalamic outputs to brain regions important for cognitive function (e.g., hippocampus). *ARC* arcuate nucleus, *PVN* paraventricular nucleus, *VMH* ventromedial nucleus (Reprinted with permission from Miller and Spencer 2014)

inflammation (with or without concomitant obesity) is associated with reduced neurogenesis, learning deficits, and dementia (for reviews, see Miller and Spencer 2014; Hsu and Kanoski 2014). Inflammation may also lead to brain atrophy and, thereby, contribute to cognitive dysfunction. Indeed, a recent systematic review which assessed the link between obesity and brain volume found that increased adiposity is associated with atrophy in the frontal and temporal lobes – brain areas critical for higher-order executive functions, associative learning, and memory (Willette and Kapogiannis 2015). Together, these findings implicate inflammation-mediated decreases in neuronal health and brain volume as one factor linking obesity to cognitive impairment.

4 Is Cognitive Impairment a Risk Factor for Future Weight Gain?

It is generally accepted that the obesity epidemic is due to the increased availability of food and food cues available in today's environment. Coined the Western diet, the foods typically consumed in Westernized countries are palatable and energy rich, characterized by high amounts of fats and simple sugars. These foods increase our motivation to eat in their own right simply by being highly palatable and, thus, tempting. However, evidence is accumulating which suggests that another reason we overeat these foods is because we are becoming less able to *resist* the temptation of eating them.

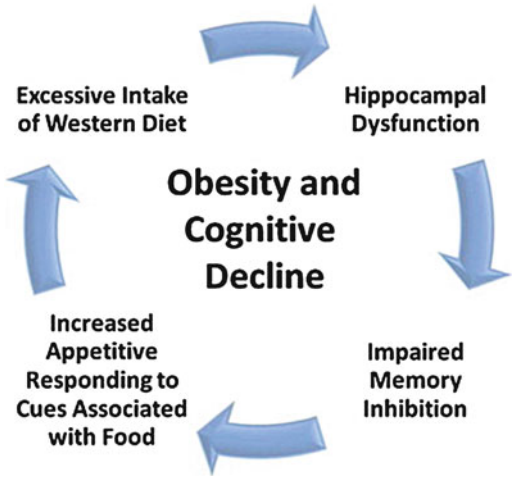

Fig. 3 A "vicious cycle" model of obesity and cognitive impairment. Consuming a high-fat diet disrupts hippocampal function, leading to deficits in cognitive control processes (e.g., memory inhibition) that are important for enabling individuals to ignore thoughts about food. Consequently, they become more reactive to food cues in the environment. This increased food-cue reactivity results in overconsumption of the Western diet, perpetuating the cycle of obesity and cognitive dysfunction

Studies in rats suggest that obesity and obesogenic diets preferentially disrupt cognitive-inhibitory processes that are important for enabling us to resist responding to incentives (see Hsu and Kanoski 2014). These cognitive-inhibitory deficits are thought to compromise one's ability to resist thinking about food reward, thereby increasing the likelihood that an individual will eat when confronted with food cues (i.e., increases food-cue reactivity). This perpetuates the overeating of high-energy foods and, thus, contributes to a "vicious cycle" of diet-induced cognitive impairment and obesity (see Fig. 3).

Cognitive-inhibitory deficits have also been linked to obesity in humans. Recent systematic reviews have shown that obesity is consistently associated with impaired executive function (Reinert et al. 2013) and brain atrophy in the regions which underlie executive function (i.e., frontal cortex, hippocampus) (Willette and Kapogiannis 2015). Cognitive inhibition contributes to executive function by enabling individuals to suppress or ignore outdated associations from memory and to resist attending to distracting stimuli in the environment. This ability to filter relevant information from irrelevant information is critical for working memory and cognitive flexibility – the primary processes associated with executive control (Miyake et al. 2000). Indeed, numerous studies have reported that obese individuals perform worse than nonobese individuals on working memory, cognitive flexibility, and inhibition – processes traditionally associated with executive control (Waldstein and Katzel 2006; Nederkoorn et al. 2006; Gunstad et al. 2007; Cserjesi et al. 2009; Verbeken et al. 2009; Fergenbaum et al. 2009; Nederkoorn et al. 2012; Schwartz et al. 2013; Wirt et al. 2014).

Consistent with the idea that these deficits may causally contribute to obesity, studies in humans have shown that poor inhibitory performance predicts increased food intake (Guerrieri et al. 2007a, b, 2008), increased weight gain (Francis and Susman 2009; Seeyave et al. 2009), and resistance to weight loss (Nederkoorn et al. 2007, 2010). Similarly, studies in rats have shown that the likelihood of becoming obese on a Western diet depends upon whether that diet produces BBB pathology and concomitant deficits in cognitive-inhibitory control (Davidson et al. 2012, 2013). Together, these data provide converging evidence that deficits in cognitive-inhibitory processes may serve as risk factors for overeating and weight gain (see Martin and Davidson 2014).

5 Childhood Obesity as a Risk Factor for Accelerated Cognitive Aging

The effects of living in an obesogenic environment are not limited to adults. Approximately 4–8 % of children today exhibit symptoms of the metabolic syndrome, and this prevalence increases to as much as 30 % in children who are obese (Li et al. 2006; Cook et al. 2008; Skelton et al. 2009). Like adults, obese children have been shown to exhibit a variety of cognitive deficits, in areas such as verbal ability,

inhibition, and working memory (for a recent systematic review, see Liang et al. 2014). Special attention has been paid to executive function, which appears to be consistently impaired in children and adolescents (Reinert et al. 2013). These impairments in cognition appear to be at least partially mediated by consumption of a Western-style diet, as consumption of energy-rich foods has been found to correlate with impaired executive function (Riggs et al. 2010a, b) and memory processing (Baym et al. 2014).

Executive function (e.g., cognitive-inhibitory control) plays a fundamental role in cognitive development in childhood (Harnishfeger and Bjorklund 1993) and has been implicated as a risk factor for future weight gain (see section Is Cognitive Impairment a Risk Factor for Future Weight Gain?). Thus, deficits in executive control could have widespread effects on behavior, including eating behavior. A particular concern is the possibility that childhood obesity may irreversibly impact brain function, producing cognitive deficits that may persist throughout the lifespan. The frontal lobes mediate many of the processes associated with executive function, and this brain region does not fully mature until early adulthood (Fuster 2002). Thus, it is possible that obesity-related insults that occur in childhood could set the stage for more serious cognitive problems in adulthood.

In addition to being exposed to the same dietary risk factors for obesity as adults (i.e., high-fat and high-sugar foods), children are at additional risk for developing MetS as a function of fetal programming. Obese mothers' metabolic derangements can impact the development of the fetus during gestation, and this can "program" the offspring to be more or less susceptible to obesity and the MetS in adulthood (Taylor and Poston 2007). Indeed, children of obese mothers are more than twice as likely to be obese themselves compared to children born of nonobese mothers (Whitaker 2004). Regarding cognitive impairment, maternal obesity has been associated with aberrant neuronal development in brain areas responsible for learning and memory function (Tozuka et al. 2009, 2010; Niculescu and Lupu 2009; Bilbo and Tsang 2010). Together, these data suggest that children are a particularly at-risk group for developing both obesity and obesity-related cognitive impairments.

6 How Do We Prevent Obesity-Related Cognitive Impairments in an Environment that Is Obesogenic?

In today's environment where access to palatable, energy-rich foods is the norm, it is not surprising that we are facing an obesity epidemic. Unfortunately, this means that in order to prevent obesity-related cognitive impairment, it is necessary to prevent or at least offset the rates of obesity and the MetS. The most obvious avenues for preventing diet-induced cognitive decline are to change one's diet or to offset diet-induced weight gain via exercise (e.g., Stranahan and Mattson 2011). Unfortunately, for most individuals, losing weight is not an easy task. Thus, it is likely that smaller interventions aimed at minimizing the metabolic disturbances associated with obesity will ultimately be more successful at preventing future cognitive decline than strategies focused on weight reduction. For instance, medications which improve hypertension and blood glucose homeostasis have been successful at improving cognitive performance in individuals and animals with AD (Valenti et al. 2014). Antidiabetic drugs like thiazolidinediones (TZDs) might also be effective at improving cognitive performance. TZDs act as PPAR-y agonists, and studies have shown that administration of TZDs and other PPAR-y agonists can promote hippocampal health and memory performance in rodent models of AD (Zolezzi and Inestrosa 2013). The use of angiotensin-II receptor blockers (ARBs or sartans) – compounds typically used to treat cardiovascular disorders – may also be used to protect against neuroinflammation and BBB dysfunction and, thereby, reduce one's risk of cognitive impairment and dementia (Villapol and

Saavedra 2015). While weight loss is easier prescribed than accomplished, there is some evidence which suggests that modest dietary changes could also have meaningful effects on neurogenesis and, therefore, be used to moderate one's risk of cognitive decline (Maruszak et al. 2014).

7 Conclusion

Evidence suggests that, without reductions in the prevalence of obesity, we can expect the prevalence of dementia to increase as the current population ages. On this basis, combating obesity should be a priority of governments and health providers. Targeting the metabolic disturbances associated with obesity will be critical, as evidence suggests that the constellation of factors associated with the MetS may independently and collaboratively predispose one to later-life cognitive impairment. These efforts should be directed primarily at obese children (who are likely to become obese adults) and at middle-aged adults who are at increased risk of developing cognitive decline and dementia in old age. More precise characterization of the cognitive deficits associated with obesity will be necessary for enabling us to determine the full impact of these impairments on behavior, particularly eating behavior and future obesity risk.

8 Cross-References

- Brain Regulation of Feeding and Energy Homeostasis
- Childhood Environment and Obesity
- Diet and Obesity (Macronutrients, Micronutrients, Nutritional Biochemistry)
- Dyslipidemia in Obesity
- Fetal Metabolic Programming
- Linking Inflammation, Obesity, and Diabetes
- Obesity and Cardiac Disease
- Overview of Metabolic Syndrome
- Prevention and Treatment of Childhood Obesity and Metabolic Syndrome
- Type 2 Diabetes: Etiology, Epidemiology, Pathogenesis, Treatment

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Linking Obesity, Metabolism, and Cancer

40

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Abstract

Obesity is an urgent and growing global health problem, reaching epidemic proportions. In addition to diabetes and cardiovascular disease, epidemiological evidence shows that people who are obese or overweight are at increased risk of developing some types of cancer. Obesity may also affect tumor progression for many cancers, and obesity presents an obstacle in cancer treatment. In this chapter, we discuss potential mechanisms linking obesity to cancer development, progression, and mortality, including energy imbalance, insulin resistance, and altered hormone signaling. We especially focus on chronic inflammation and its local and systemic effects. Understanding the mechanisms involved in obesity-cancer link is important to prevent both cancer and obesity, but also for developing potential therapeutics.

Keywords

Obesity • Cancer • Metabolism • Mechanisms • Inflammation • Prevention • Interventions

1 Key Points

1. Excess body weight is a significant health risk for cardiovascular disease, type 2 diabetes, and various types of cancer.
2. Heterogeneity of obesity exists at cellular/local and the whole body/systemic level.

3. Obesity is characterized by an increase in fat mass, increased macrophage infiltration of white adipose tissue, and abnormal adipokine and cytokine production, contributing to generation of a state of low-grade chronic inflammation.
4. Inflammation provides an important link between obesity, metabolism, and cancer.
5. There are significant differences in the inflammatory profile of distinct abdominal fat depots.

2 Introduction

Obesity rates have been steadily climbing over recent decades, with significant implications for public health. Worldwide obesity has more than doubled since 1980; in 2014, more than 1.9 billion adults were overweight, and of these over 600 million were obese (WHO 2015). Obesity is reaching epidemic proportions in the USA, affecting more than one third of the population (Ogden et al. 2014). The prediction is that by the year 2015, 2.3 billion adults will be overweight and 700 million obese. There are multiple common health consequences of overweight and obesity. It is a risk factor for cardiovascular disease, type 2 diabetes mellitus, hypertension, dyslipidemia, musculoskeletal disorders, especially osteoarthritis, some cancers, and many psychological effects and psychosocial problems (Rossen and Rossen 2012). Increased mortality has also been associated with obesity (Berrington de Gonzalez et al. 2010). In addition to its serious health consequences, obesity costs and health-care expenses for obesity-related problems of nearly 21% of annual medical spending in the USA are greater than the investment in any other medical condition (Cawley and Meyerhoefer 2012; Kral et al. 2012).

Obesity is defined as abnormal or excessive accumulation of fat. Definitions for classifying and reporting healthy weight, overweight, and obesity in populations have historically been based on measures of weight and height rather than clinical measures of adiposity. By far the most widely used weight-for-height measure is the body mass index (BMI), which is defined as weight (in kilograms) divided by height (in meters squared); BMI of 18.8–24.0 kg/m^2 indicates healthy weight, 25.0–29.9 overweight, and BMI of 30 kg/m^2 or higher obesity (Centers for Disease Control and Prevention and Overweight and obesity 2015). Although BMI is the same for both sexes and for all ages of adults, it should be considered as a rough guide, because it may not correspond to the same degree of fatness in different individuals. Additionally, heritability of obesity and variability of BMI related to the race, ethnicity, and culture indicate that the obesity standards may need to be reevaluated. There are other methods to evaluate body fat and body fat distribution, such as waist circumstances (WC), a body shape index (ABSI), and estimating the visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (SAT) by ultrasound, computed tomography, and magnetic resonance imaging. The heterogeneity of obesity is shown by existence of two distinct subsets of obese individuals, a subgroup who have reduced cardiometabolic risk despite being obese, as opposed to a subset of lean individuals with a high risk for cardiometabolic complications (Bernstein 2012; Boonchaya-anant and Apovian 2014; Navarro et al. 2015; Badoud et al. 2015). These phenotypically distinct subgroups have been recognized in the early 1980s and are known as metabolically healthy obese (MHO) and metabolically unhealthy normal weight (MUNW). The prevalence of MHO varies from 20 % to 30 % among obese individuals. Compared to regular obese individuals, MHO subjects have high levels of insulin sensitivity and the absence of diabetes, dyslipidemia, or hypertension. MHO phenotype is characterized by a more favorable inflammatory profile, smaller adipocyte cell size, less visceral fat, and less infiltration of macrophages into adipose tissue (Navarro et al. 2015).

3 The Association of Obesity and Cancer

The worldwide burden of cancer continues to grow. Cancer is the leading cause of death in developed countries and the second leading cause of death in developing countries (Torre et al. 2015; Siegel et al. 2015; Howlader

et al. 1975). About 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred in 2008 (Torre et al. 2015). A total of 1,658,370 new cancer cases and 589,430 cancer deaths are projected to occur in the USA in 2015 (Siegel et al. 2015). The number of cancer cases is expected to rise due to both worldwide population growth and an increasingly aged population.

Adiposity is associated with the risk of developing several types of cancer (Table 1). The World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) conducted a comprehensive and systemic evaluation of the available literature on diet, physical activity, weight, and cancer prevention, considering epidemiologic, clinical, and experimental data, and concluded that body fatness was an established risk factor for several cancers (World Cancer Research Fund and American Institute for Cancer Research 2007). That report, now in its second edition and routinely updated online (World Cancer Research Fund and American Institute for Cancer Research 2007; http://www.dietandcancerreport.org), has shown that excess body fat is a cause of cancer at several sites (postmenopausal breast, endometrium, colon, esophagus, gallbladder, pancreas, kidney, prostate, liver) (World Cancer Research Fund and American Institute for Cancer Research 2007; http://www.dietandcancerreport.org; De Pergola and Silvestris 2013; Byers and Sedjo 2015). WCRF/AICR has estimated that about 21 % of these obesity-associated cancers in the USA can be attributed to obesity, 17 % in Great Britain, 13 % in Brazil, and 11 % in China (http://www.dietandcancerreport.org). Very recently, Arnold et al. estimated that 3.6 % of all incident cancer in the world in 2012 was caused by obesity (Arnold et al. 2015). Large epidemiological studies and meta-analyses (Dobbins et al. 2013; Ungefroren et al. 2015) showed a statistically significant positive correlation between obesity and incidence in 5 of 11 types of cancer in men (colon, gallbladder, malignant melanoma, pancreatic, and kidney) and 8 of 13 types of cancer in women (colon, endometrial, esophagus, gallbladder, leukemia, pancreatic, postmenopausal breast, and kidney). However, no correlation was found between obesity and adenocarcinoma of the esophagus and leukemias in men, and in both sexes there was no positive correlation between obesity and multiple myeloma, non-Hodgkin's lymphoma, thyroid, and rectal cancer. Differences in adiposity-associated carcinogenic effects at different cancer sites and between men and women indicate that these obesity-associated metabolic changes are determined and dictated by the biology of that particular tissue and by the sex hormones. In majority of these studies, BMI was correlated with cancer risk. When examined links of BMI and the most common site-specific cancers using the precise statistical association between BMI and cancer epidemiology, Bhaskaran et al. (2014) revealed a nonlinear correlation in most tumor types, further suggesting that different mechanisms are associated with different cancer sites and different patient subgroups. Furthermore, their statistical methods helped to elucidate the phenomenon of BMI being positively correlated with postmenopausal breast cancer, but negatively with premenopausal breast cancer, because a nonlinear correlation with a peak at 22 kg/m^2 was found in premenopausal breast cancer; with a further increase in BMI, there was a decrease in the incidence of this cancer (Ungefroren et al. 2015; Bhaskaran et al. 2014).

3.1 Adiposity Patterns and Heterogeneity

Adiposity pattern and for adipose tissue topography, in particular the upper (central, android) and lower (peripheral, gynoid) types of obesity, might also be important in relation to cancer. Studies have demonstrated that expansion of visceral adipose tissue (VAT) rather than subcutaneous adipose tissue (SAT) depots is critical for the development of obesity-associated insulin resistance (Lee et al. 2013), and even that, in overweight/obese subjects, expansion of SAT depots may even be protective. However, absolute quantification of VAT and SAT fail to reflect the relative distribution of body fat, and data suggest that a high VAT/SAT ratio, a measure of relative body fat distribution between VAT and SAT depots, is a

Table 1 Linking obesity to risk for selected cancers: proposed mechanisms and a role of inflammation

Cancer	Associated with increased BMI and preventable[a]	Proposed mechanism(s)	Inflammation-driven cancers and inflammatory mediators most likely involved	References
Breast (postmenopausal)	17 %	Systemic or local estrogen and inflammatory factors	COX-2, CXCR4, and CCR7 in metastasis	(World Cancer Research Fund and American Institute for Cancer Research 2007; http://www.dietandcancerreport.org; Byers and Sedjo 2015; Sethi et al. 2012; Muller et al. 2001)
Endometrial	50 %	Endogenous circulating estrogen from adipose tissue	Circulating and local tissue cytokines might be involved	(World Cancer Research Fund and American Institute for Cancer Research 2007; http://www.dietandcancerreport.org; Byers and Sedjo 2015)
Ovarian	5 %	Systemic and local tissue inflammation	CXCR4, SDF-1, CXCL12, and IL-8 in invasion and growth	(World Cancer Research Fund and American Institute for Cancer Research 2007; http://www.dietandcancerreport.org; Byers and Sedjo 2015; Aggarwal and Gehlot 2009; Sethi et al. 2012)
Colorectal	16 %	Systemic inflammation, cytokines, leptin, IGF-1	IL-6, COX-2, and 5-LOX in increased risk	(World Cancer Research Fund and American Institute for Cancer Research 2007; http://www.dietandcancerreport.org; Byers and Sedjo 2015; Multhoff et al. 2012; Maury and Brichard 2010; Sethi et al. 2012)
Esophagus	35 %	Acid reflux causing local inflammation	COX-2 in increased risk, invasion, and angiogenesis	(World Cancer Research Fund and American Institute for Cancer Research 2007; http://www.dietandcancerreport.org; Byers and Sedjo 2015; Sethi et al. 2012)
Gallbladder	21 %	Gallstones causing local inflammation	MMP-9 in aggressiveness and poor prognosis; VEGF, TNF-α, and NF-κB in the lymphangiogenesis	(World Cancer Research Fund and American Institute for Cancer Research 2007; http://www.dietandcancerreport.org; Byers and Sedjo 2015; Sethi et al. 2012; Du et al. 2014)
Pancreatic	19 %	Systemic inflammation and other circulating factors	IL-1, COX-2, MMP-9 in metastasis, and cell invasion	(World Cancer Research Fund and American Institute for Cancer Research 2007; http://www.dietandcancerreport.org; Byers and Sedjo 2015; Maury and Brichard 2010; Sethi et al. 2012)
Liver	27 %	Fatty infiltration with chronic local inflammation	Oxidative stress and ROS, IL-6, and other inflammatory mediators in liver carcinogenesis	(World Cancer Research Fund and American Institute for Cancer Research 2007; http://www.dietandcancerreport.org; Byers and Sedjo 2015; Ràfols 2014; Louie et al. 1831;

(*continued*)

Table 1 (continued)

Cancer	Associated with increased BMI and preventable[a]	Proposed mechanism(s)	Inflammation-driven cancers and inflammatory mediators most likely involved	References
				Headland and Norling 2015; Aggarwal and Gehlot 2009; Sethi et al. 2012; Aleksandrova et al. 2014)
Kidney	14 %	Systemic inflammation and growth-stimulating factors	5-LOX in tumor progression	(World Cancer Research Fund and American Institute for Cancer Research 2007; http://www.dietandcancerreport.org; Byers and Sedjo 2015; Sethi et al. 2012)
Prostate	11 %	Systemic inflammation, other circulating factors, such as IGF-1	IL-6, IL-8, and COX-2 in angiogenesis and clinically more aggressive form of prostate cancer	(World Cancer Research Fund and American Institute for Cancer Research 2007; http://www.dietandcancerreport.org; Byers and Sedjo 2015; Muller et al. 2001; Sethi et al. 2012)

[a]The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) estimated the preventable fraction for selected cancers in the USA attributed to excess adiposity (World Cancer Research Fund and American Institute for Cancer Research 2007; http://www.dietandcancerreport.org)

unique risk marker independent of overall obesity. Less is known regarding associations between adipose depots and cancer risk. A recent study by Murphy et al. (2014) provides insight into relationships between specific depots and cancer risk and suggests also differential relationships among men and women; total adipose tissue and VAT were positively associated with cancer risk among women and no association with cancer risk among men (Murphy et al. 2014). Visceral abdominal fat was associated with an increased risk of colorectal adenoma; the findings of the study implicate abdominal VAT in the development and progression of colorectal adenoma, and it was a better obesity index for colorectal adenoma than BMI in both sexes (Nagata et al. 2014). There is a growing appreciation of a pathogenic role of ectopic fat, supported by recent findings that the visceral adiposity is associated with incident cardiovascular disease and cancer (Britton et al. 2013), renal cell carcinoma (Zhu et al. 2013), and gastrointestinal cancers (Harada et al. 2015). In terms of body shape, a recent study shows that body shape is not a risk for breast cancer and that being "apple shaped" is not any riskier than being "pear shaped" with more fat on the hips, thighs, and buttocks, for the breast cancer risk (Kabat et al. 2015).

Evidence shows that molecular and metabolic characteristics of white adipose tissue, immune cell infiltration, and adipokine production are associated with MHO and MUNW phenotype and that biological pathways and processes such as oxidative phosphorylation, branched-chain amino acid catabolism, and fatty acid beta-oxidation differ between these phenotypes (Badoud et al. 2015). The potential role of genetics, but also lifestyle factors such as diet, needs to be clarified in MHO (Navarro et al. 2015). However, only few studies have addressed the relationship of MHO and MUNW phenotype with cancer. One of those studies was a 15-year prospective study conducted in Cremona, Italy, where the prevalence of MHO was relatively low, only 11 % (Bernstein 2012; Calori et al. 2011). These subjects had normal sensitivity to insulin, and their all-cause cardiovascular disease and cancer mortality, adjusted for age and sex, was lower than in obese insulin-resistant people (Calori et al. 2011). Although the prevalence of MUNW

is higher and more common in Asian population, its association with cancer has not been studied, according to our knowledge.

Adipose tissue is heterogeneous even at the cellular level, consisting of two types of fat with morphological and functional diversity. White adipose tissue (WAT) stores energy reserves as triglycerides, whereas brown adipose tissue (BAT) contributes to metabolism through thermogenesis derived from oxidation of glucose and lipids (Ràfols 2014).

4 Potential Mechanisms Linking Obesity and Cancer

Understanding the link between being overweight or obese and a wide variety of cancers, as well as the biological mechanisms involved, remains an evolving and currently very active area of research. The complex physiological changes that occur with obesity include alterations in the adipose tissue production of bioactive factors, growth factors, hormones, and reactive oxygen species (ROS) that can impact the development of cancer (Ungefroren et al. 2015; Louie et al. 1831). Underlying the comorbid disease states that are associated with obesity including many cancers is a state of chronic low-level inflammation (Ungefroren et al. 2015; Louie et al. 1831). Inflammation has been implicated in every stage of cancer development including transformation, survival, proliferation, invasion, angiogenesis, and metastasis (Multhoff et al. 2012). We will briefly discuss inflammation, mechanisms linking obesity and cancer, as well as the directly or indirectly underlying inflammatory component of these mechanisms.

4.1 The Role of Inflammation

Inflammation is a complex biological response that can result in both local tissue and systemic physiological changes. Acute inflammation is a rapid high-grade response to tissue damage or pathogen invasion. The cascade of chemokines, cytokines, and immune cell infiltration into a damaged, necrotic, or infected tissue is initiated by cells of the innate immune system consisting of macrophages, mast cells, and other stromal-vascular cell types. Chemokines produced by resident cells recruit circulating neutrophils from the microvasculature into the damaged tissue. Activated neutrophils then release antimicrobial peptides and ROS to kill invading pathogens. At this point, either the wound healing response will continue, or assistance from the adaptive immune system (B and T cell mediated) will be initiated. The wound healing process involves tissue remodeling including cellular hyperplasia and angiogenesis triggered by cytokines and growth factors released into the local environment (Headland and Norling 2015).

Obesity is the result of a hypertrophic and hyperplastic response of adipocytes within adipose tissue to caloric intake in excess of the requirement for metabolic homeostasis. This is usually the result of chronic positive energy balance, decreased energy expenditure, or both. Obesity is also characterized by a state of chronic low-grade inflammation in contrast to the acute inflammatory response to microbial invasion or tissue damage described previously. In obesity, adipocyte hypertrophy can result in endoplasmic reticulum stress and inadequate microcirculation leading to tissue hypoxia. These stressors can induce modified tissue damage or wound healing response in adipose tissue characterized by the release of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), and chemokines, such as monocyte chemoattractant protein-1 (MCP-1). MCP-1 recruits monocytes into the adipose tissue that differentiate into pro-inflammatory M1 macrophages that release additional cytokines, such as interleukin-1 (IL-1) and interleukin-6 (IL-6), and chemokines, such as interleukin-8 (IL-8) and macrophage inflammatory protein-1α (MIP-1α). Additionally, chemokine and cytokine gradients attract neutrophils and more monocytes that further exacerbate the inflammatory state in a feed-forward regulation (Maury and Brichard 2010). Secreted pro-inflammatory cytokines contribute to systemic inflammation but have important localized paracrine effects promoting adipocyte insulin

resistance leading to elevated lipolysis and the increased release of free fatty acids (FFAs) that can further provoke local and systemic inflammation and lipotoxicity (Maury and Brichard 2010).

Comorbidities of obesity include type 2 diabetes, dyslipidemia, hypertension, endothelial dysfunction, and hepatic steatosis leading to increased incidence of cardiovascular disease, renal failure, and several types of cancer. These comorbidities can be attributed directly or indirectly to a prolonged chronic inflammatory state (Maury and Brichard 2010). Although these pathophysiological states are associated with increased BMI, they are most highly associated with increases in visceral obesity. It is important to recognize that chronic inflammation is a common characteristic of all adipose tissue depots in the obese state; however, the level and the contribution of a particular adipose tissue depot to local and systemic inflammation can vary dramatically (Lee et al. 2013; Maury and Brichard 2010). Adipose tissue is a highly vascularized complex tissue containing multiple cell types in addition to adipocytes including endothelial cells, preadipocytes, multipotent stem cells, fibroblasts, macrophages, monocytes, neutrophils, mast cells, natural killer (NK) cells, T cells, dendritic cells (Ràfols 2014), and mesothelial cells (only visceral adipose tissue) (Darimont et al. 2008). It is the secretory profile or secretome of the combined cell types within an adipose depot that contributes to its systemic endocrine and local paracrine effects on metabolism and disease susceptibility. Visceral adipose tissue has a greater pro-inflammatory cytokine, plasminogen activator inhibitor-1 (PAI-1), vascular endothelial growth factor (VEGF), and free fatty acid (FFA) secretory profile than subcutaneous adipose tissue by nature of its location in the visceral cavity, higher nutrient and endotoxin exposure from the portal circulation, and its differing cellular composition (Lee et al. 2013). Therefore, it is no surprise that increased visceral adipose tissue (VAT) is highly associated with inflammation-dependent disease states such as type 2 diabetes, cardiovascular disease, and cancer as discussed previously (Lee et al. 2013).

4.1.1 Hyperinsulinemia and Growth Factors

Insulin and insulin-like growth factors (IGFs) have been implicated in a wide range of cancers due to their anti-apoptotic and growth-promoting properties (Ungefroren et al. 2015; Louie et al. 1831; Taubes 2012; Gallagher and LeRoith 2011). Obesity is associated with inflammation-dependent increases in insulin resistance resulting in hyperglycemia and compensatory hyperinsulinemia and eventually type 2 diabetes (Ungefroren et al. 2015; Louie et al. 1831). High levels of insulin promote insulin-like growth factor-1 (IGF-1) production. Therefore, obese patients with type 2 diabetes have increased cancer mortality, perhaps due to hyperinsulinemia, and/or elevated IGF-1, which leads to increased cancer cell growth, proliferation, and survival. Although insulin target tissues affecting glucose metabolism exhibit insulin resistance in prediabetes or type 2 diabetes, cancer cells maintain sensitivity toward insulin, thus, allowing additional growth promotion in the hyperinsulinemic state (Ungefroren et al. 2015; Ràfols 2014). In contrast, patients with low circulating insulin and IGFs appear to be protected from cancer development (Gallagher and LeRoith 2011). Patients with type 2 diabetes, who get insulin therapy or drugs to stimulate insulin secretion, have a significantly higher incidence of cancer than those who get metformin, an insulin-sensitizing antidiabetic drug that works to lower insulin requirements (Dowling et al. 2012). Epidemiological studies have consistently associated metformin use with decreased cancer incidence and cancer-related mortality; thus, metformin is rapidly emerging as a potential anticancer agent (Dowling et al. 2012), underscoring the importance of insulin sensitivity and energy metabolism in cancer biology. Additionally, metformin can activate 5′AMP-activated protein kinase (AMPK), a central regulator of energy metabolism and promoter of fatty acid oxidation (Salani et al. 2014). Caloric restriction, which increases insulin sensitivity and reduces circulating insulin and IGF-1, is a potent suppressor of carcinogenesis (Hursting et al. 2010; Moore et al. 2008a; Jiang et al. 2008; Zhu et al. 2005). In several preclinical models, the effect of caloric

restriction on carcinogenesis reduces the PI3K/Akt/mTOR pathway activation via AMPK activation (Moore et al. 2008a; Jiang et al. 2008) and can be abrogated by restoration of IGF-1 levels (Hursting et al. 2010; Zhu et al. 2005; Hursting et al. 1993). Tumors with mutations activating the PI3K/Akt/mTOR signaling pathway are resistant to caloric restriction (Kalaany and Sabatini 2009). The PI3K/Akt/mTOR and Ras/Raf/MAPK axes are common effector pathways for many growth factors including insulin, IGF, and leptin, regulating tumor survival, growth, and proliferation (Dunn et al. 1997). Accordingly, PI3K/Akt/mTOR inhibition has been an active target to reduce carcinogenesis and tumor incidence (Fierz et al. 2010; Novosyadlyy et al. 2010; Moore et al. 2008b; Olivo-Marston et al. 2009).

4.1.2 Dysregulation of the Adipose Tissue Secretome

Adipose tissue is an endocrine organ that produces many bioactive proteins generically called adipokines which include leptin, adiponectin, and numerous others including cytokines and chemokines as well as bioactive lipids and steroid hormones (Maury and Brichard 2010).

Leptin acts centrally as an anorexic neuroendocrine hormone and in the periphery as a regulator of energy metabolism, reproduction, and immune function. The immune modulatory actions of leptin suggest that it can act as a pro-inflammatory cytokine by stimulating monocytes and lymphocytes to produce pro-inflammatory cytokines (Ungefroren et al. 2015; Louie et al. 1831; Ottero et al. 2006). In obesity, circulating leptin becomes elevated in part due to increases in subcutaneous fat (Considine et al. 1996) and results in leptin resistance, thus preventing neuroendocrine reduction in appetite. Signaling of leptin through its receptor activates numerous cascades, including the JAK-STAT, IRS-1/2, MAPK and Akt/PI3K, and decreases the activity of 5′AMP-activated protein kinase (AMPK), a master regulator of cellular energy homeostasis (Münzberg and Myers 2005; Yadav et al. 2013). Despite the leptin resistance that accompanies some of leptin's actions in obesity, elevated leptin levels can promote tumor growth and, thus, have been viewed as a major mediator of obesity-related cancers (Drew 2012; Vansaun 2013; Chen 2011; Gao et al. 2009; Yu et al. 2009; Friedman and Mantzoros 2015; Park and Ahima 2015).

Adiponectin is also secreted from adipose tissue and has insulin-sensitizing, anti-inflammatory actions and promotes fatty acid oxidation (Yadav et al. 2013). In contrast to leptin, adiponectin decreases with increasing adiposity (Vansaun 2013; Dalamaga et al. 2012; Arita et al. 1999; Perrier and Jardé 2012); inhibits proliferation of colon, prostate, endometrial, and breast cancer cells; and is associated with decreased risk of cancers of the uterus, colon, and breast in epidemiological studies (Ungefroren et al. 2015; Ràfols 2014; Khan et al. 2013). The anticancer activity of adiponectin (Perrier and Jardé 2012) may result from modulation of energy balance by decreasing insulin/IGF-1 and mTOR signaling via activation of AMPK and by exerting anti-inflammatory actions via the inhibition of pro-inflammatory signaling leading to cytokine production (Dalamaga et al. 2012). The association between the adiponectin-to-leptin ratio and metabolic syndrome as well as some types of cancer has been suggested as an additional important parameter (Hursting and Hursting 2012; Cleary et al. 2009).

The role of novel adipokines, such as omentin-1, visfatin, and vaspin, in obesity and cancer is under investigation.

Omentin-1, a 34 kDa adipokine that is highly expressed in visceral adipose tissue, has been shown to have both insulin-sensitizing and anti-inflammatory activities (Yang et al. 2006; Yamawaki et al. 2011; Kazama et al. 2012). Also similar to adiponectin, omentin-1 is decreased with increasing adiposity (de Souza Batista et al. 2007). Although it is not clear if omentin-1 can affect cancer growth, it has been recently shown that omentin-1 has the ability to promote apoptosis by p53 deacetylation (Zhang and Zhou 2013). *Visfatin* or nicotinamide phosphoribosyltransferase (Nampth) is found in adipose tissue as well as other tissues and has pro-inflammatory properties (Maury and Brichard 2010). Vaspin (visceral adipose tissue-derived serpin), a member of the family of serine protease inhibitors, is an

additional novel adipokine with insulin-sensitizing effects. However, high circulating levels of omentin-1, visfatin, and vaspin were recently shown in patients with colorectal cancer, indicating that their definitive role in the obesity-dependent cancer has yet to be determined (Fazeli et al. 2013).

Vascular endothelial growth factor (*VEGF*) is a growth factor that promotes endothelial cell growth and angiogenesis and is elevated in inflamed adipose tissue (especially visceral). Locally increased levels of VEGF contribute to tumor neovascularization and metastasis (Lee et al. 2013; Aggarwal and Gehlot 2009).

Pro-inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor alpha (TNF-α) are highly elevated in adipose tissue from obese individuals and contribute to chronic localized as well as systemic inflammation. In addition to creating an insulin-resistant state in adipose tissue, these factors play a crucial role in tumor growth and invasiveness (Iyengar et al. 2015). IL-1 and TNF-α activate nuclear factor κB (NF-κB)-dependent increases in pro-inflammatory cytokines, angiogenic factors (VEGF and IL-8), matrix metalloproteinases (MMPs) for remodeling and invasion, chemokines and inflammatory enzymes, prostaglandin-endoperoxide synthase 2 (PGHS-2 or COX-2), and 5-lipoxygenase (5-LOX). IL-6 promotes growth and anti-apoptotic pathways through IL-6R/JAK activation of STAT3-dependent transcription (Multhoff et al. 2012).

Chemokines are soluble chemotactic cytokines that are grouped into four classes based on the positions of key cysteine residues: C, CC, CXC, and CX3C. Several studies have reported the involvement of chemokines and chemokine receptors in cell proliferation, migration, invasion, and metastasis of different types of tumors (Sethi et al. 2012; Muller et al. 2001). They are produced in large amounts from inflamed obese adipose tissue, such as MCP-1 (CCL2), and with IL-8 further exacerbate the inflammatory state by increasing monocyte and neutrophil infiltration of the tissue. IL-8, acting as a chemokine and a pro-angiogenic factor, has been linked with progression, metastasis, and poor prognosis for cancers of the colon, liver, prostate, lung, ovary, and melanoma (Aggarwal and Gehlot 2009; Sethi et al. 2012; Aleksandrova et al. 2014). Expression of CXCR4, the chemokine receptor that binds stromal cell-derived factor-1 (SDF-1), has been associated with metastasis and poor prognosis of a variety of cancers (Aggarwal and Gehlot 2009; Sethi et al. 2012). Although, the chemokine receptor CXCR4 is expressed on adipocytes and macrophages in adipose tissue, its role in this tissue still remains unknown (Yao et al. 2014).

A list of various ILs and chemokines associated with cancer initiation and promotion and a role of COX-2, 5-LOX, and MMPs in cancer are briefly summarized in Table 1 (Byers and Sedjo 2015; Louie et al. 1831; Multhoff et al. 2012; Headland and Norling LV. The resolution of inflammation: Principles and challenges. Semin Immunol 2015; Maury and Brichard 2010; Sethi et al. 2012; Muller et al. 2001; Aleksandrova et al. 2014; Du et al. 2014).

Steroid hormones and their pathologic impact, including estrogen, progesterone, androgens, and glucocorticoids, in obesity-dependent cancers are great (Hursting et al. 2008; Kaaks et al. 2001). Adipose tissue can produce significant amounts of estrogens via aromatase-catalyzed conversion of gonadal and adrenal androgens to estrogen in men and postmenopausal women (Kaaks et al. 2001). In obesity, the elevated pro-inflammatory environment induces elevated expression of aromatase in adipose tissue, thereby contributing to higher local and systemic levels of estrogen (Iyengar et al. 2015). Estrogen and estrogen receptor-α (ER-α) have been implicated in the pathogenesis of postmenopausal breast and endometrial cancers by inducing cell proliferation, VEGF expression, and angiogenesis, and inhibiting apoptosis, and targeting estrogen as a preventive intervention has been pointed out by clinical data (Institute of Medicine 2012). Selectively, reducing aromatase expression and excessive estrogen production has been targeted to reduce ER-dependent obesity-associated cancer (Bulun et al. 2012). Treatment with exemestane, an aromatase inhibitor, has exhibited decreases in relative risk of invasive breast cancer by 65 % (Hursting et al. 2012; Goss et al. 2011). Although androgen levels are not consistently associated with prostate cancer

risk in men, obesity has been associated with poor prognosis and more aggressive prostate tumors. Thus, it is possible that androgen-independent activation of androgen receptor by elevated IL-6 and IGF-1 may be the primary mechanism for aggressive prostate cancer in obesity (Iyengar et al. 2015). Glucocorticoid production from adipose tissue is elevated in obesity and contributes to local and systemic insulin resistance, increased lipolysis, and elevated FFA levels (Maury and Brichard 2010; Iyengar et al. 2015; Hursting et al. 2008).

Bioactive lipids mediate a wide range of biological functions. In the obese insulin-resistant state, adipocytes, particularly visceral adipocytes, are highly lipolytic. Free fatty acids (FFAs) released in elevated amounts lead to ectopic deposition in non-adipose tissues such as the liver, muscle, and pancreas causing lipotoxicity, worsening insulin resistance, and pancreatic beta cell dysfunction (Maury and Brichard 2010; Iyengar et al. 2015). FFAs released into the tumor microenvironment can encourage tumor growth by supplying necessary metabolic fuels for energy metabolism and generation of pro-tumorigenic signaling lipids (Louie et al. 2013). In addition to ectopic tissue accumulation, saturated FFAs can initiate pro-inflammatory signaling to NF-κB through binding and activation of toll-like receptor 4 (TLR4) (Maury and Brichard 2010). Pro-inflammatory signaling by FFAs or cytokines triggers NF-κB-dependent transcription of several genes promoting tumor formation and development including cyclooxygenase-2 (PGHS-2 or COX-2) and 5-lipoxygenase (5-LOX) that produce bioactive pro-inflammatory and tumorigenic lipids, prostaglandin E_2 (PGE_2) and leukotrienes, respectively (Sethi et al. 2012; Nakanishi and Rosenberg 2013).

4.2 Emerging Mechanisms Linking Obesity and Cancer

4.2.1 Interactions with the Tumor Microenvironment

The tumor microenvironment is a complex interplay of cellular, extracellular matrix (ECM), secretory factor, and metabolite interactions that promote all stages of tumorigenesis. In its simplest form, this environment is composed of the tumor cells, the surrounding normal tissue or stromal cells, tumor-associated inflammatory cells, the secretome unique to this environment, as well as systemic factors that may impact tumor growth such as elevated insulin, IGF-1, or systemic inflammation in type 2 diabetes. In obesity-associated cancers such as colon, renal, breast, liver, endometrial, prostate, and pancreatic, the proximal location of dysfunctional adipose tissue in the microenvironment greatly enhances the tumorigenic nature of these complex interactions. Obese adipose tissue and tumors both resemble tissues that are wounded and are undergoing remodeling and repair processes (Iyengar et al. 2015). At these sites, hypoxic conditions induce hypoxia-inducible factor 1α (HIF-1α)-dependent increases in several genes, such as *VEGF*, vascular endothelial growth factor receptor (*VEGFR*), cytokine-inducible nitric oxide synthase (*iNOS*), *COX-2*, and erythropoietin (*EPO*), that promote angiogenesis/neovascularization, cell proliferation, and inflammation. Even under normoxic conditions elevated IL-1β and TNF-α have been shown to maintain HIF-1α activity. Elevated HIF-1α is associated with increased metastasis and poor prognosis for many cancers (Sethi et al. 2012). Tissue remodeling in obese adipose tissue is indicated by the presence of crown-like structures (CLS), dead adipocytes surrounded by macrophages (Lee et al. 2013). As discussed earlier, these stresses induce an ever-escalating cascade of prostaglandin E_2 (PGE_2), chemokines, cytokines, and immune cell infiltration that create the state of chronic inflammation. As part of the chronic inflammatory/wound healing environment, elevated remodeling enzymes such as matrix metalloproteinase (MMP)-2, MMP-7, and MMP-9 and urokinase plasminogen activator (u-PA) promote cancer cell invasion and metastasis (Multhoff et al. 2012). Additionally, elevated ROS (reactive oxygen species) released by infiltrating myeloid cells increase oxidative stress in the microenvironment contributing to DNA damage, mutagenesis, and further activation of pro-inflammatory signaling to

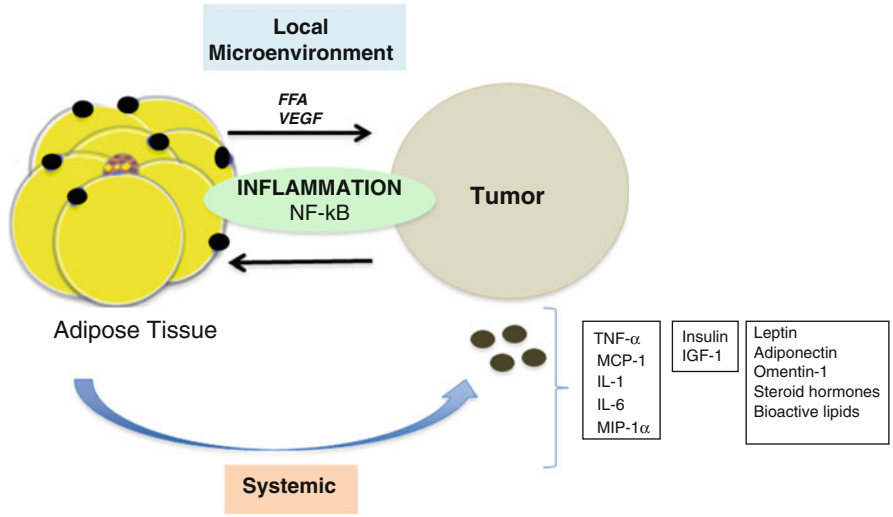

Fig. 1 Obesity alters adipose tissue's production of cytokines/adipokines, growth factors, and steroid hormones that can impact tumor development. *FFA* free fatty acids; *IL-1* interleukin-1; *IL-6* interleukin-6; *IGF-1* insulin-like growth factor-1; *MCP-1* monocyte chemoattractant protein-1; *MIP-1α* macrophage inflammatory protein-1α; *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells; *VEGF* vascular endothelial growth factor

NF-κB (Sethi et al. 2012; Diakos et al. 2014). Although the emphasis has been on adipose tissue contribution of adipokines, cytokines, chemokines, and bioactive lipids to tumorigenesis, activation of central transcriptional pathways such as HIF-1, signal transducer and activator of transcription 3 (STAT3), and NF-κB is important in the tumor as well as the dysfunctional adipose tissue. STAT3 and NF-κB-dependent transcription synergizes to increase tumor inflammation, decrease antitumor responses, and promote tumor growth and metastasis. These synergistic interactions within the tumor and between obese adipose tissue and the tumor underscore the overwhelming contribution of inflammation, particularly NF-κB activation in the tumor microenvironment (Multhoff et al. 2012) (Fig. 1). Thus, critical targets such as NF-κB and COX-2 have become important for cancer prevention.

Activity of Natural Killer (NK) Cells

Adiposity is known to be associated with impaired immune competence, and thus alterations in the immune system could play a role in cancer risk in obese patients. Obese patients exhibit lower activity of NK cells (Moulin et al. 2008) and consequently lower cytotoxic activity against precancerous and cancer cells. However, a weight loss of 26 % after 6 months, as a result of a stomach bypass surgery, led to an increase in NK cell cytotoxic activity (Moulin et al. 2008). Furthermore, it is known that an important cause of obesity-induced insulin resistance is chronic systemic inflammation originating in VAT and that VAT inflammation is associated with the accumulation of pro-inflammatory macrophages in adipose tissue, but the immunological signals that trigger their accumulation are complex. Very recently it was found that a phenotypically distinct population of tissue-resident NK cells might represent a crucial link between obesity-induced adipose stress and VAT inflammation (Wensveen et al. 2015). Obesity drove the upregulation of ligands of the NK cell-activating receptor NCR1 on adipocytes; this stimulated NK cell proliferation and interferon-γ (IFN-γ) production, which in turn triggered the differentiation of pro-inflammatory macrophages and promoted insulin resistance. Deficiency of NK cells, NCR1, or IFN-γ prevented the accumulation of pro-inflammatory macrophages in VAT and greatly ameliorated insulin sensitivity. Thus, NK cells may also be key regulators of macrophage

polarization and insulin resistance in response to obesity-induced adipocyte stress (Wensveen et al. 2015).

Role of the Microbiome

The role of gut microbiota in metabolic disorders is increasingly gaining importance. The gut microbiome has been implicated as a critical player in the development of both obesity and diabetes (van Olden et al. 2015; Tai et al. 2015). The involvement of gut microbiota in the generation of obesity-associated low-grade inflammation and diabetes (Cani et al. 2012) has been recently discussed. Maintenance of gut microbiota homeostasis is therefore important in metabolic diseases. Metabolites from the gut microbes can contribute to local and systemic metabolism as well as to gut barrier integrity. Compromised barrier integrity may lead to leakage of inflammatory mediators, such as endotoxin, into the systemic circulation leading to increase in systemic inflammation and insulin resistance (Upadhyaya and Banerjee 2015).

Role of Epigenetics

Another topic recently emerged is the role of epigenetics, the interaction of epigenome with the environment, including nutrition, that can alter patterns of gene expression. Although DNA methylation and histone modification have been investigated, recent focus in on miRNAs. MicroRNAS (miRNAs) are small noncoding RNAs that regulate gene expression at the post-transcription level and, thus, biological processes in different tissues. A major function of miRNAs in adipose tissue is to regulate the differentiation of adipocytes and consequently specific metabolic and endocrine function. Although numerous miRNAs are present in human adipose tissue, the expression of only few is altered in individuals with obesity and diabetes (Arner and Kulyté 2015). Furthermore, studies have revealed that miRNAs play crucial roles in regulating brown adipocyte differentiation (Yuntao and Xiangyang 2015) and are important in obesity and related metabolic disorders, indicating new strategies for the treatment of these diseases.

5 Prevention and Interventions

5.1 Prevention

Obesity is preventable. Throughout history, various methods addressing obesity have been documented, and many of these methods actually mirror strategies seen today. Ancient Egyptians practiced binging and purging, Pythagoras (570–490 BC) recommended eating in moderation, while Iccus and Herodicus (500–400 DC) combined exercise with diet for optimal health (Rossen and Rossen 2012). Hippocrates of Kos (460–370 BC), "father of medicine," was among the first to realize the danger of obesity, and Tobias Venner (1577–1660), an English physician and medical writer, was recognized as the first to use a term "obesity." Interestingly, one of the earliest images of the body made by humankind, the Venus of Willendorf, shows that features of fatness and fertility would have been highly desirable for people who lived in a harsh ice-age environment.

Based on the available evidence, WCRF/AICR developed guidelines and personal recommendations for individuals, as well as goals for the population as a whole, made by world experts, including those from the International Obesity Task Force, to prevent both obesity and cancer (World Cancer Research Fund and American Institute for Cancer Research 2007; http://www.dietandcancerreport.org). Although setting these targets was a vital first step, equally important has been understanding how to achieve them. This is a reason why WCRF/AICR published an evidence-based Policy and Action for Cancer Prevention report that provides evidence-based recommendations to key groups in society on how to help people make healthier choices to reduce their chances of developing cancer (http://www.dietandcancerreport.org). Similar recommendations and guidelines on nutrition and physical activity for cancer prevention were given by the American Cancer Society (ACS) (Kushi et al. 2012).

Obesity is often an indicator of unhealthy lifestyle. Strategies, such as healthy diet, change in

lifestyle, or even pharmacological interventions, that disrupt the obesity-cancer axis may be useful for reducing the rise of cancer or its progression.

Some phytochemicals, such as resveratrol, curcumin, and quercetin, have been shown to be potent in breaking the obesity-cancer link by interacting with inflammatory and growth factor signals that underlie this link (Ford et al. 2013). Also naturally appearing and widely distributed in animal and plant tissues, inositol phosphates (if water soluble) (Vucenik and Stains 2012; Kim et al. 2014) or inositide (if lipid bound) (Manna and Jain 2015) has shown treatment implications in obesity, diabetes, and cancer. Mediterranean diet, a healthy combination of dietary factors and lifestyle changes, has been shown to be beneficial for cardiovascular disease and also to have a preventive impact on cancer (Ostan et al. 2015). The combination of polyphenols contained in fruits, vegetables, grains, legumes, and olive oil has been recognized for its antioxidant and anti-inflammatory properties contributing to antitumor and anti-atherogenic effects. Polyphenols control and reduce inflammation through a series of pathways preventing cancer and other age-related diseases with an inflammatory pathogenesis. Moreover, resveratrol, quercetin, and other polyphenols exert their anticancer and chemopreventive action through mechanisms that mimic caloric restriction (sirtuin and mTOR pathways) (Ostan et al. 2015). However, the mechanism behind these effects of phytochemicals on cancer is very complex and still unclear, because these compounds certainly do much more than just "disrupt the obesity-cancer axis."

5.2 Interventions

The number of cancer survivors is steadily increasing. Although obesity has been an established factor for cancer incidence, accumulating evidence suggests that obesity is predictive of poor cancer prognosis among cancer survivors (Institute of Medicine 2012). There are several challenges and various modalities of cancer treatment in obese patients, in particular related to dosage, pharmacokinetics, and resistance to chemotherapy (Kaidar-Person et al. 2011; Lashinger et al. 2014). There is still a research gap in our knowledge of the role of obesity in cancer survival and recurrence, and therefore, we need to identify new targets and strategies for improved cancer outcomes in obese patients (Institute of Medicine 2012; Lashinger et al. 2014).

Results from diet and weight loss studies show that cancer survivors are motivated and able to make dietary and lifestyle modifications. The Women's Intervention Nutrition Study (WINS) (Chlebowski et al. 2006) and the Women's Healthy Eating and Lifestyle (WHEL) (Pierce et al. 2007) trials conducted among early-stage breast cancer survivors tested the effects of dietary interventions on cancer recurrence and survival. By promoting a low-fat diet through individualized counseling provided by registered dietitian in WINS trial, there were significantly lower rates of recurrence observed in intervention arm at 5 years (Chlebowski et al. 2006; Demark-Wahnefried et al. 2012). In contrast, the WHEL intervention used telephone-based dietary counseling to promote a daily intake of vegetable, fruits, and fiber, and although intake of fruits and vegetable was increased and intake of fat was decreased, there were no differences in weight change between arms. Additionally, after a median follow-up of 7.3 years, there were no between-arm differences in recurrence (Pierce et al. 2007; Demark-Wahnefried et al. 2012). The FRESH START trial conducted on newly diagnosed breast and prostate cancer survivors resulted in a modest but significant weight loss as a consequence of lower-fat, high-fruit, and high-vegetable diets (Demark-Wahnefried et al. 2012; Demark-Wahnefried et al. 2007). However, only few interventions have pursued weight loss as a specific arm (Demark-Wahnefried et al. 2012). The Healthy Weight Management (HWM) (Mefferd et al. 2007) and the Survivors Health And Physical Exercise (SHAPE) (Taylor et al. 2010) interventions in breast cancer survivors tested the impact of a cognitive behavioral weight loss

program plus telephone counseling against a wait-list control, and both interventions resulted in significant improvements in physical activity and weight loss. Although few physical activity trials have focused on survival, they have shown improvements in many healthy outcomes in cancer survivors, including health-related fitness, fatigue, depression, and quality of life (Demark-Wahnefried et al. 2012). A multinational trial in Canada and Australia, the Colon Health and Life-Long Exercise Change (CHALLENGE) trial, is currently open to accrual and incorporates intervention approaches shown effective (Courneya et al. 2008). The Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) trial is designed as a vanguard component of a fully powered trial of at least 2,500 women with breast cancer recurrence end points (Rock et al. 2013). With a goal to reduce breast cancer recurrence, this study has high potential to have a major impact on clinical management and outcomes after a breast cancer diagnosis. This trial initiates the effort to establish weight loss support for overweight or obese breast cancer survivors as a new standard of clinical care. However, while weight loss may be a good cancer prevention strategy, it could actually be harmful in patients who have already succumbed to disease. During the weight loss, white adipose tissue (WAT) is stressed and undergoes remodeling, and it remains to be seen how tumor cells respond to this change; for instance, they could take advantage of WAT-derived factors easier. While awaiting definitive evidence from ongoing randomized trials, breast cancer patients can reasonably be counseled to avoid weight gain and reduce body weight if overweight or obese and increase or maintain a moderate level of physical activity (Chlebowski 2013).

While lifestyle interventions for weight loss are efficacious, sometimes their long-term sustainability is limited. Therefore, in addition to these nutrition interventions, several pharmacological interventions may also prove to be useful in targeting obesity-cancer risk. These interventions may include FDA-approved weight loss drugs (orlistat, lorcaserin, phentermine-topiramate), although these drugs might be associated with side effects that may not be acceptable to patients (Goodwin and Stambolic 2015; Mordes et al. 2015). Another agent that target the obesity-associated physiology and signaling pathways is metformin, previously discussed (Dowling et al. 2012; Salani et al. 2014; Goodwin and Stambolic 2015). Additionally, bariatric surgery is very effective for weight loss and reversal of type 2 diabetes. However, this is an invasive approach that is not effective in the long term for some patients. It has been shown that some traditional Chinese medications may be effective for appropriate patients in a need of weight loss (Mordes et al. 2015).

Targeting brown fat is a new method to reduce obesity. Traditionally, white fat has been the primary focus of obesity research. However, over the last few years, there has been a revival of interest in the brown adipose tissue (BAT) (Ràfols 2014; Sidossis and Kajimura 2015). In contrast to white adipose tissue that stores energy, BAT dissipates energy and produces heat (Ràfols 2014; Sidossis and Kajimura 2015). This process is mediated by the unique mitochondrial uncoupling protein 1 (UCP1) localized in the inner membrane. Notably, the amount of brown fat is inversely correlated with obesity and BMI (Sidossis and Kajimura 2015). The morphological and imaging studies that demonstrate that BAT is functional in adults lead to an explosion of research that seeks to pharmacologically convert white to brown fat in order to burn off excess calories and combat human obesity (Zafir 2013; Gunawardana and Piston 2012; Stanford et al. 2013; Villarroya et al. 2013; Cypess and Kahn 2010; Frühbeck et al. 2009; Tseng et al. 2010). This new type of brown-like adipocyte was termed beige/brite adipocytes or inducible brown adipocytes. Beige/brite cells reside within anatomical sites of classical white fat throughout the body and are highly activated in response to thermogenic stimuli, including endogenous hormones, with increased levels of thermogenic genes and increased respiration rates. This activation of beige/brite adipocytes is referred to as a “browning” phenomenon. However, the stimulation of brown fat in

traditional white fat depots must be tightly controlled as brown fat activation is associated with increases in vascularity and secretion of angiogenic and growth factors (Wang et al. 2015). Indeed, it is known that these characteristics are essential steps for breast cancer progression and dissemination (Bernstein 2012). In particular, recent emphasis has been made on the association of specific brown fat features and the so-called white fat browning with the functions of normal and mutated tumor suppressor genes, such as *PTEN* (Ortega-Molina et al. 2012) and *BRCA1* (Jones et al. 2011). More research is needed to clarify the potential of brown fat and to better understand its role in obesity and cancer.

6 Conclusion

Strategies, either dietary, lifestyle, or pharmacological, that disrupt the obesity-cancer axis may be useful for reducing the rise of cancer or its progression. Identification of key molecules that can serve as a biological markers, targets, and modulators is critical to break the association of obesity and cancer. Inflammation is a major link between obesity and cancer, and inflammation-associated molecules can be activated by a number of environmental and lifestyle-related factors. More than half of the cancers occurring today are preventable by applying knowledge that we already have, because tobacco, obesity, and physical inactivity are all modifiable causes of cancer that generate the most disease (Colditz et al. 2012). The obstacles are in part societal, and to achieve maximal possible cancer prevention, we need better ways to implement what we know.

7 Cross-References

- ▶ Adipokines and Metabolism
- ▶ Adipose Structure (White, Brown, Beige)
- ▶ Bariatric Surgery
- ▶ Body Composition Assessment
- ▶ Carbohydrate, Fat, and Protein Metabolism in Obesity
- ▶ Diet and Obesity (Macronutrients, Micronutrients, Nutritional Biochemistry)
- ▶ Diet, Exercise, and Behavior Therapy in the Treatment of Obesity and Metabolic Syndrome
- ▶ Dyslipidemia in Obesity
- ▶ Epidemiology of Obesity in the United States
- ▶ Global, National, and Community Obesity Prevention Programs
- ▶ Gut Microbiome, Obesity, and Metabolic Syndrome
- ▶ Insulin Resistance in Obesity
- ▶ Linking Inflammation, Obesity, and Diabetes
- ▶ Pharmacotherapy of Obesity and Metabolic Syndrome
- ▶ Principles of Energy Homeostasis
- ▶ Social and Community Networks and Obesity

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Endocrine Disorders Associated with Obesity

41

Hyeong-Kyu Park and Rexford S. Ahima

Contents

Abstract

Several endocrine disorders, including diabetes, insulinoma, Cushing's syndrome, hypothyroidism, polycystic ovarian syndrome, and growth hormone deficiency, are associated with obesity. The mechanisms for the development of obesity vary according to the primary actions of these hormones on energy balance, adipose, and other tissues. This chapter describes the pathogenesis of obesity and metabolic dysfunction associated with excess insulin or glucocorticoids and deficiency of thyroid hormone or growth hormone.

Keywords

Cushing's syndrome • Growth hormone deficiency • Hyperinsulinism • Hypothyroidism • 11β-(Beta)-hydroxysteroid dehydrogenase • Insulinoma • Obesity • Type 2 diabetes

1 Introduction

Hyperinsulinism, hypercortisolism, hypothyroidism, and growth hormone deficiency are often associated with weight gain. Insulin is a potent anabolic hormone, and treatment with insulin or some antidiabetic drugs results in weight gain through direct effects on adipogenesis and lipid storage. Insulinoma is a rare cause of hyperinsulinism associated with hypoglycemia, hunger, and rapid weight gain. Excessive glucocorticoid exposure in Cushing's syndrome results in central

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obesity, sarcopenia, osteoporosis, hypertension, and hyperlipidemia. The local production of active glucocorticoids in adipose tissue by 11β-(beta)-hydroxysteroid dehydrogenase type 1 has been implicated in obesity, insulin resistance, and hypertension. Hypothyroidism increases body weight by decreasing thermogenesis and increasing fluid retention and interstitial accumulation of glycosaminoglycans. Hypothyroidism also increases cholesterol synthesis and impairs insulin sensitivity. Growth hormone deficiency in adults decreases lean tissue mass and increases fat. The focus of this chapter will be on putative mechanisms linking obesity to excessive exposure to insulin and glucocorticoids and thyroid and growth hormone deficiencies.

2 Insulin

Insulin is secreted by the β (beta) cells of the pancreas, primarily in response to glucose, and amino acids and nonesterified fatty acids (NEFAs) can also augment glucose-induced insulin secretion. During the postprandial period, elevated blood glucose stimulates pancreatic β (beta) cells to secrete insulin, which promotes glycogen storage in the liver and skeletal muscle and triglyceride storage in adipose tissue and liver. The cellular action of insulin is initiated by binding to its cell surface receptor, which consists of two α (alpha) subunits and two β (beta) subunits that form a hetero-tetrameric complex. Insulin binds to the extracellular (alpha) subunits, transmitting a signal across the plasma membrane that activates the intracellular tyrosine kinase domain of the β (beta) subunit. Insulin binding to the external component of its receptor results in activation of receptor tyrosine kinase (Newsholme et al. 2014). The activated insulin receptor (IR) kinase phosphorylates its substrate proteins on tyrosine residues. IR substrates include IRS (IR substrate) proteins, Shc, Cbl, APS, and Gab-1 (Grb2-associated binder-1). The insulin signaling network involves three major pathways, the phosphatidylinositol 3-kinase (PI 3-kinase), the mitogen-activated protein kinase (MAPK), and the Cbl/CAP pathways (Pessin and Saltiel 2000). A pathway leading to activation of MAPK mediates the growth-promoting effects of insulin by phosphorylating transcription factors leading to activation of gene expression, whereas the PI 3-kinase and Cbl/CAP pathways, triggered by insulin, generate a diverse array of biologic responses (Avruch et al. 2001; Khan and Pessin 2002). The major metabolic pathways stimulated by insulin are glycolysis, glycogen synthesis, lipogenesis, and protein synthesis. In contrast, insulin inhibits gluconeogenesis, glycogenolysis, lipolysis, fatty acid oxidation, and protein degradation.

Insulin has been known to increase glucose utilization by enhancing glucose uptake to skeletal muscle and fat. Insulin increases the rate of glycolysis by increasing glucose transport and the activities of hexokinase and 6-phosphofructokinase in muscle. Glycogen synthase, the key regulating enzyme for glycogen synthesis, is activated by insulin. When glycogen stores in muscle are replete, the glucose taken up is converted to lactate. Lactate, produced and released by muscle and adipose tissue, is taken up by the liver and converted to glucose. Conversion of glucose to lactate occurs in many tissues, but only muscle and adipose tissues are sensitive to insulin. Lactate is converted to pyruvate, which is a precursor for acetyl-CoA (Rossetti and Giaccari 1990; Dimitriadis et al. 2011). During fasting, the fall in insulin and increase in counter-regulatory hormones, such as glucagon, epinephrine, glucocorticoids, and growth hormone, stimulate glycogenolysis and gluconeogenesis in the liver, leading to glucose release to ensure adequate fuel supply to the brain and other vital organs.

Insulin also plays an important role in lipid metabolism. Adipose tissue triglycerides (TGs) represent the major source of stored fuel available for mobilization when energy requirements are increased or when glucose availability is reduced. Plasma NEFA is derived from lipolysis of adipose tissue TG via hormone-sensitive lipase (HSL). Elevated insulin levels suppress adipose tissue lipolysis through inhibition of the HSL activity, thereby reducing the release of NEFA and glycerol. Insulin resistance attenuates lipolysis, especially upper-body or visceral fat, in obesity. Thus, obese individuals with a predominance of intra-abdominal fat

have higher rates of NEFA mobilization and greater resistance to the anti-lipolytic effects of insulin when compared with individuals with lower-body obesity (Guo et al. 1999; Savage and Semple 2010). Insulin also stimulates de novo lipogenesis from glucose in the liver and adipose tissue. In adipose tissue, insulin increases glucose uptake, thereby increasing the supply of lipogenic substrates. Insulin is a strong activator of lipogenesis pathway through increased expression of lipogenic enzymes such as fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC). Insulin stimulates the reesterification of fatty acids in adipose tissue and the liver in the form of TG. Insulin also increases lean and muscle mass, by suppressing proteolysis and enhancing protein synthesis (Capeau 2008).

2.1 Hyperinsulinism and Obesity

Obesity and diabetes are closely linked and increasing worldwide. Because most patients with type 2 diabetes are overweight or obese at the time of diagnosis, iatrogenic weight gain is not only unwelcome but represents an important clinical issue that can become a barrier to successful management. Unfortunately, insulin and several oral antidiabetic drugs increase weight. For example, after 1 year of treatment, a study showed that patients on thiazolidinedione (TZD) treatment gained 5.0 kg, in comparison with 3.3 kg in those using insulin and 1.8 kg in those treated with sulfonylureas (SUs). In contrast, patients on metformin lost 2.4 kg (Nichols and Gomez-Caminero 2007). In the United Kingdom Prospective Diabetes Study (UKPDS), an increase in weight was associated with intensified treatment and improved glycemic control. The patients on intensive treatment gained 3 kg more than conventionally treated patients during the 10-year follow-up period, with most of the weight increase occurring within the first 12 months. Weight gain was seen with all drugs used for intensive intervention, with the exception of metformin. Weight gain was highest among the insulin-treated patients, who gained a mean of 6.5 kg (Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group 1998; Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group 1998).

Weight gain in type 1 diabetes is often perceived as desirable; however, overweight or obesity in type 1 diabetes can become a problem with intensive insulin therapy. The Diabetes Control and Complications Trial (DCCT) showed that insulin-associated weight gain was greater in patients receiving intensive treatment compared to conventional treatment (5.1 vs. 3.7 kg, during the first 12 months of therapy), but the mean weight of both groups increased to values beyond ideal. After 12 months of therapy, the intensively treated group had a weight that was 10 % above ideal. After 8 years, body weight continued to increase every year in both groups – more so in the intensively treated cohort. After about 6 years of follow-up, the patients in the intensively treated group gained nearly 5 kg more than their conventionally treated counterparts (Weight gain associated with intensive therapy in the diabetes control and complications trial. The DCCT Research Group 1988; Influence of intensive diabetes treatment on body weight and composition of adults with type 1 diabetes in the Diabetes Control and Complications Trial 2001; Russell-Jones and Khan 2007).

How does chronically elevated insulin or improvement in glycemic control in diabetes result in weight gain? A possible explanation is a defensive or unconscious increase in food intake caused by the fear or experience of hypoglycemia. In fact, some patients increase their intake of carbohydrates episodically or chronically to counteract a threat or experience of hypoglycemia. Increased insulin level in response to increased caloric intake promotes adipogenesis and lipid storage. Weight gain in treated diabetes may also result from the correction of glycosuria which decreases the energy lost in the urine. If the food intake is not reduced to compensate for improved glycemic control, the reduction in glycosuria will result in a net gain in weight (Carver 2006). Subcutaneous administration of insulin may also contribute to

Table 1 Hormones and drugs associated with weight gain

Drug class	Drugs that may cause weight gain	Alternatives that cause less weight gain, weight loss, or are weight neutral
Diabetes treatment	Insulin, sulfonylureas, thiazolidinedione	Metformin, DPP-IV inhibitors, SGLT2 inhibitors, GLP-1 analogues, pramlintide, acarbose
Steroid hormones	Corticosteroids, progestational steroids	NSAIDs
Oral contraceptives	Progestational steroids, hormonal contraceptives	Barrier methods, IUDs
Endometriosis treatment	Depot leuprolide acetate	Surgical methods
Antihistamines/ anticholinergics	Diphenhydramine, doxepin, cyproheptadine	Decongestants, steroid inhalers
Antihypertensives	α-Blocker, β-blocker	ACE inhibitors, calcium channel blockers
Antipsychotic	Risperidone, olanzapine, clozapine	Ziprasidone, aripiprazole
Antidepressants and mood stabilizers	TCAs, paroxetine, mirtazapine, citalopram, venlafaxine, MAOIs	Bupropion, nefazodone
Anticonvulsants	Carbamazepine, gabapentin, valproate	Lamotrigine, topiramate, zonisamide

ACE angiotensin-converting enzyme, *DPP-IV* dipeptidyl peptidase-IV, *GLP-1* glucagon-like peptide-1, *IUD* intrauterine device, *MAOI* monoamine oxidase inhibitor, *NSAID* nonsteroidal anti-inflammatory drug, *TCA* tricyclic antidepressant, *SGLT2* sodium glucose co-transporter 2

weight gain in diabetes. When insulin is given subcutaneously, the absorbed insulin first circulates systemically, so muscle and adipose tissues are over-insulinized while the liver is under-insulinized. It is possible that systemically elevated insulin levels promote fat accumulation, which in turn increases in the therapeutic insulin requirements (Russell-Jones and Khan 2007).

Weight management via diet and exercise is essential for all patients with diabetes. Metformin is the most commonly used first-line therapy for type 2 diabetes and often induces weight loss or is generally considered weight neutral (Table 1). Among other oral antidiabetic drugs, dipeptidyl peptidase-IV (DPP-IV) inhibitors are weight neutral and the sodium glucose co-transporter 2 (SGLT2) inhibitors can result in significant weight loss (Tomkin 2014; Hasan et al. 2014; Meneghini et al. 2011). Thus, adjunctive treatment with metformin, SGLT2 inhibitors, DPP-IV inhibitors, and glucagon-like peptide-1 (GLP-1) analogues should be encouraged in type 2 diabetes to lower insulin doses and limit weight gain. Moreover, practitioners should consider weight neutral alternatives of medications for hypertension, depression, and other diseases when treating patients with diabetes (Table 1).

Insulinoma, the most common functioning islet cell tumor of the pancreas, is a rare cause of rapid weight gain. Patients with insulinoma present with symptoms of hypoglycemia secondary to excessive and uncontrolled secretion of insulin. The symptoms are episodic and range from intense hunger, palpitations, and sweating to neuropsychiatric manifestations, such as anxiety, confusion, and coma. Symptoms often occur in the morning after an overnight fast and may be precipitated by exercise. Patients with insulinoma learn to avoid these symptoms by eating frequent meals, often high sugar snacks, which promotes weight gain. The diagnosis of insulinoma is established with the determination of fasting hyperinsulinemia (plasma insulin >6 μIU/ml) and symptomatic hypoglycemia (fasting plasma glucose <45 mg/dl). Increased C-peptide and proinsulin levels also distinguish insulinoma from factitious insulin therapy (Vaidakis et al. 2010). Several options are available for imaging and localizing insulinoma tumors, including ultrasonography, computed tomography, and intra-arterial calcium stimulation with venous sampling. Surgical resection is the treatment of choice and offers the only chance of cure of insulinoma (Tucker et al. 2006; Grant 2005).

3 Glucocorticoids

Cortisol is the main active glucocorticoid (GC) in human and an important regulator of many physiological pathways, particularly during stress or illness. Secretion of GCs by the adrenal cortex is normally regulated by the hypothalamo-pituitary-adrenal (HPA) axis (Fig. 1). Activation of the HPA axis starts with the secretion of hypothalamic corticotropin-releasing hormone (CRH), stimulation of pituitary pro-opiomelanocortin (POMC) gene transcription, secretion of the POMC-encoded adrenocorticotropic hormone (ACTH), and stimulation of adrenal GC synthesis and secretion (Fig. 2). GCs, in turn, inhibit CRH gene expression and secretion at the hypothalamic level and POMC transcription and ACTH secretion in the anterior pituitary, thereby establishing a regulatory feedback loop (Malkoski and Dorin 1999; Watts 2005). GCs mediate their physiologic effects by binding to an intracellular receptor, the GC receptor, a member of the hormone receptor subclass of the nuclear receptor superfamily of transcription factors. Upon GC binding in the cytosol, the GC receptor translocates into the nucleus where it serves as a DNA sequence-specific transcriptional regulator of distinct GC-responsive target genes (Tata 2002). The main biological functions of GC include the suppression of inflammation and control of energy homeostasis. Excessive GC from exogenous treatment, e.g., for asthma and inflammatory conditions, or from endogenous overproduction due to pituitary adenoma, ectopic ACTH-producing tumors, or adrenal tumors results in centripetal obesity, sarcopenia, hyperglycemia, insulin resistance, dyslipidemia, fatty liver, hypertension, and immunodeficiency (Table 1). Some of these complications of GC excess (Cushing's syndrome) resemble the metabolic syndrome associated with common forms of obesity (Vegiopoulos and Herzig 2007).

3.1 Cushing's Syndrome

Cushing's syndrome can be classified into (i) ACTH-dependent Cushing's syndrome, in which inappropriately high plasma ACTH concentrations stimulate the adrenal cortex to produce excessive amounts of cortisol and (ii) ACTH-independent Cushing's syndrome, in which excessive production of cortisol by abnormal adrenocortical tissue causes the syndrome and suppresses the secretion of both CRH and ACTH. Rarely, Cushing's syndrome may be caused by ectopic CRH secretion, bilateral primary pigmented nodular adrenal hyperplasia, and macronodular adrenal hyperplasia and adrenocortical hyperfunction associated with McCune-Albright syndrome and Carney's complex (Newell-Price et al. 1998).

ACTH-dependent Cushing's syndrome accounts for about 85 % of cases of endogenous hypercortisolism. Of the latter, autonomous pituitary ACTH secretion, Cushing's disease, is responsible for 80 %; the rest are caused by ectopic ACTH or, rarely, CRH secretion. Benign cortisol-secreting adenomas or adrenocortical carcinomas are responsible for about 15 % of endogenous cases (Tsigos and Chrousos 1996). The incidence of pituitary-dependent Cushing's disease and adrenal adenomas in women is three to four times that of men. The typical symptoms and signs of Cushing's syndrome include a rapid increase in weight, central obesity, mooning and plethora of the face, dorsocervical fat pad (buffalo hump) and supraclavicular fat pad, hypertension, glucose intolerance, oligomenorrhea or amenorrhea, decreased libido in men, and spontaneous ecchymoses, proximal muscle wasting and weakness, and the development of multiple wide purplish striae on the abdomen or proximal extremities. Depression and insomnia are common in Cushing's syndrome. Patients may have mild hirsutism and acne, but severe androgenization, especially hirsutism and virilization, strongly suggests adrenal carcinoma. Cutaneous hyperpigmentation occurs in patients with ectopic ACTH syndrome in whom plasma ACTH concentrations are markedly elevated. Thinning of the skin and osteoporosis, associated with low back pain and vertebral collapse, are more common in older patients with Cushing's syndrome (Newell-Price et al. 1998; Orth 1995).

The key biochemical features of Cushing's syndrome comprise of excessive endogenous

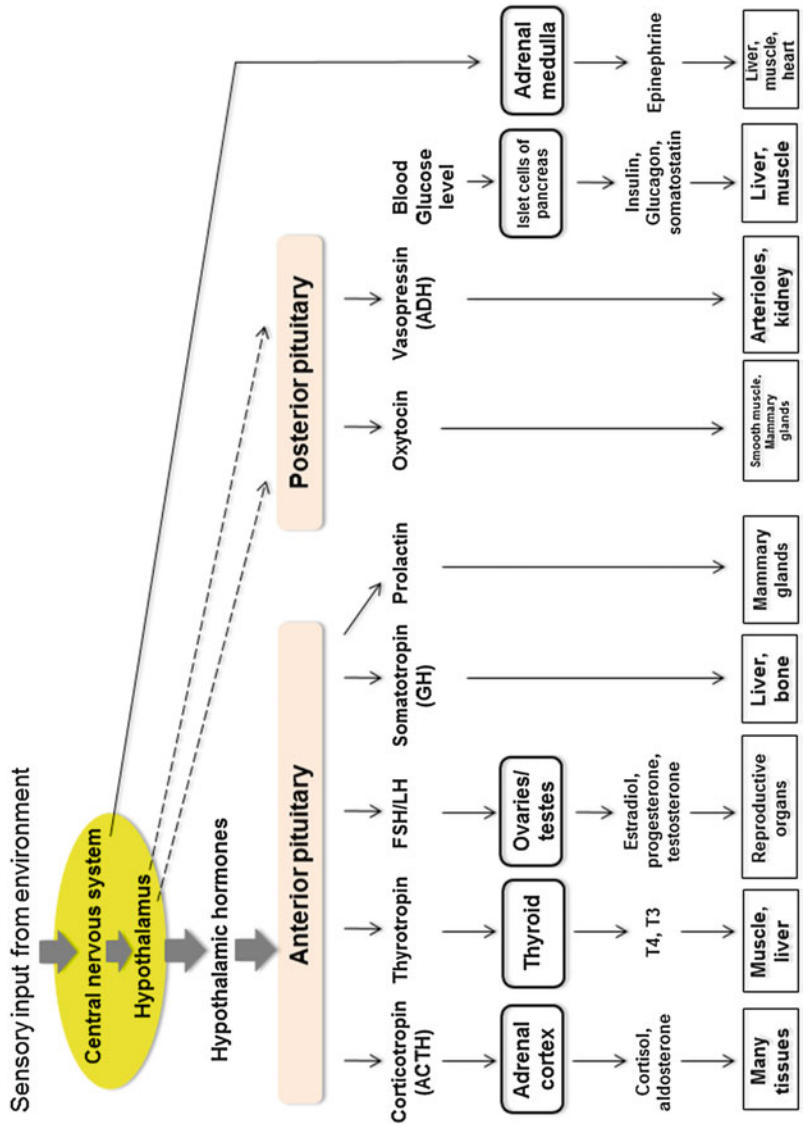

Fig. 1 Major neuroendocrine systems

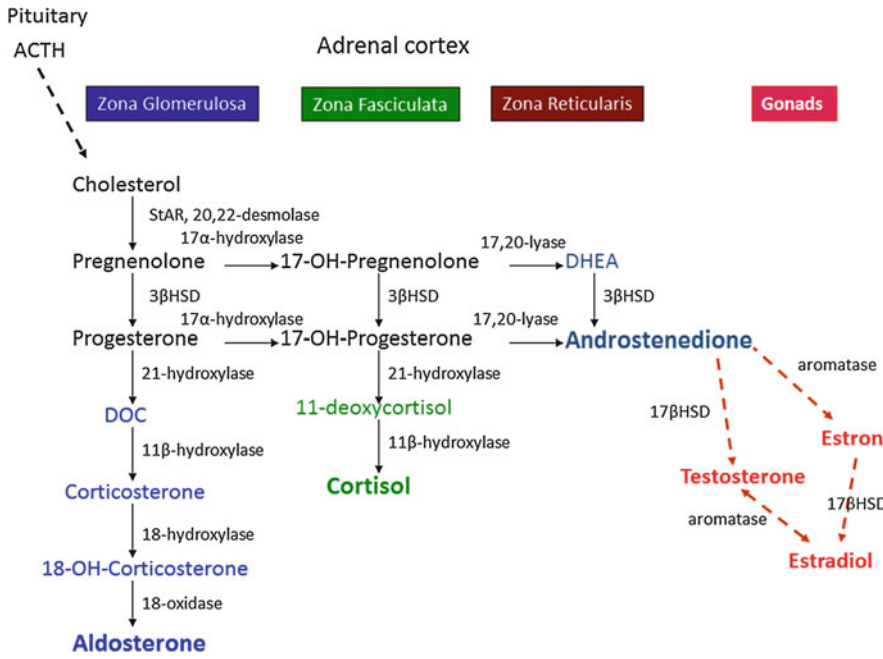

Fig. 2 Steroid hormone biosynthesis in adrenal cortex

secretion of cortisol, loss of the normal feedback of the HPA axis, and disturbance of the normal circadian rhythm of cortisol secretion. The determination of 24-h excretion of cortisol in urine (UFC, urinary free cortisol) is a reliable measure of cortisol secretion. UFC integrates the plasma-free cortisol concentrations during the entire day, with a raised level being consistent with Cushing's syndrome. In a patient thought to have Cushing's syndrome, cortisol should be measured in two or three consecutive 24-h urine specimens. Occasionally, cortisol production in Cushing's syndrome may fluctuate over several days to months. This periodic, cyclic, or episodic hypercortisolism requires several UFC determinations over a period of 3–6 months to establish a firm diagnosis (Tsigos and Chrousos 1996). The loss of circadian rhythm with absence of a late-night cortisol nadir in patients with Cushing's syndrome provides the basis for measurement of a late-night salivary or midnight serum cortisol. Salivary cortisol has been reported to correlate well with simultaneous serum cortisol value (Dorn et al. 2007). Healthy individuals usually have salivary cortisol levels of <145 ng/dL at bedtime (Trilck et al. 2005). Using different assays and various diagnostic criteria, investigators have reported that late-night salivary cortisol levels on two separate evenings yield a 92–100 % sensitivity and a 93–100 % specificity for the diagnosis of Cushing's syndrome (Nieman et al. 2008; Raff 2013). Midnight serum cortisol can be assessed when the individual is in the sleeping or awake state, using different diagnostic criteria. Awake midnight serum cortisol greater than 8.3–12 μg/dL had 90 % sensitivity and 96 % specificity for the diagnosis of Cushing's syndrome (Reimondo et al. 2005).

An overnight 1 mg dexamethasone suppression test (DST) is a simple screening test for endogenous hypercortisolism. The test involves the oral administration of 1 mg dexamethasone between 11 pm and midnight, after which a plasma cortisol sample is obtained between 8 and 9 am the next morning. A cortisol concentration of 1.8 or 3.6 μg/dL or less achieves high sensitivity; however, up to 30 % of false-positive may occur as a result of primary obesity, chronic illness, and psychiatric disorders and even in normal individuals (Nieman et al. 2008). The 2-day,

low-dose DST (0.5 mg every 6 h for 2 days) identifies patients with Cushing's syndrome. Morning serum cortisol above 1.8 μg/dL after low-dose DST is highly suggestive of Cushing's syndrome.

The next challenge after establishing high cortisol levels is to identify the source of excess cortisol. Immunoradiometric assays (IRMA) provide highly reproducible and sensitive ACTH measurement. Plasma ACTH concentrations <5–10 pg/mL suggest an adrenal source of cortisol. Normal or elevated ACTH concentrations suggest a pituitary or an ectopic source of ACTH. The standard 2-day, high-dose DST (2 mg every 6 h for 2 days) distinguishes Cushing's disease, in which there is only relative resistance to GC negative feedback, from the ectopic ACTH syndrome, in which there is usually complete resistance. The high-dose DST is performed on 24 h collections of urine for the measurement of UFC, and the degree of suppression is calculated from day 1 to day 3 after the administration of oral dexamethasone. Suppression of UFC by 90 % has 100 % specificity and 83 % sensitivity for the diagnosis of pituitary disease (Flack et al. 1992). As an alternative, a single 8-mg dose of dexamethasone is given orally at 11 pm and plasma cortisol is measured at 8 am before and after dexamethasone administration. This test has a sensitivity ranging from 57 % to 92 % and a specificity ranging from 57 % to 100 % (Newell-Price et al. 1998). The most direct way to demonstrate pituitary hypersecretion of ACTH is to document a central-to-peripheral-vein gradient in blood draining the tumor (Orth 1995).

3.2 Pseudo-Cushing's Syndrome

Patients with certain non-endocrine disorders may exhibit some of the clinical or biochemical features of Cushing's syndrome. As many as 80 % of patients with major depressive disorder have abnormal cortisol secretion. Their hormonal abnormalities presumably result from hyperactivity of the HPA axis that disappears with the remission of depression (Gold et al. 1986). Chronic alcoholism can mimic Cushing's syndrome; however, liver dysfunction is prominent, and the hormonal abnormalities disappear rapidly during abstinence from alcohol as their liver function returns to normal. The mechanism of the hypercortisolism in chronic alcoholism may involve either increased CRH secretion or impaired hepatic metabolism of cortisol (Orth 1995).

The dexamethasone-CRH test distinguishes patients with pseudo-Cushing's syndrome from those with Cushing's syndrome. The test is performed with low-dose DST followed by CRH (1 μg/kg body weight) stimulation and cortisol measurements. In patients with pseudo-Cushing's, the pituitary corticotroph is appropriately suppressed by GCs and does not respond to CRH, while in Cushing's syndrome the corticotroph tumor is generally resistant to dexamethasone and responds to CRH. Therefore, plasma cortisol level at 15 min after CRH injection being greater than 1.4 μg/dL supports the diagnosis of Cushing's syndrome, while lower values are seen in normal individuals and those with pseudo-Cushing states. Measurements of late-night salivary or midnight serum cortisol can also be used to differentiate patients with Cushing's syndrome from those with pseudo-Cushing states. The circadian rhythm of cortisol is preserved in pseudo-Cushing states but disrupted in Cushing syndrome (Nieman 2002). While true hypercortisolism will persist and the symptoms worsen over time, hypercortisolism associated with pseudo-Cushing's states typically resolves spontaneously or following definitive treatment, e.g., antidepressant treatment or abstinence from alcohol (Tsigos and Chrousos 1996).

3.3 Linking Cortisol Metabolism and Obesity

Although there is a striking resemblance between some of the physical and biochemical features of Cushing's syndrome and the metabolic syndrome associated with primary obesity, the plasma cortisol levels tend to be normal or reduced in the latter. This paradox was explained by the

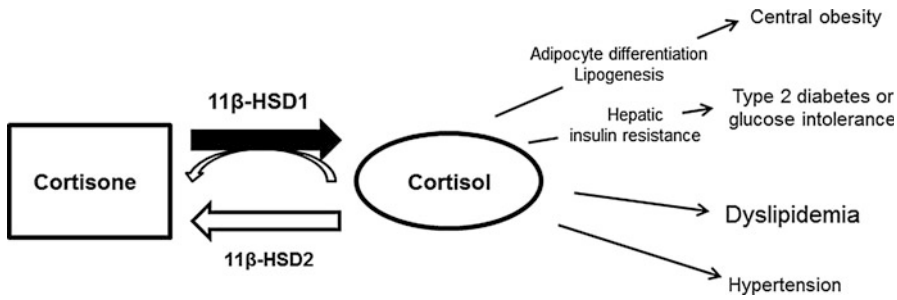

Fig. 3 Role of 11β-(beta)-hydroxysteroid dehydrogenase type 1 (11β-HSD1) in the metabolic syndrome. 11β-HSD1, highly expressed in liver and adipose tissue, generates active cortisol from inactive cortisone. In contrast, 11β-HSD2 is mainly expressed in the kidney and colon and converts cortisol to cortisone. Enhanced activity of 11β-HSD1 in adipose tissue has been implicated in central obesity, insulin resistance, type 2 diabetes, dyslipidemia, and atherogenic cardiovascular diseases. Inhibition of 11β-HSD1 might be a promising target for treating metabolic syndrome

discovery that intracellular GC reactivation occurs in the adipose tissue and liver of obese rodents and humans. 11β-(Beta)-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is the enzyme that mediates conversion of inactive cortisone to active cortisol in human (Fig. 3) and deoxycorticosterone to corticosterone in rodents. Tissue-specific dysregulation of cortisol metabolism due to increased adipose and decreased hepatic 11β-HSD1 activities has been shown in human obesity (Stomby et al. 2014).

11β-HSD1 is located within the endoplasmic reticulum and is highly expressed in the liver and adipose tissue (Chapman et al. 2013). Transgenic mice overexpressing 11β-HSD1 in adipose tissue exhibited elevated intra-adipose and portal, but not systemic corticosterone levels, abdominal obesity, insulin resistance, hyperglycemia, hyperlipidemia, and hypertension (Masuzaki et al. 2001, 2003). Hepatic overexpression of 11β-HSD1 in mice produced mild insulin resistance, fatty liver, hyperlipidemia, and hypertension, but not obesity or glucose intolerance (Paterson et al. 2004). In contrast, 11β-HSD1-knockout (11β-HSD1–/–) mice had improved glucose tolerance, improved lipid profile, and reduced weight and visceral fat when fed a high-fat diet (Kotelevtsev et al. 1997; Wake and Walker 2006). However, the role of 11β-HSD1 in human obesity, metabolic syndrome, and type 2 diabetes has been inconsistent, perhaps as a reflection of variability of subjects and different ethnic populations and methods of investigation. The decrease in hepatic 11β-HSD1 activity that occurs in primary obesity is not observed in type 2 diabetes (Valsamakis et al. 2004). It is possible that a reduction in 11β-HSD1 activity is a compensatory mechanism that preserves insulin sensitivity and decreases hepatic glucose output. Many studies have demonstrated increased 11β-HSD1 expression and activity in subcutaneous and omental adipose tissue in human obesity. 11β-HSD1 inhibitors have been tested in rodents and shown to reduce adiposity, enhance insulin sensitivity, and improve lipid profile. GC receptor antagonists have also resulted in favorable metabolic effects in rodents. A number of selective 11β-HSD1 inhibitors have been tested in obese humans and shown to improve metabolic outcomes albeit minimally (Stomby et al. 2014). However, any therapeutic benefits have to be weighed against potential detrimental effects on the HPA axis (Tomlinson and Stewart 2007).

4 Thyroid Hormone

Thyroid hormone is required for the normal function of tissues, with major effects on oxygen consumption and metabolic rate. Thyroid hormone also plays critical roles during embryogenesis and early life and has profound effects in adult life, including the regulation of protein, carbohydrate, and lipid metabolism (Yen 2001). The

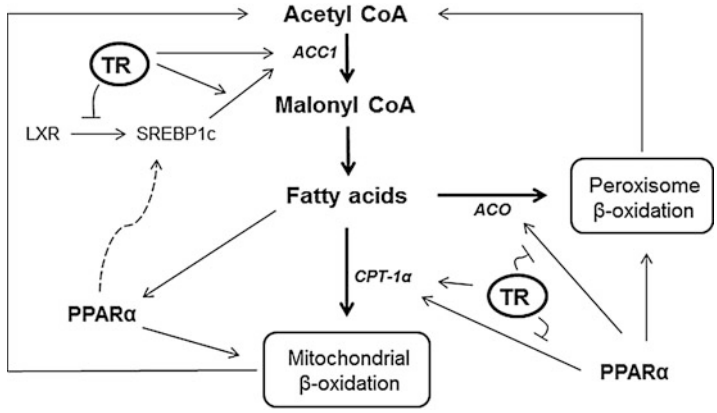

Fig. 4 Effects of thyroid hormone on fatty acid metabolism in the liver. The ACC1 promoter contains a thyroid hormone receptor response element (TRE) and sterol regulating element-binding protein response element (SRE). Thyroid hormone directly stimulates the synthesis of ACC1 which catalyzes the formation of fatty acids. Thyroid hormone increases fatty acid oxidation by upregulating expression of CPT-1α (alpha). Unliganded thyroid hormone receptor (TR) blocks stimulation of CPT-1α (alpha) and ACO by PPARα (alpha). *ACC* acetyl-CoA carboxylase, *ACO* acetyl-CoA oxidase, *CPT* carnitine palmitoyltransferase, *PPAR* peroxisome proliferator-activated receptor

synthesis and secretion of thyroid hormone are regulated by a feedback system, the hypothalamo-pituitary-thyroid (HPT) axis. Thyrotropin-releasing hormone (TRH) is synthesized in the paraventricular nucleus of the hypothalamus and transported via axons to the median eminence, where it is released into the portal capillary plexus and stimulates TSH synthesis and secretion of thyroxine (T4) and triiodothyronine (T3) (Shupnik et al. 1989). T4 is more abundant but less potent than T3. Plasma and cellular T3 levels are mainly derived from T4 conversion via type 1 (D1) and type 2 (D2) 5′-deiodinases. D1 is located on the cell membrane and generates circulating T3, and D2 is expressed in the cytoplasm and rapidly produces T3. The adrenergic system stimulates D2 activity. D2 is highly expressed in the hypothalamus and pituitary and produces T3 that mediates the negative feedback regulation of TSH and TRH (Bianco et al. 2002; Oetting and Yen 2007). Only 0.03 % of the total serum T4 is free or unbound, and the remainder is bound to carrier proteins, e.g., thyroxine-binding globulin (TBG), albumin, and thyroid-binding prealbumin. Approximately 0.3 % of the total serum T3 is free, and the remainder is bound to TBG and albumin.

Free thyroid hormone enters target cells and acts mainly through its nuclear receptors, thyroid hormone receptor (TR) α (alpha) and β (beta). TR forms a heterodimeric complex, with retinoid X receptor (RXR), which binds to a thyroid hormone response element (TRE) to regulate the expression of genes involved in the metabolism of lipids, carbohydrates, bile acids, and other processes. The binding of T3 to TR stimulates gene expression, while the unliganded TR binds to a TRE and represses gene expression. Thyroid hormone increases the basal metabolic rate via Na/K ATPase and also interacts with the adrenergic nervous system to produce heat in response to cold exposure (Liu and Brent 2010). This process, termed adaptive thermogenesis, occurs in rodent brown adipose tissue (BAT), requires both TRα (alpha) and TRβ (beta), and involves uncoupling protein (UCP)-1 expression. In addition, T3 stimulates lipolysis in adipose tissue and fatty acid oxidation in the liver (Fig. 4) and reduces cholesterol by increasing the expression of low-density lipoprotein receptor. Glucose metabolism is also modulated by thyroid hormone. Excess thyroid hormone stimulates hepatic gluconeogenesis and glucose production, increases GLUT4 in skeletal muscle, and reduces insulin levels, partly by accelerating insulin degradation (Potenza et al. 2009). T3 stimulates carbohydrate-response element-binding protein

(ChREBP), a transcription factor that increases glycolysis and de novo lipogenesis in the liver (Liu and Brent 2010).

4.1 Clinical Features of Hypothyroidism

Weight gain is a common complaint in hypothyroid patients. The commonest cause of hypothyroidism in developed countries is autoimmune thyroiditis. Radioiodine ablation or surgical thyroidectomy as treatment for hyperthyroidism or thyroid cancer can also lead to hypothyroidism if thyroxine replacement is inadequate. Hypothyroidism may be drug induced (e.g., lithium, amiodarone) or result from disorders of the pituitary (secondary) or hypothalamus (tertiary). In the United States, hypothyroidism develops in about 5 % of the population, especially in women older than 60 years. Antithyroid peroxidase (TPO) antibodies are associated with hypothyroidism, and this is more common in women and with aging (Hollowell et al. 2002). In addition to modest weight gain, other features of hypothyroidism include a general slowing down, mental depression, cold intolerance, constipation, dryness of the skin, and brittleness of the hair. As the disorder becomes more fully established, the classic features of nonpitting edema (myxedema) of the skin, periorbital edema, hoarseness, sinus bradycardia, hypothermia, and delayed relaxation of the deep tendon reflexes appear (Vaidya and Pearce 2008).

The serum TSH is the most sensitive test for detecting early thyroid failure. An increase in TSH precedes a decline of serum free T4 by many months and sometimes years. Serum T3 concentrations are often normal. Adults presenting with symptomatic hypothyroidism often have a TSH level >10 mU/L and reductions in the serum free or total T4 concentrations. Some adults have less severe hypothyroidism, with a serum TSH that is increased (typically between 5 and 10 mU/L), but a serum T4 concentration within the reference range. This is termed "subclinical hypothyroidism" and in many patients represents a state of compensated or mild thyroid failure (Vaidya and Pearce 2008). Subclinical hypothyroidism increases with age and is more common in women. However, after the sixth decade, the prevalence in men approaches that of women, with a combined prevalence of 10 %. Antithyroid antibodies can be detected in 80 % of patients with subclinical hypothyroidism, and 80 % of patients with subclinical hypothyroidism have a serum TSH less than 10 mU/L. Patients with subclinical hypothyroidism have a high rate of progression to clinically overt hypothyroidism, ~2.6 % each year if TPO antibodies are absent and 4.3 % if they are present. A TSH level greater than 10 mIU/L predicts a higher rate of progression of hypothyroidism (Fatourechi 2009). Laboratory investigation of hypothyroidism may reveal a mild anemia, increased creatine phosphokinase concentrations suggesting myopathy, and an abnormal lipid profile with increased total and low-density lipoprotein cholesterol and decreased high-density lipoprotein cholesterol concentrations (Woeber 2000).

Central hypothyroidism is a rare cause of hypothyroidism characterized by a defect of thyroid hormone production due to insufficient stimulation by TSH of a normal thyroid gland. Hypothyroidism can be congenital or acquired in the case of lesions affecting either the pituitary (secondary hypothyroidism) or the hypothalamus (tertiary hypothyroidism). The diagnosis is based on biochemical tests showing reduced serum free or total T4 concentration and inappropriately low TSH level. TRH testing may help in the differential diagnosis between tertiary (hypothalamic) and secondary (pituitary) hypothyroidism. In the latter, TSH response may be absent or impaired, whereas tertiary hypothyroidism is characterized by normal, exaggerated, or delayed TSH responses to TRH injection (Lania et al. 2008).

4.2 Hypothyroidism and Obesity

Subjects with overt hypothyroidism have variable degrees of weight gain. An increase in body weight associated with hypothyroidism may arise from body fat accumulation, water retention, and increased deposition of glycosaminoglycans

(Santini et al. 2014). Thyroid hormone is required for the normal regulation of resting energy expenditure (REE). In hypothyroid patients receiving long-term T4 treatment who maintained a euthyroid state, small changes in the daily dose to ensure that serum free T4 concentrations stayed within the normal range were associated with detectable increases in REE. Serum TSH, the most sensitive marker of thyroid hormone action, is inversely correlated with REE (al-Adsani et al. 1997), and spontaneous fluctuations in free T4 concentration have been associated with significant changes in REE (Boivin et al. 2000; Silva 2003). Several studies have demonstrated a positive cross-sectional association between serum TSH levels and the body mass index. Increased serum TSH levels within the normal reference range are strongly and linearly associated with weight gain (Knudsen et al. 2005; Nyrnes et al. 2006; Fox et al. 2008).

Hypothyroidism is also associated with cardiac wall stiffness, bradycardia, and depressed myocardial contractility, which account for reduced cardiac output (Fazio et al. 2004). A low cardiac output and a decrease in renal blood flow and glomerular filtration rate lead to impaired renal water excretion, which contributes to edema and weight gain (Montenegro et al. 1996). Hypothyroidism also causes generalized interstitial deposition of glycosaminoglycans, which in turn leads to fluid and sodium retention. Hyaluronan, an abundant non-sulfated glycosaminoglycan, accumulates in many tissues including the skin, myocardium, kidney, and vasculature in severe, long-standing hypothyroidism due to a reduced clearance rate and increased synthetic rate. Hyaluronan exhibits a remarkable avidity for water, thus causing the tissues to expand greatly (Smith et al. 1982; Gianoukakis et al. 2007). Restoration of euthyroidism by T4 treatment increases REE and decreases weight, mainly by decreasing the lean mass and not fat mass. Thyroxine treatment normalizes the tissue composition and increases water excretion (Laurberg et al. 2012).

Preliminary studies suggest that thyroid hormone mimetics targeting different isoforms of TR may be a potential therapy for obesity and dyslipidemia (Baxter and Webb 2009; Santini et al. 2014; Senese et al. 2014). The presence of BAT in adults has also spurred enormous interest in the potential therapeutic benefit of thyroid hormone. Thyroid hormone signaling through induction of D2 has a central role in brown adipogenesis in mice. High intracellular expression of D2 in adult BAT enhances thermogenic pathways, including expression of the PPARγ-coactivator-1α and UCP-1 in mice (Castillo et al. 2011). Severe hypothyroidism in a child (TSH, 989 μIU/mL; free T4, 0.10 ng/dL; low thyroglobulin, 3.0 ng/mL) was associated with abundant BAT in the supraclavicular fossa. After 2 months of thyroid hormone treatment, the patient became euthyroid (TSH, 4.3 μIU/mL; free T4, 1.49 ng/dL; T3, 102 ng/dL) and the supraclavicular BAT decreased (Kim et al. 2014). In contrast, patients with Graves' disease did not show evidence of increased BAT as measured with 18-F-fluorodeoxyglucose (18-F-FDG) positron-emission tomography and computed tomography (PET-CT), and hyperthyroid patients treated with methimazole did not develop increased BAT activity (Zhang et al. 2014). Moreover, treatment with T3 did not alter the sympathetic and BAT activity, energy expenditure, or body mass index in patients with hypothalamic obesity secondary to childhood craniopharyngioma resection (van Santen et al. 2015).

5 Growth Hormone

Growth hormone (GH) is produced by somatotroph cells of the anterior pituitary gland. GH secretion is stimulated by GH-releasing hormone (GHRH) and inhibited by somatostatin. GH secretion is inhibited by insulin, glucose, and fatty acids, while arginine stimulates GH secretion (Meinhardt and Ho 2006). GH secretion is pulsatile, and the amplitude of the pulses is highest at night. The 24-h GH secretion is maximal during puberty and declines gradually thereafter in both women and men. GH binds and activates receptors on hepatocytes and other cells, leading to the tyrosine phosphorylation and association with JAK2. Several of the proteins phosphorylated

and activated by the GH receptor through JAK2 serve as adapters, linking GH signaling to a variety of signal transduction pathways. IRS-1, IRS-2, Shc, and the EGF receptor all have been implicated as GH-regulated docking proteins, providing connections to the PI3 kinase and MAP kinase pathways (Vance and Mauras 1999; Woelfle et al. 2005). GH is the main regulator of insulin-like growth factor (IGF)-1. The liver is a major target tissue of GH action and produces IGF-1 and IGF-binding protein-3 (IGFBP-3) in response to GH. IGFBP-3 prolongs the half-life of IGF-I. Unbound IGF-1 mediates a negative feedback control of GH secretion by acting directly on the somatotroph and on hypothalamic GHRH and somatostatin neurons (Meinhardt and Ho 2006). A number of studies have demonstrated that both GH and IGF-1 play key roles in the normal growth of bone and muscle. GH has been shown to inhibit adipocyte differentiation (Garten et al. 2012).

5.1 Metabolic Complications of GH Deficiency

Growth hormone deficiency (GHD) may be isolated or occur as part of multiple hormone deficiencies. GHD often results from damage to the pituitary gland or hypothalamus, caused by a tumor or following surgical resection or radiotherapy. The syndrome associated with GHD includes metabolic and cardiovascular complications, osteopenia and osteoporosis, and reduced quality of life. Patients with GHD typically have increased abdominal fat, reduced exercise capacity, and elevated levels of total and low-density lipoprotein cholesterol. Triglycerides may be elevated and high-density lipoprotein cholesterol reduced in GHD (Shalet et al. 1998). Studies have shown that the atherogenic lipid profile contributes to the increased coronary risk in GHD patients, particularly in women. Central adiposity in GHD is associated with elevated fasting insulin levels and insulin resistance (Carroll et al. 1998).

GH secretion is pulsatile and has a short half-life; therefore, serum GH may be undetectable in normal subjects, and a single random GH measurement cannot identify GHD. Serum IGF-1 concentrations below the normal range are suggestive of GHD, but do not rule out the diagnosis. Moreover, reduced IGF-1 levels are seen in several conditions, e.g., starvation, chronic liver and kidney diseases, hypothyroidism, and diabetes. GHD is evaluated using provocative dynamic tests. Insulin tolerance test (ITT), considered the gold standard test of GHD, is accurate if the plasma glucose concentration is less than 2.2 mmol/L (40 mg/dL). A peak GH response to hypoglycemia of <3 μg/L measured by polyclonal competitive radioimmunoassay, or GH <5.1 μg/L, measured by immunochemiluminescent two-site assay, has sufficient specificity and sensitivity for the diagnosis of GHD in adults. However, it is important to be aware that insulin resistance in severe obesity can attenuate the hypoglycemic effect of ITT and thus diminish the GH response. The ITT is contraindicated in patients with ischemic heart disease, cerebrovascular disease, or seizure disorders. Precautions should be taken if ITT is done in patients older than 60 years. The combined administration of arginine and GHRH is the most promising alternative testing of GH secretion (Gasco et al. 2008; Casanueva et al. 2009).

The goal of GH replacement is to correct the abnormalities associated with GHD syndrome. GH dosing regimens should be individualized, at a starting dose of 300 μg/day and an increase in daily dosing of 100–200 μg/day for every 1 or 2 months. A typical median maintenance GH dose is 400 μg/day. It is recommended that GH be administered in the evening to mimic the nocturnal rise in GH levels. GH treatment is titrated according to the clinical response, side effects, and IGF-I levels. Age, sex, and estrogen status should also be considered in the determination of the GH dosage. Patients should be monitored at 1–2-month intervals during the dose titration and then at 6-month intervals during the maintenance phase. As with other hormonal replacement therapies, the GH dose may vary over time and should be monitored and adjusted. Given the potential pitfalls of GH therapy, patients with GHD should

be managed by an endocrinologist or internist with expertise in pituitary disease (Ho and Participants 2007; Johannsson 2009).

6 Conclusion

Obesity can be a manifestation of hypothyroidism, hyperinsulinism, hypercortisolism, or growth hormone deficiency and is often associated with glucose intolerance or diabetes, dyslipidemia, hypertension, and increased risk of atherogenic cardiovascular diseases. In contrast to primary obesity, obesity resulting from abnormal regulation of insulin, glucocorticoids, thyroid hormone, or growth hormone tends to have a rapid onset and progression and to be associated with symptoms and signs of the underlying diseases. Understanding the pathogenesis, clinical features, and laboratory evaluation of endocrinopathies enables a specific treatment strategy that often cures obesity and related metabolic disorders.

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7 Cross-References

- Adipose Structure (White, Brown, Beige)
- Body Composition Assessment
- Insulin Resistance in Obesity
- Pancreatic Islet Adaptation and Failure in Obesity and Diabetes

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Kidney Disease in Obesity and Metabolic Syndrome

42

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Abstract

Chronic kidney disease (CKD) is a progressive medical condition that affects over 26 million adults in the United States. Metabolic syndrome (MetS) and the components of the metabolic syndrome are likely to contribute to the development and progression of CKD. While diabetes and hypertension are the most common causes of CKD and proteinuria, there is a complex interplay of all five criteria of the MetS that exacerbate the disease process. Basic science research has evaluated the pathologic mechanisms underlying the progression of CKD due to the individual MetS criteria. Epidemiologic studies have attempted to identify whether MetS is truly a causative factor, rather than a marker, of CKD development and progression. Novel biomarkers have been implicated in the pathophysiology. Clinical trials of therapeutics targeting the independent components of the MetS have shown some promising results. In this chapter, we will review all of these issues with emphasis to human studies in the relationship of metabolic syndrome and its components with chronic kidney disease incidence and progression.

Keywords

Metabolic syndrome • Chronic kidney disease • Obesity

1 Introduction

The definition of chronic kidney disease in the K/DOQI clinical practice guidelines is based on "function" determined by glomerular filtration rate (GFR) and "damage" assessed by the presence of increased urine excretion of protein or albumin (National Kidney 2002). Based on this definition, over 26 million adults in the United States have chronic kidney disease (CKD) with another 20 million at risk for CKD (Coresh et al. 2003). Kidney disease is the ninth leading cause of death in the United States (Albright et al. 2009). CKD is a silent disease where symptoms may not arise until the disease has progressed to end-stage renal disease (ESRD). Individuals with CKD are at greater risk for mortality (Physical activity and cardiovascular health. NIH Consensus Development Panel on Physical Activity and Cardiovascular Health 1996). Unfortunately, many individuals with CKD are never diagnosed and/or made aware of their CKD or their risk for CKD (Tuot et al. 2011).

2 Metabolic Syndrome

The metabolic syndrome (MetS) is defined as the presence of three or more of the following risk factors: elevated blood pressure, low high-density lipoprotein (HDL) cholesterol level, high triglyceride level, elevated glucose level, and abdominal obesity (Grundy et al. 2005). The prevalence of MetS is approximately 22 % in US adults, with higher prevalence noted in ethnic minorities such as Mexican Americans (32 %) and African Americans (42 %) (Ford et al. 2008; Mendy et al. 2014).

Many of the criteria that comprise MetS are well-established risk factors for the development and progression of chronic kidney disease (CKD), but the relative contribution of these individual components remains poorly explored (Nashar and Egan 2014). While there appears to be a close association between MetS and CKD, drawing conclusions about causal relationships is difficult because of the complex interplay between the individual components of MetS (Locatelli et al. 2006). Epidemiologic studies have shown that MetS is itself an independent risk factor for CKD, even when excluding individuals with diabetes and hypertension, the two most common etiologies of CKD (Peralta et al. 2006). Several studies using the National Health and Nutrition Examination Survey (NHANES III) data suggest that the presence of all five criteria of MetS is associated with significantly higher odds of decreased glomerular filtration rate (<60 ml/min/1.73 m2) and moderate to severely increased urine albumin excretion (previously referred to as "microalbuminuria") compared to individuals with only one or zero MetS criteria (Chen et al. 2004). Similar findings have been replicated in studies performed in a variety of

differing ethnicities (see section on "Population-Specific Findings and CKD"). Prospective studies in those with MetS but without initial kidney disease show a more precipitous decline in estimated glomerular filtration rate (GFR) in those with more components of the MetS (Ninomiya and Kiyohara 2007). In longitudinal studies with longer-term follow-up, MetS has been associated with progression of chronic kidney disease and development of proteinuria (Lora et al. 2009). Conversely, a retrospective study has recently shown that those with CKD were more likely to have all five of the MetS criteria as far back as 20–30 years prior to the CKD diagnosis (McMahon et al. 2014). When addressed individually in meta-analyses, each criterion of the MetS contributes independently to the development of CKD, suggesting that dyslipidemia (elevated triglycerides and low HDL levels) may also be an important modifiable risk factor for the prevention of CKD in addition to diabetes, hypertension, and obesity (Thomas et al. 2011).

2.1 Dyslipidemia

Dyslipidemia is becoming increasingly acknowledged as a risk factor for the progression of CKD (Hunsicker et al. 1997; Samuelsson et al. 1997). An elevated ratio of LDL/HDL predicts a more rapid estimated GFR decline particularly in individuals with hypertension (Manttari et al. 1995). In the Atherosclerosis Risk in Communities (ARIC) study, a prospective epidemiologic study conducted in four US communities, individuals without CKD but with higher triglyceride and lower HDL levels were at increased risk for GFR decline over time, irrespective of LDL levels and the presence or absence of diabetes (Muntner et al. 2000). In Kidney Early Evaluation Program (KEEP) participants with diabetes mellitus and CKD, increases in HDL levels were associated with decreased odds of moderately increased urine albumin excretion. However, overall glycemic control compared to dyslipidemia was a more significant predictor of increased albuminuria, a marker of CKD progression (Bose et al. 2012).

2.2 Hypertension

Hypertension is an established risk factor for CKD (Klag et al. 1996). Hypertension is present in the vast majority of patients with metabolic syndrome (80 %) and enhances cardiovascular risk (Mancia et al. 2007) as well as the development and progression of CKD. Over two-thirds of essential hypertension cases may be attributed to obesity and increased renal sodium reabsorption through aldosterone release and sympathetic activity (Hall et al. 2003). Long-term activation of the sympathetic nervous system in metabolic syndrome is thought to contribute to hypertension via numerous pathologic mechanisms to be detailed later in this chapter (Deedwania 2011). In hypertensive patients, it is postulated that insulin resistance and obesity are associated with glomerular hyperfiltration, a proposed mechanism for renal injury leading to CKD (Dengel et al. 1996) which may be most operative in patients with reduced nephron number such as a solitary functioning kidney or CKD (Griffin et al. 2008).

2.3 Waist-Hip Circumference/Body Mass Index (BMI)

Abdominal obesity is defined as a waist circumference $\geq$102 cm in men and $\geq$88 cm in women because these thresholds discerned obese from nonobese adults with a high waist-hip ratio in a Scottish population (Lean et al. 1995). In population-based studies and clinical practice, however, obesity is usually defined by an individual's BMI. Because BMI reflects an individual's muscle, fat, and bone mass, BMI may not necessarily be the best assessment of obesity for determining cardiovascular or kidney disease risk. However, several studies have demonstrated associations between elevated BMI and CKD (Kramer et al. 2005) and ESRD (Hsu et al. 2009). Among individuals with baseline kidney disease, a BMI $\geq$40 kg/m^2 was associated with a threefold higher risk of end-stage renal disease (ESRD) compared to individuals with an ideal BMI (18.5–24.9 kg/m^2).

Because diabetes and hypertension are strongly associated with abdominal adiposity (Harris et al. 2000; Wang et al. 2005), waist circumference (WC) may show stronger associations with ESRD risk compared to BMI. Unfortunately, very few studies have explored the independent role of abdominal adiposity on CKD risk. In a subcohort of the Women's Health Initiative (WHI), which included 20,117 postmenopausal women with a mean follow-up period of 11.6 years, abdominal adiposity as measured by WC was significantly associated with an increased risk for ESRD (Franceschini et al. 2014). The mean age of this cohort was 63.9 years at baseline, and 38.3 % were African Americans. After adjustment for age, baseline eGFR, race, education, and smoking status, a WC >88 cm was associated with a 2.68-fold higher rate of ESRD compared to WC ≤88 cm. However, this association was markedly attenuated after adjustment for diabetes and hypertension. Thus, the association between obesity and CKD risk in older adults appears to be mediated largely by traditional obesity-associated risk factors (hypertension and diabetes) and not by specific effects of obesity itself, such as hyperfiltration.

3 Population-Specific Findings and CKD

Due to the differing prevalence of MetS across populations and the complicated relationship between each individual MetS component and CKD risk, associations between MetS and CKD appear to differ by demographic factors.

Among African American participants of the Jackson Heart Study, elevated blood pressure, triglycerides, fasting blood glucose, and abdominal obesity were significantly associated with increased odds of chronic kidney disease (Mendy et al. 2014). Those with MetS, defined as having three or more of the five criteria, had a 2.22-fold (adjusted odds ratio [AOR] 2.22; 95 % CI, 1.78–2.78) increase in the odds of CKD compared to participants without MetS. Interestingly, the combination of elevated fasting glucose, elevated triglycerides, and abdominal obesity was associated with the highest odds for CKD (AOR 25.11; 95 % CI, 6.94–90.90). The African American Study of Hypertension and Kidney Disease (AASK) study, a randomized controlled trial of blood pressure goal and pharmacologic agents among African Americans with CKD at baseline, showed that MetS leads to greater degrees of proteinuria and mortality but was not independently associated with CKD progression in this population (Lea et al. 2008). Additionally, none of the individual components of the MetS predicted CKD progression in multivariable analysis.

The burden of cardiometabolic abnormalities is high in Hispanic/Latinos but varies by age, sex, and Hispanic/Latino background (Heiss et al. 2014). In the HCHS/SOL, a longitudinal cohort study of 16,415 Hispanics self-identified as Mexican, Puerto Rican, Cuban, Dominican, and Central or South American and recruited from four urban metropolitan areas (Bronx, NY; Chicago, IL; Miami, FL; and San Diego, CA), the metabolic syndrome was present in 36 % of women and 34 % of men. The prevalence of the metabolic syndrome increased with age among both men and women. Among women, the metabolic syndrome prevalence ranged from 27 % in South Americans to 41 % in Puerto Ricans. Among men, MetS prevalence ranged from 27 % in South Americans to 35 % in Cubans.

Investigations among Asian populations have confirmed that MetS is a risk factor for the development of CKD. In a prospective cohort study of Japanese adults, a 5-year follow-up revealed an increased risk of the development of CKD among those with MetS. A larger prospective study of healthy Korean men without hypertension or diabetes showed that increased triglyceride and low HDL levels significantly increased the risk of CKD (Ryu et al. 2009). A cross-sectional study of more than 15,000 Chinese adults confirmed that the presence of increasing criteria of metabolic syndrome contributes to greater risk of CKD development (Chen et al. 2007).

In the Strong Heart study, a prospective epidemiologic study of American Indians, MetS was significantly and independently associated with a 30 % increased risk of incident CKD during 9 years of follow-up (Lucove et al. 2008). The relationship of MetS to incident CKD was driven

by the development of diabetes, though hypertension emerged as the most influential MetS criterion in the absence of diabetes in those who developed CKD.

4 Pathologic Mechanisms of Renal Injury in the Metabolic Syndrome

Given the numerous risk factors for CKD included in the MetS criteria, it is likely that a complex interplay of multiple pathologic mechanisms ultimately leads to an overall decline in renal function. Furthermore, the subsequent renal damage may lead to worsening control of these risk factors, propelling patients with MetS into a vicious cycle toward chronic kidney disease (Guarnieri et al. 2010). Figure 1 summarizes the pathophysiology of MetS that leads to CKD.

4.1 Inflammation

Within the US adult population, a graded association between number of MetS components and inflammation as measured by C-reactive protein (CRP) levels greater >3 mg/L has been documented (Beddhu et al. 2005). Inflammation was significantly associated with hypertension, obesity, and low HDL levels at all levels of GFR. Insulin resistance and abdominal obesity are significantly and positively correlated with C-reactive protein (CRP) levels (Festa et al. 2000). Individuals with MetS and inflammation, as defined by an elevated CRP level, have an increased risk for CKD both within the general population and among elderly adults (Lee et al. 2007; Fakhrzadeh et al. 2009).

4.2 Diabetes and Insulin Resistance

Insulin resistance, the presumptive operative mechanism for glucose intolerance in type 2 diabetes mellitus, also leads to inflammation and resulting oxidative stress (Locatelli et al. 2006), as insulin is an anti-inflammatory hormone. The molecular mechanism linking insulin resistance to inflammation has been postulated to be stress of the endoplasmic reticulum, where misfolded proteins will impair insulin signaling under stressful conditions (Ozcan et al. 2004). Endoplasmic reticulum stress in the kidney leads to proteinuria-induced podocyte injury via glycosylation of nephrin, an important component in the integrity of the "slit-diaphragm" structure of the glomerulus (Inagi 2009).

Insulin resistance and dysglycemia among those with MetS and CKD have also been shown to contribute independently to arterial stiffness, even in the absence of diabetic CKD or significant hypertension (Chan et al. 2013; Kangas et al. 2013). Elevated insulin levels lead to increased production of insulin-like growth factor 1 (IGF-1) from vascular smooth muscle cells and stimulation of mesangial and proximal tubular cells to secrete transforming growth factor-beta (TGF-β) (Khamaisi et al 2002; Perlstein et al. 2007). Increased IGF-1 levels promote the activity of connective tissue growth factor, a pro-fibrotic cytokine in renal tubular cells and interstitial fibroblasts, while allowing for unabated extracellular matrix expansion through the decreased activity of matrix metalloproteinase-2 (Wang et al. 2001). Insulin resistance also contributes to worsening renal hemodynamics and subsequent downstream glomerular damage through angiotensin 1 receptor overactivity, causing vasoconstriction and volume retention (Banach and Rysz 2010).

4.3 Triglycerides and Fatty Acids

Excess intracellular free fatty acids (FFA) and their metabolites can promote insulin resistance and exert cytotoxic effects on other organs (Wahba and Mak 2007). In the kidney specifically, triglyceride-rich lipoproteins and FFA (along with their metabolites) may cause renal mesangial and epithelial cell injury, thereby promoting CKD progression (Abrass 2004). Renal lipotoxicity is supported by animal models, such as the obese Zucker rat. The obese Zucker rat develops hyperlipidemia associated with early podocyte damage and infiltration of macrophages into glomeruli

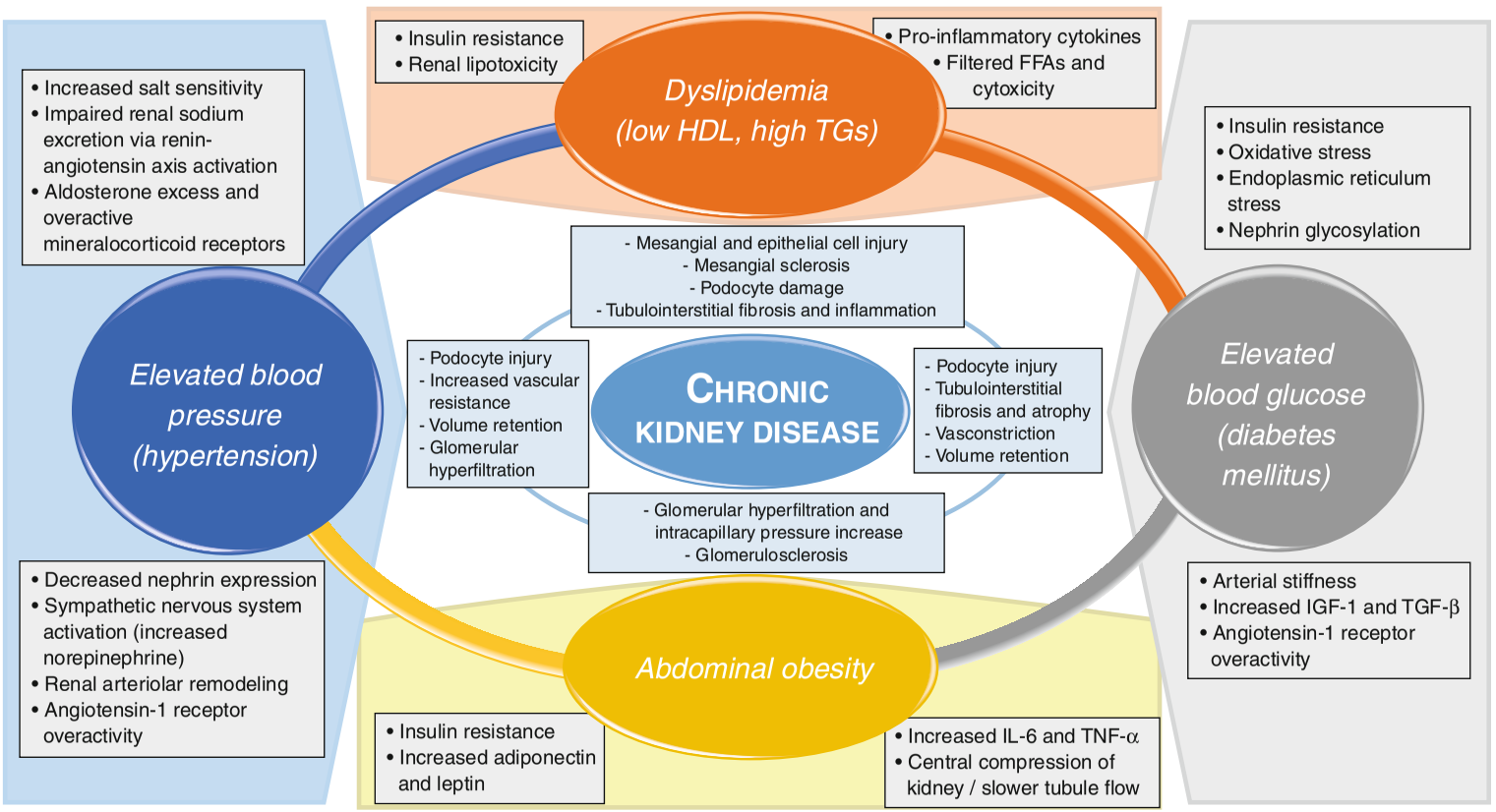

Fig. 1 The outer circle is composed of the criteria of MetS, accompanied by the physiologic mechanisms that contribute to chronic kidney disease. The inner circle within each criteria represents the pathologic findings that results from these physiologic changes, leading to chronic kidney disease. *Abbreviations FFAs* free fatty acids, *HDL* high-density lipoprotein, *IGF-1* insulin-like growth factor 1, *IL-6* interleukin-6, *TGs* triglycerides, *TGF-β* transforming growth factor-beta, *TNF-α* tumor necrosis factor-alpha

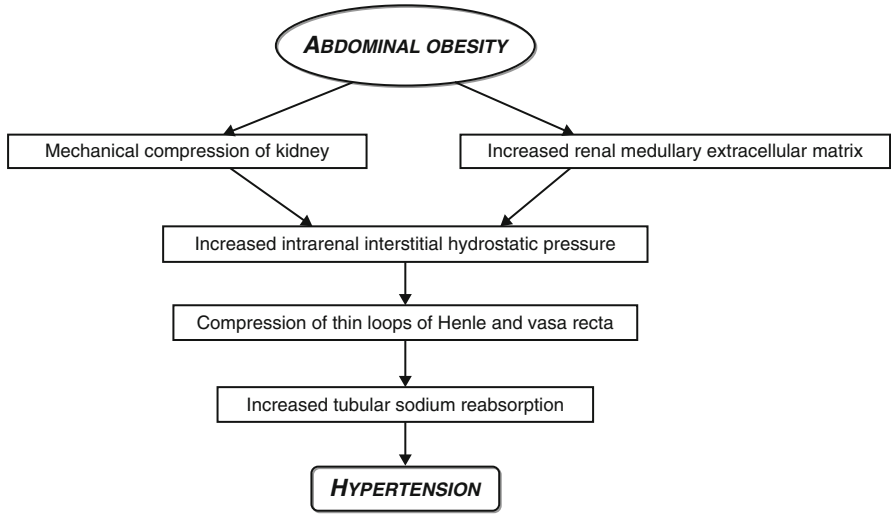

Fig. 2 Abdominal obesity can lead to hypertension via two pathways with the common end result of elevated intrarenal interstitial hydrostatic pressure leading to systemic hypertension

(Coimbra et al. 2000). Administration of lipid-lowering agents ameliorates the kidney damage (proteinuria and glomerulosclerosis) associated with hyperlipidemia in the obese Zucker rat (Kasiske et al. 1992). Renal lipotoxicity has been shown elegantly in patients with proteinuric renal diseases and the nephrotic syndrome, where albumin-saturated free fatty acids are filtered in excess, with predominant reabsorption through the proximal tubule. The reabsorption of these fatty acids contributes to significant tubulointerstitial inflammation and fibrosis (Thomas et al. 2002). Dyslipidemia has also been connected to damage of the podocytes as well as the glomerular capillary endothelial and mesangial cells, leading to mesangial sclerosis (Cases and Coll 2005). Clinical trials examining the link between lipids and kidney disease risk have not shown consistent results. In the Study of Heart and Renal Protection (SHARP), lowering LDL cholesterol by 1 mmol/L with simvastatin and ezetimibe did not slow CKD progression within 5 years (Haynes et al. 2014).

4.4 Hypertension

There is clinical evidence for increased salt-sensitive hypertension in patients with MetS, especially in obese individuals (Fujita 2010). Figure 2 demonstrates the etiologies and common causal pathway of obesity-related hypertension. Salt sensitivity seems to worsen in nondiabetic patients who satisfy more of the MetS criteria (Chen et al. 2009). While the pathophysiology is not fully known, it has been suggested that these patients have impaired renal sodium excretion due to increased renin-angiotensin axis activity and aldosterone excess (Gluba et al. 2013). This excess of aldosterone, often seen in obesity and hyperinsulinemia, can exert a variety of different deleterious effects, including overactivity of mineralocorticoid receptors in the vasculature and the brain as well as decreased expression of nephrin, a likely mechanism for how the proteinuria and podocyte injury in MetS could be partially attributable to aldosterone (Mundel and Shankland 2002; Fujita 2010). Longer-term activation of the sympathetic nervous system, with increased levels of plasma norepinephrine, may contribute to hypertension through increased renal tubular sodium reabsorption, vasoconstriction, or remodeling of the renal arterioles leading to increased vascular resistance and glomerular damage (Deedwania 2011). Hypertension is often exacerbated in this patient population through angiotensin I receptor overactivity, causing further vasoconstriction and volume expansion (Banach and Rysz 2010).

However, renal dysfunction and fibrosis can appear well before the formal diagnoses of hypertension, hyperlipidemia, or diabetes. Though the MetS population has increased microvascular disease along with tubular atrophy, interstitial fibrosis, arterial sclerosis, and global and segmental sclerosis (Alexander et al. 2009), it is unclear which risk factors in the constellation of insulin resistance, hypertension, dyslipidemias, and abdominal obesity are most influential in the production of pro-inflammatory cytokines (i.e., interleukin-6 and tumor necrosis factor-alpha) and pro-fibrotic factors (Singh and Kari 2013), though the presence of obesity seems to contribute to all of these risk factors. Activation of mineralocorticoid receptors may upregulate the inflammatory state associated with obesity since mineralocorticoid antagonists actually downregulate gene expression of multiple pro-inflammatory cytokines such as TNF-α (alpha) and monocyte chemoattractant protein and IL-6 (Guo et al. 2008; Hirata et al. 2009).

4.5 Obesity

The factors which mediate the association between abdominal obesity and CKD likely include inflammation, insulin resistance (Bastard et al. 2006), activation of the renin-angiotensin-aldosterone axis and sympathetic nervous system (Thethi et al. 2012), increased oxidative stress (Furukawa et al. 2004), and high caloric intake (Afshinnia et al. 2010). These factors may lead to hypertension, diabetes, and increased urinary albumin excretion, known risk factors for ESRD (Astor et al. 2011). Beyond simply storing energy, adipocytes produce numerous bioactive molecules, including leptin and adiponectin, which provide cellular protection from the adverse consequences of excess caloric intake. Leptin acts centrally in the central nervous system to decrease appetite, and leptin enhances energy expenditure through stimulation of the sympathetic nervous system and oxidation of muscle fatty acids (Havel 2004). In the kidney, it induces proliferation of glomerular endothelial cells and increases TGF-β_1 (beta) synthesis and collagen type IV production.

Because leptin is primarily metabolized in the kidney, it has been difficult to discern its independent effects on kidney function. Animal models of chronic leptin infusion develop albuminuria and glomerulosclerosis (Wolf and Ziyadeh 2006). Increased leptin has been associated with more rapid decline in GFR over time particularly in women (Pedone et al. 2015).

Adiponectin normally sensitizes tissues to insulin by inhibiting peroxisome proliferator-activated receptor-α (alpha) in the liver, a promoter of gluconeogenesis (Berg et al. 2001), and increasing cellular glucose uptake (Kadowaki et al. 2006). The effects of adiponectin are mediated through activation of AMP protein kinase (AMPK), which switches cells from ATP consumption to active ATP production through fatty acid and glucose oxidation. Activated AMPK also interacts with leptin and ghrelin to influence satiety and facilitates the transportation of GLUT4 into skeletal muscle and other organs. Thus, AMP activity is indirectly associated with energy storage, especially in visceral adipocytes.

It has been postulated that reduced adiponectin levels in visceral adiposity directly impact urinary albumin excretion. This hypothesis is supported by the fact that adiponectin receptors are present on podocytes. Adiponectin-null mice demonstrate podocyte foot process effacement and increased urinary albumin excretion; urinary albumin excretion decreases when adiponectin is repleted in adiponectin-null mice (Sharma et al. 2008). Additionally, adiponectin knockout mice with five-sixths nephrectomy show higher urinary albumin excretion and stronger expression of vascular cell adhesion molecule-1, TNF-α (alpha), and NADPH oxidase compared to adiponectin wild-type mice with five-sixths nephrectomy. Infusion of adiponectin into these mice improved glomerular hypertrophy and tubulointerstitial fibrosis and reduced urinary albumin excretion along with various measures of inflammation to levels similar to wild-type mice with five-sixths nephrectomy.

The link between obesity and kidney disease risk is frequently attributed to hyperfiltration or elevated intraglomerular capillary pressure. Glomerular capillary pressure cannot be directly

measured in humans, but it is known that single-nephron GFR must increase with weight gain due to a higher metabolic rate. Studies in humans show higher absolute GFR and effective renal plasma flow (RPF) among obese individuals compared to nonobese individuals. However, adjusting for body surface area strongly attenuates these differences. In human kidneys, both GFR and RPF may increase via alteration of glomerular afferent and efferent arteriolar resistance and expansion of glomerular capillary surface area without necessarily heightening glomerular capillary pressure (Griffin et al. 2008). Nephron number does not increase with weight gain, and higher GFR translates to higher single-nephron GFR. Therefore, individuals with low nephron number due to previous nephrectomy, CKD, or low nephron number at birth may have to increase intracapillary pressure in order to obtain a certain level of GFR to meet metabolic needs. Consequentially, such individuals with low nephron number may hold higher risk for increased glomerular intracapillary pressures and subsequent glomerulosclerosis with excessive weight gain (Hostetter et al. 1982; Luyckx and Brenner 2005). Nephron number among humans actually varies substantially ranging from 230,000 to 1.8 million in one multiethnic autopsy study of 67 cases from Australia and the United States (Hoy et al. 2003). Autopsy data demonstrate that body size is strongly and directly correlated with glomerular diameter (Kasiske and Napier 1985). With weight gain, glomerular diameter increases, and kidney injury could occur via increasing glomerular capillary wall tension. As Laplace's law states that the glomerular capillary wall tension will increase as glomerular radius increases (see Fig. 3):

$$\text{LaPlace's law}: \text{Tension} = (\text{Pressure} \times \text{Radius}) \times /2 * (\text{Wall Thickness})$$

In addition, as glomerular diameter increases, the podocyte density will decrease because podocytes have limited ability to replicate. Due to glomerular hypertrophy in the obese state, podocyte density may be relatively decreased, resulting in susceptibility to increased glomerular capillary pressures (Wiggins 2007). Podocytes adapt to the increased glomerular diameter via podocyte hypertrophy which may lead to detachment of the foot processes from the basement membrane and subsequent increased urinary albumin excretion (Rennke and Klein 1989).

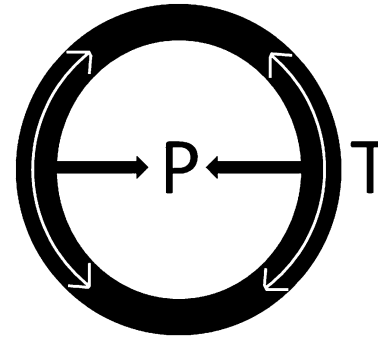

Fig. 3 LaPlace's law states that increased glomerular capillary radius will lead to increases in wall tension, creating elevated glomerular capillary pressures and eventual hypertrophy. *T* tension, *P* pressure

5 Clinical Trials/Therapeutics: Slowing CKD Progression

Overall, there are several possible mechanisms for progression to chronic kidney disease in individuals with MetS. Since many of the criteria are risk factors for each other's development, it is unclear which component(s) we should be targeting most aggressively. However, there are a number of therapeutic efforts aimed at ameliorating the components of MetS in order to break the vicious cycle of progressive CKD from the compounding risk factors. In this section, we will present the broad range of therapeutic interventions being employed, their comparative effectiveness, and ongoing clinical trials, summarized in Table 1.

5.1 Lifestyle Modifications

Lifestyle changes in the form of weight reduction, dietary habits, and increased physical activity for treatment of modifiable risk factors can be

Table 1 Therapeutic options are divided into their targeted MetS criteria, and the effects on renal function are provided from various studies

MetS criterion	Therapeutic option	Interpretation of the data
Obesity	Lifestyle modifications	Overall, difficult to maintain
	Physical activity	Beneficial effects often negated by the presence of other MetS criteria in regression models
	Dietary habits	Reductions in dietary phosphorus and waist circumference improve albuminuria
	Weight loss	Role in slowing CKD progression unclear, but moderate weight loss improves GFR and albuminuria
	Orlistat	Can be effective for weight loss, but side effect of malabsorptive diarrhea may contribute to acute kidney injury and nephrocalcinosis
	Bariatric surgery	Helps resolve other MetS criteria; results overall positive for slowing CKD, but similar risks as orlistat given malabsorption
Dyslipidemia	Statins	Most larger studies are of the ESRD population, and current data regarding CKD progression is conflicting (though cardiovascular risk improved)
	Ezetimibe	Often studied in combination with statins; well tolerated in CKD
	Niacin	Added benefit of triglyceride reduction and positive effects on phosphate metabolism; clinical trials limited by side effect profile
	Fibrates	Extensive renal clearance, requiring dose adjustment; studies show both a moderate, reversible rise in creatinine and an increased risk of rhabdomyolysis when administered with a statin
	Omega-3 polyunsaturated fatty acids	Reductions in albuminuria, but no effect on GFR
Hypertension	ACE-i/ARB	Consensus 1st-line recommendation for MetS patients
	Thiazide diuretics	May worsen some components of MetS; need to watch for hyperuricemia and hypokalemia, which can lead to worsening CKD
Diabetes mellitus	Thiazolidinediones	Reduce albuminuria and improve other MetS criteria; may be more effective when started early in CKD course
	Dipeptidyl peptidase-4 (DPP-4) inhibitors	Less clinical experience; safe, but need dose adjustment
	Glucagon-like peptide-1 (GLP-1) receptor agonists	Minimal study data; case reports of acute kidney injury due to GI side effects/losses
	Sodium-glucose transporter-2 (SGLT-2) inhibitors	Newest diabetes mellitus medications; currently under active investigation to study its potential renoprotective effects in diabetic nephropathy

ACE-I angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CKD* chronic kidney disease, *ESRD* end-stage renal disease, *GFR* glomerular filtration rate, *GI* gastrointestinal, *MetS* metabolic syndrome

successful, but behavior change is difficult to maintain. Patients with preexisting CKD have shown some improvements in GFR with low-intensity aerobic exercise (Pechter et al. 2003) but not in those with coexisting diabetes without significant weight loss (Leehey et al. 2009). Among adults with CKD in the US population, a healthy lifestyle as measured by the absence of smoking, obesity and the presence of regular physical activity were all associated with decreased mortality, though nonsmoking status showed the strong association with survival (Ricardo et al. 2013).

Improved dietary habits were not associated with mortality improvement among CKD patients in a previous study (Ricardo et al. 2013), but an observational analysis of the PREMIER trial, a randomized trial using behavioral interventions to improve blood pressure in those with normal kidney function, did show that reduced dietary phosphorus intake was associated with decreased 24 h urinary albumin excretion. Reductions in

waist circumference were also significantly associated with decreases in albuminuria, especially in those with known prior MetS (Chang et al. 2013).

As described previously, obesity is both an independent risk factor for CKD progression and contributory to the development and progression of the other criteria of the MetS. Weight loss interventions have been shown to improve urinary protein excretion, blood pressure, and GFR, but its role in slowing CKD progression is less clear (Ibrahim and Weber 2010). Moderate weight loss, especially in combination with increased exercise, in those with MetS but without preexisting CKD, does associate with improved GFR and a reduction in albuminuria (Straznicky et al. 2011). In a small study of those with severe obesity, careful measures of GFR with inulin and para-aminohippurate (PAH) clearances showed substantial differences in glomerular hyperfiltration with more significant weight loss (Chagnac et al. 2003).

Given the difficulty in sustaining effective lifestyle modifications and weight loss, several medications and therapeutic interventions have been investigated in those with MetS. Orlistat (tetrahydrolipstatin) is an inhibitor of gastric and pancreatic lipases responsible for the breakdown of triglycerides in the intestine, preventing the absorption of free fatty acids. In combination with a calorie-restricted diet, orlistat has been shown to be an effective weight loss medication but may also improve other cardiovascular risk factors for those with MetS, including insulin resistance, hypertriglyceridemia, and low HDL levels (Reaven et al. 2001). However, the side effects of malabsorptive diarrhea may be too troublesome for many patients, and there has been subsequent data suggesting increased rates of acute kidney injury (Weir et al. 2011). Additional case reports indicate orlistat's role in progressive renal impairment through significant renal tubular atrophy and interstitial fibrosis, where discontinuation of the drug stopped the decline in renal function (Coutinho and Glancey 2013). In a similar mechanism also experienced by bariatric surgery patients, unabsorbed dietary fat binds calcium, leading to excessive absorption of free oxalate (secondary hyperoxaluria) and deposition in the renal parenchyma known as nephrocalcinosis. Increased oxalate excretion is not associated with restrictive surgeries such as sleeve procedure and is most operative with the Roux-en-Y procedures.

Bariatric surgery has become increasingly popular as an adjunctive therapy in weight loss for the morbidly obese. However, bariatric surgery has also shown great promise in improving MetS as a whole, given the downstream effects of obesity on the remaining MetS criteria. A retrospective study comparing Roux-en-Y gastric bypass surgery to a monitored weight reduction program among patients with diagnosed MetS showed markedly decreased prevalence of MetS in the surgical cohort. The mean number of MetS components decreased from 3.7 to 1.9. Though a significant amount of study participants remained obese after surgery, just a 5 % excess weight loss was a significant predictor of MetS resolution (Batsis et al. 2008). Other similar studies using MetS criteria as endpoints to measure the effectiveness of bariatric surgery show similarly striking results (Mattar et al. 2005). No renal outcomes were assessed in these studies, but overall concerns for kidney dysfunction are similar to those for orlistat, given the malabsorptive nature of the procedure (Chauhan et al. 2010). A meta-analysis measuring the impact of different weight loss interventions such as dietary restrictions, exercise, antiobesity medications, and bariatric surgery on proteinuria and renal function showed significant improvements in creatinine clearance with bariatric surgery (Afshinnia et al. 2010).

5.2 Lipid-Lowering Medications

Statin therapies initially showed great promise in slowing the progression of chronic kidney disease; (Chan et al. 2008; Kasahara et al. 2014); however, more recent larger trials have not shown a benefit for CKD progression. The majority of evidence linking lipid-lowering therapy with CKD risk reduction is based on observational studies alone (Sharp Collaborative 2010). The

randomized clinical trial, Study of Heart and Renal Protection (SHARP), investigated the effect of dual therapy with simvastatin and ezetimibe on LDL levels, showing a comparable safety profile and improved efficacy versus placebo and simvastatin alone (Sharp Collaborative 2010). This combination lipid-lowering therapy was successful in reducing the primary outcome of major atherosclerotic events, but there was no effect on progression of CKD. Additionally, a post hoc analysis of the TNT (Treating to New Targets) study of patients with coronary heart disease showed that aggressive lipid-lowering therapy with high-dose atorvastatin was safe and effective in the higher-risk population of those with concurrent CKD for reducing cardiovascular events but did not report any effects on CKD progression (Shepherd et al. 2008). A similar type of analysis within the MEGA (Management of Elevated Cholesterol in the primary prevention Group of Adult Japanese) study population originally evaluating the effectiveness of pravastatin in preventing cerebro- and cardiovascular events showed improvement of GFR in patients with moderate CKD in both the experimental and control groups (Nakamura et al. 2009). However, the most recent meta-analysis investigating the effect of statins on CKD, excluding dialysis patients, demonstrated consistent decreases in major cardiovascular events with statin use, but the effects of statin use on kidney function were not consistent across studies (Palmer et al. 2014). Among a large Japanese population with CKD and dyslipidemia, the ongoing ASUCA (ASsessment of clinical Usefulness in CKD patients with Atorvastatin) trial is currently evaluating whether atorvastatin may have renoprotective effects (Ueshima et al. 2013).

Niacin's presumed role in increasing HDL cholesterol while helping to lower total and LDL cholesterol and triglycerides makes it an attractive medication for lipid management in the metabolic syndrome. However, the AIM-HIGH investigators conducted a large trial including patients with preexisting cardiovascular disease and showed little clinical benefit in the prevention of cardiovascular events with the introduction of niacin to those who had already effectively lowered their LDL-C levels with statins (AIM-HIGH investigators 2011). In the CKD population, the phosphate-lowering effects of niacin may offer potential benefits (Ahmed 2010). In animal models of CKD, niacin improved hypertension, proteinuria, glomerulosclerosis, and tubulointerstitial injury, presumably through the attenuation of oxidative stress and enhanced lipid metabolism (Cho et al. 2009). Interestingly, this study did not show an appreciable decline in plasma lipid concentrations. Despite its prospects as a beneficial lipid-lowering option in patients with CKD, niacin's well-known side effect of flushing has prevented further clinical trials in these patients.

Since patients with CKD often have a mixed dyslipidemia and statins may not be effective on their own, many patients may require adjunctive therapies. Omega-3 polyunsaturated fatty acids not only lower lipid levels but also lower blood pressure and reduce inflammation. However, a meta-analysis of 17 trials including 626 participants with CKD showed that omega-3 fatty acid supplementation significantly reduces urinary protein excretion but has no effect on GFR decline (Miller et al. 2009). Ezetimibe is used in combination with statins and has been shown to be well tolerated in patients with varying degrees of renal dysfunction (Sharp Collaborative 2010; Landray et al. 2006). Fibrates are generally renally cleared and require extensive dose adjustment and careful monitoring in those with CKD (Evans et al. 1987). This class of medications has been shown to cause a moderate, reversible rise in serum creatinine (Broeders et al. 2000), but it is not clear whether this creatinine rise reflects any true decline in GFR (Hottelart et al. 1999). While the formulations approved in the United States (fenofibrate and gemfibrozil) are less likely to cause this creatinine increase, gemfibrozil is more likely to cause rhabdomyolysis when combined with a statin by raising the serum concentration of the statin through cytochrome P450 interactions (Jacobson and Zimmerman 2006; Davidson et al. 2007). A long-term randomized control trial of fenofibrate monotherapy in type 2 diabetes mellitus patients did not show any long-term renal dysfunction, with the added

benefit of less albuminuria progression (Keech et al. 2005). However, a large trial of combination therapy with fibrates and statins (ACCORD) did not show any benefit toward cardiovascular outcomes compared to statins alone (Ginsberg et al. 2010).

5.3 Anti-hypertensives

While all anti-hypertensive therapies have been shown to reduce the risk of a major cardiovascular event in those with metabolic syndrome, clinical trials in this arena have been limited by their relative short follow-up periods of a maximum of 5–6 years (Segura and Ruilope 2006). A meta-analysis of randomized trials comparing the effectiveness of different anti-hypertensive therapies ultimately did not indicate a preferred medication (Turnbull et al. 2008), but an angiotensin-converting enzyme inhibitor (ACE-i) or angiotensin receptor blocker (ARB) is the consensus recommendation for those with MetS (Bestermann et al. 2005). Given the increased risk for insulin resistance in this patient population, ACE-i or ARB initiation seems to have a protective benefit against the development of diabetes, with a reduction in the incidence of diabetes of 25–27 % (Abuissa et al. 2005). There is a wide range of literature supporting the use of ACE-i or ARB therapies to slow the progression of CKD, even in obese patients (Mallamaci et al. 2011). However, post hoc analyses of the influential Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) with MetS patients did not prove that anti-hypertensive medications with a presumed favorable metabolic profile should be preferred. In fact, black participants with MetS in this trial had a higher risk of the development of end-stage renal disease with ACE inhibition (lisinopril) compared to a thiazide diuretic (chlorthalidone) (Wright et al. 2008). However, thiazide diuretics, while effective in their reduction of cardiovascular events, can worsen many of the components of MetS including insulin resistance, dyslipidemia, and weight gain (Martinez-Mir et al. 1993; Jacob et al. 1998). For those with CKD, thiazides may be particular risky given the numerous clinical trials that have implicated hyperuricemia and hypokalemia in the exacerbation of MetS (Reungjui et al. 2008). Persistent hypokalemia has been shown to lead to insulin resistance and glucose intolerance (Helderman et al. 1983; Zillich et al. 2006). Even low-dose thiazide therapy can induce hyperuricemia, which large studies indicate can negate any cardiovascular protection afforded by anti-hypertensive therapy (Alderman et al. 1999). In addition to these electrolyte and metabolic derangements, diuretics have been associated with acceleration of renal disease (Savage et al. 1998; Hawkins and Houston 2005). The mechanisms of this injury remain unclear but could be related to hypokalemia-induced renal hypertrophy and tubulointerstitial fibrosis, persistent volume depletion, or chronic hypoglycemia (Reungjui et al. 2007). Chronic hyperuricemia has also been implicated in the development of renal disease, and serum uric acid-lowering therapies can slow progression in patients with CKD (Siu et al. 2006). The current NIH-funded Preventing Early Renal Loss in Diabetes (PERL) Study will shed light into whether moderately elevated serum uric acid has a pathogenetic role in the deterioration of kidney function.

5.4 Diabetes Medications

While insulin remains the most effective and reliable treatment for diabetes mellitus, there is now a wide variety of oral medications that are available for improving glycemic control. These medications have differing effects on renal function, and some are even contraindicated in chronic kidney disease. Metformin is a first-line medication for diabetes due to its favorable metabolic profile (i.e., weight loss) and beneficial effects on insulin resistance and endothelial function in those with MetS (Vitale et al. 2005); however, its use in CKD may predispose patients to the development of a severe lactic acidosis. As an alternative, data from a number of both human and animal studies demonstrates that thiazolidinediones (TZDs) reduce urinary albumin excretion (Yoshimoto et al. 1997; Bakris et al. 2003)

and indirectly prevent renal injury through improvement in many of the components of the metabolic syndrome and risk factors for progressive diabetic nephropathy including hyperinsulinemia, hypertension, dyslipidemia, endothelial dysfunction, and inflammatory cytokines (Sarafidis and Bakris 2006) In a larger, multicenter study, pioglitazone showed a significantly greater reduction in urinary albumin excretion compared to metformin in drug-naïve type 2 diabetics (Schernthaner et al. 2004). Though the data supporting TZD therapy and decreased albuminuria is consistent, there are no current clinical trials investigating whether TZDs have any utility in preventing progressive renal dysfunction perhaps due to their association with congestive heart failure.

There is strikingly less clinical experience with the incretin-based therapies in CKD, including dipeptidyl peptidase-4 (DPP-4) inhibitors (i.e., sitagliptin and saxagliptin) and glucagon-like peptide-1 (GLP-1) receptor agonists (i.e., exenatide). Though most DPP-4 inhibitors are renally excreted, their pharmacokinetics are predictable, and they have been used with good effect in CKD because they can be dose-adjusted according to the degree of GFR impairment. The effects of GLP-1 agonists in those with CKD are even more poorly understood, though they are primarily renally excreted as well. There have been a few case reports of acute kidney injury with GLP-1 agonists, usually attributed to hypovolemia secondary to gastrointestinal adverse effects (Scheen 2014).

The newest class of oral diabetes medications to gain FDA approval is the sodium-glucose transporter-2 (SGLT-2) inhibitors (i.e., dapagliflozin, empagliflozin, and canagliflozin), bringing glycemic control back to the level of the kidneys. Shortly after hitting the market in Europe and the United States, a flurry of clinical and molecular investigations has shown the potential for direct renoprotective actions including the attenuation of diabetes-associated glomerular hyperfiltration and tubular hypertrophy. Experimental studies in the early 1980s first revealed these glucose transporters in the proximal tubules, known as the sodium-glucose cotransporters (SGLT) (Barfuss and Schafer 1981). While the SGLT-2 transporter in the initial segment of the proximal tubule absorbs the majority of the filtered glucose load (90 %), SGLT-2 inhibition results in a compensatory increase in glucose reabsorption through SGLT-1 transporters in animal models further along in the proximal tubule (Rieg et al. 2014).

Though there is still debate about the mechanism of glomerular hypertrophy and hyperfiltration in the setting of diabetes, the prevailing etiology to date appears to be a volume and plasma ANP-independent increase in proximal tubule sodium reabsorption and tubuloglomerular feedback (Vervoort et al. 2005; Vallon and Thomson 2012). Tubuloglomerular feedback is a process by which changes in delivery of chloride to the macula densa in the distal tubules results in changes in GFR through modulation of the glomerular afferent arteriole. In experiments with diabetic rats, hyperglycemia increases proximal tubular reabsorption via sodium-glucose transporters, decreasing chloride delivery to the macula densa. This decrease in the negative tubuloglomerular feedback activity results in an increased single-nephron GFR (Thomson et al. 2004).

While there is some conflicting data concerning early intervention in diabetic patients with evidence of glomerular hyperfiltration and its effect on the progression of CKD and diabetic nephropathy, the majority of recent evidence suggests considerable benefit (Magee et al. 2009; Moriya et al. 2012; Ruggenenti et al. 2012). Given this promising evidence, numerous clinical trials have been designed to test that SGLT-2 inhibitors can improve hyperglycemia, glomerular hyperfiltration/hypertrophy, and the downstream renal consequences.

Influenced by smaller studies of various SGLT-2 inhibitors in both type 1 and type 2 diabetics showing significant increases in glucosuria, serum hemoglobin A1c, and the attenuation of renal hyperfiltration (Defronzo et al. 2013; Cherney et al. 2014), randomized controlled trials have been conducted to evaluate larger cohorts of diabetic patients. While meta-analyses of these trials consistently show improved glycemic

control and weight loss with SGLT-2 inhibitors (both as monotherapy and combined with other oral hypoglycemic agents), their short-term study follow-up periods have not afforded us the opportunity to explore their potential longer-term renoprotective effects (Musso et al. 2012; Vasilakou et al. 2013). However, a recently published study of dapagliflozin in type 2 diabetics with moderate renal impairment did not show any significant improvement in glycemic control or serum creatinine but did result in weight loss and reduced blood pressure (Kohan et al. 2014). An ongoing randomized, double-blind, placebo-controlled multicentered clinical trial entitled CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy) is currently studying whether canagliflozin has a renal and vascular protective effect in reducing the progression of renal impairment.

6 Future Directions

With the rising prevalence of the metabolic syndrome, we have also seen an increase in the burden of chronic kidney disease. Early targeting of the individual components of MetS may help to prevent the development and slow the progression of CKD, but the evidence remains sparse due to the lack of long-term clinical trials dedicated to CKD management. The proposed mechanisms of kidney injury described above are both measurable and amenable to intervention. Since much of our current understanding of the relationship of the metabolic syndrome, its independent components, and CKD is based on large cross-sectional studies or post hoc analyses of clinical trials, there is still debate as to whether MetS is a marker, rather than a causative factor, of CKD. Randomized clinical trials in patients with metabolic syndrome focusing on renal outcomes should help shed light on which components independently drive the relationship between MetS and CKD, while prioritizing the treatments that are most effective in treating these risk factors.

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Part VI

Prevention and Treatment

Diet, Exercise, and Behavior Therapy in the Treatment of Obesity and Metabolic Syndrome

43

Kelly C. Allison and David B. Sarwer

Contents

Abstract

Weight management and improvement in metabolic functioning can be achieved through a variety of dietary approaches and physical activity regimens. The inclusion of and adherence to behavioral modification strategies can further enhance weight loss. These three aspects of behavioral change for weight management are complementary and are used in combination in the most robust approaches to treatment. Specific approaches and techniques are reviewed in this chapter. Weight loss maintenance remains challenging, and with weight regain, improvements in metabolic functioning worsen once more. More research is needed to help match individuals to weight management approaches that may increase adherence and long-term maintenance of weight loss and health benefits.

Keywords

Lifestyle modification • Caloric restriction • Physical activity • Behavioral modification • Telemedicine • Weight maintenance • Dietary interventions

1 Introduction

Individuals who are overweight and obese have many reasons that they would be motivated to lose weight and maintain that weight loss. These reasons may include medical motivators, such as

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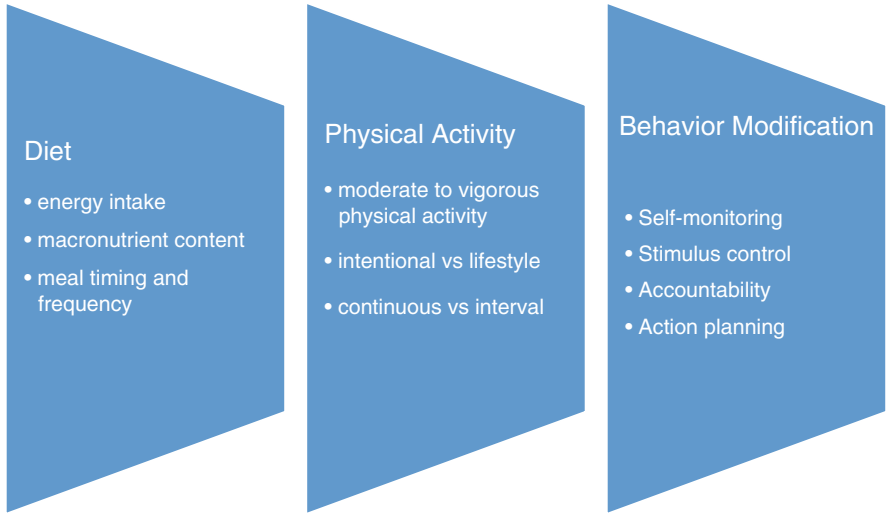

Fig. 1 The three components of lifestyle modification for weight management and improvements in metabolic functioning. Each factor contains different approaches that may be more appealing or feasible to individuals based on behavioral and taste preferences, genetics, or disease profiles

improvement of cardiovascular health, better management of type 2 diabetes and sleep apnea, and prevention of certain cancers. However, even with severe health concerns, individuals are not always motivated to action by them. Psychosocial factors, such as quality of life, self-esteem, and body image, also serve as motivating factors for weight management, including improving one's ability to walk farther distances, get up and down off of the floor while playing with one's children or grandchildren, and being able to travel or visit amusement parks and other public spaces more comfortably. For most, it is likely a combination of these factors that results in readiness for behavioral change that is necessary for weight loss treatment.

Typically, behavioral weight management interventions consist of three complimentary elements: first, the diet, the combination of macronutrients, how many calories, and other dietary features such glycemic index, specific types of fats or carbohydrates, and the timing of meals; second, physical activity, which is recommended for weight loss as well as weight maintenance; and finally, behavioral modification strategies which are used to assist in following the diet and engaging in physical activity. These strategies typically include attention to goal setting, self-monitoring, and stimulus control. These three elements are discussed in detail below (Fig. 1).

2 Dietary Approaches

2.1 Low Fat, Low Calorie

Over the years, diet fads have come and gone and in some cases come back again. To help protect the public against possibly harmful dietary prescriptions, clinical practice guidelines recently were established by a collaboration of authorities from several scientific societies which detail dietary guidelines for healthy eating and weight loss (Gonzalez-Campoy et al. 2013). The US Departments of Agriculture and Health and Human Services historically have also provided healthy eating guidelines for the public (USDA 2010). The government's approach has consistently been based on a low-fat dietary approach. The current recommendations, found at www.choosemyplate.gov, promote the daily intake of 5–6 servings of lean protein (1 ounce of meat or fish per serving), 5 servings of fruit and vegetables (1/2 cup per serving), 6–8 servings of grains (focusing on 50 % of those from whole grains, e.g., ½ cup of brown rice or ½ an English muffin),

and 3 cups of dairy for adults. Consumption of oils and refined sugar is to be limited.

This generally low-fat, low-calorie approach, with macronutrient goals of 20–35 % of intake from fats, 45–60 % from carbohydrates, and 15–20 % from proteins, has been used by many successful weight loss interventions, such as the Diabetes Prevention Program, Look AHEAD, and POWER Trials (DPP Research Group 2002; Look AHEAD Research Group 2010; Wadden et al. 2011; Appel et al. 2011). Other organizations such as the American Heart Association and the American Cancer Society, along with commercial programs such as Weight Watchers, use this approach, even though each is presented through different means (e.g., points instead of calories with Weight Watchers). The idea behind a low-fat, low-calorie diet is based on the premise that a serving of fat is more calorically dense (9 kcals per gram) than that of protein or carbohydrate (each 4 kcals per gram). Thus, when eating a low-fat diet, one can consume a higher volume of food than on a higher-fat diet. This may translate into feeling like one can eat more food and for a longer period of time, while also filling the stomach with a higher volume of food than one could consume with a higher fat intake. These approaches typically prescribe an intake goal of 1,200–1,500 kcals for individuals weighing less than 250 lbs and 1,500–1,800 kcals for those weighing more than 250 lbs. Persons at higher weights will require more kcals per day given their higher metabolic needs.

A low-fat approach particularly focusing on decreasing saturated and trans fats may be useful for individuals with diabetes mellitus and/or cardiovascular disease, as these fats are known to increase risk for cardiovascular events and impair insulin sensitivity (Vetter et al. 2014). Low-fat approaches have been widely tested and typically yield a weight reduction of 5–10 % of initial weight, which can provide clinically meaningful improvements in metabolic parameters (Jensen et al. 2014; Pascale et al. 1995; Wing and Marquez 2008). As an example, the Look AHEAD study included 5145 overweight and obese older Americans with type 2 diabetes mellitus randomized to Intensive Lifestyle Intervention (ILI; including a low-fat diet and ongoing group and individual weight management counseling) or to a Diabetes Support and Education group (DSE; yearly support meetings)(Ryan et al. 2003). Both groups continued care with their physician for management of their diabetes and other health issues over the 12 years of the study; the occurrence of cardiovascular events was the study's primary outcome. The ILI group showed greater weight loss throughout the study as compared to the DSE group (8.6 % vs 0.7 % at 1 year; 6.0 % vs 3.5 % at final assessment). However, this weight loss did not reduce the rate of cardiovascular events (Look AHEAD Research Group 2013). There were other significant improvements in the ILI group, including greater reductions in HbA1c levels, sleep apnea (Foster et al. 2009), urinary incontinence (Phelan et al. 2012), and depression (Faulconbridge et al. 2012), and improvements in quality of life (Williamson et al. 2009), physical functioning (Foy et al. 2011), and mobility (Rejeski et al. 2012).

2.2 High Protein

While the low-fat/low-calorie approach espouses the idea that "a calorie is a calorie" no matter what its dietary quality, other dietary prescriptions have focused on factors such as satiety promoting foods, glycemic control, or reduction of cravings for refined flour and sugar. Perhaps the most widely known and tested approach after the low-fat diet is the high-protein diet, popularized in the Atkins diet (Atkins 1972) and the South Beach Diet (Agatstan 2003). High protein consumption is considered between 1.2 and 1.6 g protein * kg^{-1} * d^{-1}, which is about 25–30 % of daily intake. This translates to 25–30 g of protein (Leidy et al. 2015). To put this in perspective, Americans typically consume 14–16 % of energy intake from protein, according to the data from the National Health and Nutrition Examination Survey (NHANES) (Phillips et al. 2015). The top sources of protein in America, as reported in NHANES, are (1) poultry, (2) other meats, (3) mixed dishes of meats, poultry, and fish, (4) bread, rolls, and tortillas, and (5) milk (Phillips et al. 2015).

Protein is known to have a higher thermic effect than that of carbohydrate and fat and has been shown to promote satiety more than the other macronutrients (Astrup et al. 2015, Leidy et al. 2015). Protein may also help maintain lean muscle mass which could help prevent the body from becoming more efficient in using its energy stores and, thus, requiring fewer calories for continued weight loss. For these reasons, this approach is intuitively appealing to many individuals and anecdotally is often particularly appealing to men.

While laboratory studies show positive effects of high protein meals, such as lowered ghrelin levels and increased satiety through higher peptide YY (PYY) and glucagon-like peptide 1 (GLP-1) levels, longer-term studies show mixed effects for weight loss and cardiovascular improvements. One large meta-analysis examined 24 controlled trials, including 1,063 overweight or obese adults, comparing higher-protein (27–35 % of daily intake from protein) with lower-protein (16–21 % of intake from protein) energy restriction diets for an average duration of 12 weeks (Wycherley et al. 2013). While energy deficits were similar between the diets, higher-protein diets led to greater weight and body fat loss, lower fasting triglycerides, and preservation of more lean body mass compared with the lower-protein diets. However, no differences were found between the diets for fasting glucose, fasting insulin, blood pressure, and total, LDL, and HDL cholesterol. Similar findings have been shown through a meta-analysis of high-protein diets for persons with diabetes (Dong et al. 2013).

In general, those who are able to stay on the high-protein diet more consistently are the ones who lose the most weight, maintain that weight loss, and show the cardiovascular benefits. Schwingshackl and Hoffmann (2013) showed that at 12 months, the benefits shown above for 12 weeks were no longer significant between higher-protein and lower-protein diets.

Others have shown that during weight loss maintenance, only about 40 % of those aiming to follow a higher-protein diet were doing so (Bueno et al. 2013).

2.3 Low Glycemic Index Diet

The glycemic index (GI) refers to the degree to which foods containing carbohydrates affect the release of blood glucose after the food is consumed. Foods have been ranked on a 0–100 scale, with glucose and white bread being the standard for comparison at a GI of 100. Low GI foods fall between 0 and 55, intermediate fall between 55 and 69, and high range from 70 to 100. The GI of foods is affected by many factors, such as processing, cooking, and storage (Makris and Foster 2011). Thus, it can be a complicated approach to follow. Examples of some low GI fruits would be cherries, plums, grapefruit, and peaches, while low GI vegetables include broccoli, cabbage, mushrooms, tomatoes, and green beans. Not as intuitive may be low GI snack foods, which include Nutella and Snickers bars, among others such as nuts and hummus, as compared to high GI snack items of pretzels, rice cakes, and scones. However, the aim of reducing spikes in blood glucose and insulin response may be particularly important to those with metabolic syndrome, polycystic ovarian syndrome (PCOS), and type 2 diabetes. Energy intake levels are not reduced just by eating a low GI diet. Therefore, calorie restriction must be combined with the low GI approach for weight loss.

In general, weight loss and glucose control outcomes from studies of low GI diets have been mixed. A Cochrane review examined six RCTs with a total of 202 participants (Thomas and Elliott 2007). Intervention length ranged from 5 weeks to 6 months. Decreases in body mass, total fat mass, and BMI were significantly greater among participants receiving low GI diets compared to other diets. Decreases in total cholesterol and LDL cholesterol were also significantly greater with low GI compared to other diets.

In 2009, low GI diets were reviewed again for their effect on glucose control. Thomas and Elliott (2007) examined 11 RCTs involving 402 participants. There was a significant decrease in HbA1c. One trial (Giacco et al. 2000) demonstrated significantly reduced episodes of hypoglycemia with the low GI compared to high GI diet (difference of −0.8 episodes per patient per month), while

another showed a smaller proportion of participants reporting 15 or more hyperglycemic episodes per month (35 % vs. 66 %) (Gilbertson et al. 2001). Even though these reviews found statistically significant benefits of the low GI diet on body mass and glycemic control, the clinical significance of these changes for a given individual is unclear.

2.4 Combining High Protein and Low Glycemic Index Approaches

A recent, well-controlled trial examined the possible additive effects of the low GI and the high-protein dietary approaches. The Diet, Obesity and Genes (DiOGenes) trial included families with at least one overweight or obese parent and at least one child in the household across eight European cities (Astrup et al. 2015). All of the parents ($n = 932$ adults) received a very low-calorie diet (800 kcal per day) for 8 weeks, aiming for a minimum weight loss of 8 %. The mean weight loss over this period of time was 11 kg. Families of those who reached this level ($n = 773$ adults from 634 families) were randomized to one of four six-month dietary interventions to maximize and maintain weight loss and a control group (no assigned dietary intervention for 6 months). The interventions included (1) high-protein, high GI diet; (2) high-protein, low GI diet; (3) normal protein, high GI diet; and (4) normal protein, low GI diet.

There was superior adherence in the high-protein and low GI group (Astrup et al. 2015). Only the low-protein, high GI group gained significant weight as compared to the control arm. For the other groups, the authors concluded that participants in the high-protein arms regained 2.8 kg less weight and 1.6 kg less fat mass than the normal protein groups over 6 months, but no consistent effect of GI level on weight was found. The low GI groups showed more substantial decreases in high-sensitivity C-reactive protein blood levels than the high GI diet groups. The low GI, high-protein group showed lower insulin response, and both low GI groups produced significant decreases in fructosamine levels during the 6-month intervention. The authors suggest that there is a sizable genetic component that may indicate who might benefit most from these approaches (Astrup et al. 2015). Clearly, the idea of matching diets based on genetic, environmental, and psychosocial factors is the next frontier in weight management research (Field et al. 2013).

2.5 Moderate Fat Diets (Mediterranean Diet)

Moderate fat diets have been popularized by the Mediterranean Diet and generally contain 35–45 % fat. These diets promote the use of healthy fats such as olive oil, nuts, legumes, fish, and poultry. The aim of the Mediterranean Diet is to target both weight loss and improvements in cardiovascular risk factors. A Cochrane review also has examined the impact of this diet approach on individuals at high CVD risk (Rees et al. 2013). Included in the review were studies of 52,044 participants from 11 randomized controlled trials that used at least two of the following parameters to define a Mediterranean Diet: (1) high monounsaturated/saturated fat ratio, (2) low to moderate red wine consumption, (3) high consumption of legumes, (4) high consumption of grains and cereals, (5) high consumption of fruits and vegetables, (6) low consumption of meat and meat products and increased consumption of fish, and/or (7) moderate consumption of milk and dairy products.

There was large variability in the diets, so general results were modest, with no effect on mortality, but modest reductions in LDL cholesterol. Studies with more of the components listed above had stronger CVD-related outcomes, including lower total cholesterol.

More recently, the PREDIMED (Prevención con Dieta Mediterránea) trial included 7447 older (mean age 67 years) Spanish adults at high risk for CVD events, randomizing them to one of three groups: (1) Mediterranean diet (MeDiet) supplemented with extra virgin olive oil (EVOO), (2) MeDiet supplemented with nuts, and (3) control diet (advice on a low-fat diet)

(Martinez-Gonzalez et al. 2015). There was no specific caloric reduction or advice for physical activity included. Over a mean follow-up period of 4.8 years, participants in both of the MeDiet groups significantly reduced their risk of a CVD event by about 30 % and peripheral artery disease by 64 % and 46 %, respectively, as compared to controls. Additionally, nondiabetic participants in the MeDiet with EVOO reduced their risk of developing diabetes as compared to control participants by 40 %. These significant differences were realized despite no significant weight loss at 3 years in any group on average (0.4 kg gain in controls, 0.1 kg gain in MeDiet + EVOO, and −0.02 kg loss in MeDiet + nuts) (Razquin et al. 2009). However, risk reductions were associated with degree of weight loss.

2.6 Newer Dietary Approaches

New dietary trends are constantly finding their way to the public. Some of the approaches gaining attention have been the Paleo diet and an intermittent fasting diet (described below). The typical western American diet can be characterized by high levels of processed meat and other foods, high-fat dairy products, and refined grains, all of which are associated with the increased incidence of type 2 diabetes, hypertension, and dyslipidemia (Masharani et al. 2015). Diets metabolically matched to primitive human diets of hunter and gatherers, the Paleolithic-type diet, consisted of meats, fish, fruits, vegetables, and nuts (Frassetto et al. 2009). Paleo diets typically are also lower in sodium and very much higher in potassium, antioxidants, micronutrients, and fiber and with a much lower diet acid content, and some believe that widespread acceptance could reduce the risk of our modern-day diseases (Cordain 2002). However, only small, short-term studies of Paleo diets have been reported (e.g., Masharani et al. 2015), so evidence is still lacking on the typical weight loss outcomes and impact on cardiovascular and metabolic disease risk.

Similarly, large trials for "intermittent fasting" or "modified fast" diets have yet to be conducted. This approach commonly consists of fasting for 2 days, followed by 5 days of ad libitum eating. It is simple in its approach but likely too difficult to continue longer term, as subjective hunger is increased during the fasting period (Johnstone 2015). Small studies have shown that the calorie deficit created during the fast is not completely compensated for during the days of ad lib eating, thus producing weight loss. A small meal may be added to the fasting period to make this approach more acceptable. Overall, this approach would likely be used as a short-term weight loss approach, as few people would likely be able to maintain such a pattern long term.

3 Exercise

As noted above, exercise often is included in weight management approaches as one part of a multifaceted approach to create an energy deficit large enough to produce weight loss. The American College of Sports Medicine (ACSM; Donnelly et al. 2009) recommends that adults engage in greater than or equal to 150 min per week of moderate to vigorous physical activity (MVPA) (equivalent to 1,200 kcals burned) to prevent weight gain and perhaps promote modest weight loss.

Activity levels are often measured in metabolic equivalents, METs, which are the amount of oxygen required and the number of calories one burns at rest. Moderate activity would be a workout reaching three to six METs (e.g., walking at 4 miles per hour), while vigorous activity would be working at greater than six METs (e.g., jogging at 6 miles per hour). These are very high levels of physical activity for most individuals who are obese and sedentary; the preponderance of evidence indicates that most individuals cannot reach these levels. Thus, exercise alone, without caloric restriction and modification in the nature of the diet, is insufficient to produce meaningful weight loss.

Exercise is perhaps most touted as a reliable predictor of weight loss maintenance. Several studies have shown that individuals who have lost weight and who exercise most days of the week are more likely than those who do not exercise to maintain their weight loss. Based on these

studies, the ACSM's guidelines recommended greater than or equal to 250 min of exercise per week (equivalent to about 2,000 kcals burned) for weight maintenance (Donnelly et al. 2009). The exercise described in the ACSM guidelines refers to cardiovascular exercise where one's heart rate is elevated for at least 10 min at a time. This may include a variety of activities, such as brisk walking, swimming or water aerobics, aerobic fitness classes, or cardiovascular workout machines, such as the elliptical or stationary bike. Strength training alone does not produce weight loss or reductions in fat mass, although it increases lean muscle mass (Janssen and Ross 1999).

The National Weight Control Registry (NWCR) was established in 1993 to study the correlates of long-term weight maintenance. Participants in the registry, who now are over 6,000, have lost at least 30 lbs and maintained that loss for at least 1 year. Regular MVPA has consistently been identified as one of the main predictors of weight loss maintenance. Specifically, about 90 % of participants reported engaging in exercise as part of their weight management efforts, and they were engaging in large amounts of exercise – walking the equivalent of 28 miles per week (Klem et al. 1997). More refined analysis of activity using accelerometers (as opposed to self-reported activity levels) has also been reported among 90 participants: 26 from the NWCR, 30 normal-weight controls, and 34 overweight controls (Catenacci et al. 2011). NWCR subjects showed sustained moderate or vigorous physical activity for a mean of 41.5 min/day (or about 290 min/week), which was significantly more than that observed in obese controls by 19.2 min/day (roughly 134 min/week). Those in the NWCR also engaged in 25.8 min/day (roughly 181 min/week) of sustained MVPA above that observed in normal-weight controls, although this did not reach significance (Catenacci et al. 2011). These levels of physical activity observed through actigraphy in this subsample of NWCR participants are similar to that reported through self-report measures and provide more evidence of the consistently high levels of physical activity associated with successful weight loss maintenance.

Similarly, participants of the Look AHEAD trial assigned to ILI who reached a weight loss of at least 10 % of initial body weight at 4 years were exercising significantly more than those who achieved less than a 10 % weight loss, as well as those who had gained weight from baseline (Wadden et al. 2011) is a (Look AHEAD). This most successful group was expending almost 2,000 kcal/week through activity. Most recently, the role of moderate to vigorous physical activity was also identified as a predictor of weight loss at 24 months among the POWER UP trial participants. Volger and colleagues (2013) showed that individuals engaging in physical activity who received a lifestyle intervention through their primary care physician's office, either with or without meal replacements or weight loss medications, were more likely to be engaging in more moderate to vigorous physical activity at 24 months than individuals in a comparison group who received no specific intervention beyond publically available written materials.

3.1 Exercise Versus Lifestyle Activity

Structured exercise produces the effects on weight management described above. However, increasing lifestyle activity has also been shown to have benefits. The basis for lifestyle activity lies in NEAT – non-exercise activity thermogenesis. This includes energy expended during everyday activities, such as walking, climbing steps, housework or yard work, or even fidgeting. Most often, this type of activity is measured in steps through a pedometer or newer smart activity trackers, such as phones and smart wrist or arm bands. For every increase in 2,100 steps per day, BMI is reduced by 0.4 kg/m^2 (holding energy intake equal) (Donnelly 2009). As a point of reference, 2,000 steps is about a mile. The overall goal for steps per day would be 10,000 steps. This represents at least a 3,000-step increase over what most Americans are walking as a baseline, with sedentary adults logging even less at 3,000 or fewer steps per day (Tudor-Locke and Bassett 2004). Examining average activity levels from a different

perspective, Americans are engaging in 103 min per day of sporadic physical activity, with 100 min of that being of light intensity (Robson and Janssen 2015).

Andersen et al. (1999) and colleagues elegantly compared the effects of a dietary intervention plus a structured aerobic activity regimen provided at a gym versus an intervention that encouraged increasing lifestyle activity, both recommended for the same number of minutes per week. They found that participants in the increased lifestyle activity condition showed less weight regain at 1 year and performed similarly to those in the aerobic group on metabolic parameters, such as reductions in LDL cholesterol and triglycerides.

3.2 Effects of Exercise on Metabolic Parameters

Although the effect of physical activity on weight loss is not as large as many individuals seeking treatment would prefer, exercise can improve cardiovascular and metabolic parameters and reduce mortality risk independent of weight loss (Ross et al. 2000). As such, the saying "fit versus fat" has become a hot topic among both researchers in the field and the general public. However, body fat still confers risk for CVD outcomes and mortality independently of exercise, so physical activity does not cancel that effect (see Jakicic and Davis 2011).

Arem et al. (2015) recently provided a pooled analysis of over 660,000 participants across studies of the National Cancer Institute Cohort Consortium examining the 2008 physical activity guidelines and their effect on mortality risk. They reported that engagement in any moderate or vigorous activity reduced risk by 20 % as compared to those engaging in no activity. Those who engaged in one to two times the recommended amount of activity per week – 7.5 metabolic equivalent hours per week – decreased their mortality risk by 31 %. Activity at higher levels was associated with slightly higher reductions in mortality risk and was not considered harmful. This protective effect was found across BMI categories, while others have found that participation in moderate to vigorous lifestyle activity was beneficial in reducing mortality risk in those with a BMI $< 30\ kg/m^2$, but not in those with obesity (Willey et al. 2015). This lack of effect on mortality rates among persons with obesity may illustrate the independent effect of degree of fat on mortality risk, despite the influence of activity.

3.3 Continuous Versus Interval Training

Traditional lifestyle modification programs stress the number of minutes spent engaging in MVPA each week. Interval training has become increasingly popular as a means of increasing cardiovascular fitness and strength. A recent systematic review compared the effects of high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) on vascular functioning and other metabolic outcomes among patients with impaired vascular function (Ramos et al. 2015). They examined seven randomized trials with 182 participants. The most common prescription of HIIT included four intervals of four minutes at a maximum heart rate of 85–90 %, with three minutes of active recovery targeting 60–70 % of maximum heart rate. This routine was most often studied three times per week for 12–16 weeks. This was compared to traditional continuous moderate activity – the MICT group. Overall, HIIT was more effective in improving vascular function, cardiorespiratory fitness, and insulin sensitivity and reducing oxidative stress and inflammation as compared to MICT (Ramos et al. 2015). Thus, varying one's intensity of activity may provide higher benefit to improvements in cardiovascular and metabolic risk factors as compared to traditional constant moderate to vigorous physical activity.

4 Behavioral Modification

Within lifestyle modification programs for weight loss, behavioral modification plays a central role in successful treatment. Self-monitoring of caloric

intake and physical activity is critical to help patients to engage in and maintain changes in these behaviors. Cognitive-behavioral strategies can help patients identify maladaptive eating and activity behaviors and promote the development of healthy behaviors.

Behavioral modification interventions may be delivered through different modalities, including individual counseling sessions with a nutritionist, psychologist, physician, or other ancillary medical staff. This is time intensive and expensive, however, so group interventions are often employed. Not only are groups more cost effective than individual treatment, they also provide social support and can help participants be more engaged and feel more accountable for their efforts. These modalities have historically been delivered in person, but telemedicine options are also popular now, including telephone counseling, with or without supplemental computer-based applications, webpage support, or Wi-Fi scale technology. Interventions are also delivered directly through Internet-based sites or applications.

4.1 Self-Monitoring

Self-monitoring of food intake and physical activity is likely the most important skill to help patients successfully engage in self-regulation of these behaviors and promote weight loss and maintenance (Sarwer et al. 2004, 2014). Patients are typically asked to monitor their weight on a regular basis (at least weekly but in some programs daily) and also keep records of their daily food intake, total calories, and physical activity. Self-monitoring provides patients with feedback on their targeted behavior as well as opportunity to modify these behaviors as appropriate. Regular self-monitoring of food intake and weekly weighing are perhaps the strongest predictor of initial weight loss as well as larger weight losses at the end of treatment, as seen in numerous studies (e.g., Wadden et al. 2005, 2011).

Self-monitoring can help patients stay within their recommended treatment plan on a daily basis and regardless of whether the plan is coming from a commercial weight loss program, dietitian, or physician. Self-monitoring also can be used during treatment sessions with providers. Treatment providers often spend part of the treatment sessions reviewing the patient's food and activity records. The provider helps participants identify strategies to cope with identified problems and, thus, increase their adherence to the prescribed eating and activity plans. Although the provider introduces a new topic each week, sessions focus more on the participants reviewing their progress than on the practitioner's lecturing.

Self-monitoring is increasingly done using technological advances such as physical activity monitors that can be worn on the body and smart phone applications and websites that can promote self-monitoring and, in some cases, allow for this information to be shared with treatment providers in a timely fashion (Thomas et al. 2011). Interventions may also be conducted through websites and applications exclusively. Web-based weight loss programs generally produce weight losses of 2–5 kg and in most cases are superior to no treatment comparison groups. However, these weight losses are less than those reported through most typical in-person weight management studies, which are usually closer to 7–10 kg (Thomas and Bond 2014). As with in-person interventions, self-monitoring and feedback from a monitor seem to improve outcomes.

Financial incentives for weight loss, often combined with other aspects of technology-based weight loss interventions, have been associated with larger weight losses than control groups who just received information on behaviors necessary for weight loss (Kullgren et al. 2013; Volpp et al. 2008). Financial incentives in the form of payment, as well as in the form of returning a monetary deposit committed by participants at the beginning of the study, produce larger weight losses than groups without a financial incentive (Volpp et al. 2008), and evidence shows that group incentives produce greater weight loss at 24 weeks than individual incentives (Kullgren et al. 2013).

4.2 Cognitive-Behavioral Strategies

Lifestyle modification programs also teach patients cognitive-behavioral skills (Sarwer et al. 2014). Patients practice setting short-term, reasonable, specific, and measurable goals for the development of more adaptive and healthy behaviors. Assessing progress toward these goals on a weekly basis and with the treatment provider is another cornerstone of most treatment. The discussion between the patient and provider allows for a functional analysis of specific eating and activity behaviors that conditions patients to identify the events or cues that occur before and after a targeted behavior. It also allows both individuals to determine what is causing and maintaining the maladaptive behavior and make changes in these events or cues to promote the engagement in healthier behaviors. Stimulus control principles also are used to change the internal and external cues associated with targeted eating and activity behaviors. Patients are taught to change their immediate environments (e.g., the home and workplace) so that they facilitate, rather than hinder, positive behavior change. For example, stimulus control can focus on reducing exposure to particularly tempting high-calorie foods, increasing the availability and visibility of healthy food, and creating cues for physical activity.

Problem solving is another core behavioral skill. Patients identify a problem in detail, brainstorm potential solutions to the problem, consider the pros and cons of each option, choose a solution, develop a plan to implement it, and evaluate the effectiveness of the chosen solution once the behavior has been implemented (Sarwer et al. 2014). Making these plans as specific as possible and checking in with patients regarding their intentions to try to enact the plan during the coming week are necessary for adherence. Additionally, relapse prevention skills help patients to anticipate and develop strategies for dealing with high-risk situations, such as a stressful project at work or a vacation, and plan how they will respond to lapses in adherence.

Most lifestyle modification programs also teach cognitive restructuring, in which patients identify and modify automatic thoughts and develop rational responses to these thoughts as a way of changing behavior. For example, an individual might think, "That bag of chocolate bars is on sale. I'll buy it just in case the kids have friends over this weekend." The provider would help the patient challenge this thought by reviewing the potential consequences of buying a bag of chocolate. Would he or she be able to abstain from eating those bars and save them for visitors? If the person chose to eat the chocolate, would it taste good and be rewarding? Likely, yes, it would provide a short-term reward. However, it may be difficult to limit the consumption of the chocolate to a specified serving size when a full bag is present. Thus, after the initial feeling of reward, longer-term feelings of guilt, as well as physical consequences, such as lack of weight loss or possible weight gain, would likely result. Such use of Socratic questioning helps the patient generate their own solutions to weight loss barriers. This exercise also increases the patient's ability to identify triggers to overeating and automatic thoughts that lead to undesirable outcomes, allowing the individual to stop in the moment and respond in a manner more consistent with his or her weight loss or weight maintenance goals.

5 Summary

Lifestyle modification plays a key role in weight management efforts. Its components include picking a specific dietary plan, promoting moderate to vigorous physical activity, and using behavioral modification strategies. Different dietary approaches produce weight loss successfully, typically between a 5 % and 10 % loss of initial body weight, which is related to improvements in cardiovascular and metabolic parameters. Over time, weight regain happens with all approaches as dietary adherence wanes. In general, an individual's ability to integrate the changes adapted through a dietary approach would need to be perceived as doable for long-term adherence and weight loss maintenance. Thus, what one person finds appealing for a dietary prescription, say, high protein, may be quite difficult for someone else, say, someone who prefers vegetarian, low-fat

options. Supplementing the dietary approach with physical activity generally increases weight loss and, most consistently, predicts longer-term weight loss maintenance. The use of behavioral modification techniques helps improve adherence to a diet and exercise plan through specific action plans and accountability.

Future research in this area likely will focus on matching lifestyle modification strategies to individuals based on genetics, taste and behavioral preference, disease burden profiles, and brain imaging techniques. More research is also needed to understand the possible role of financial incentives for weight management for larger, community-based weight management efforts. Until then, providing ample support to those seeking weight loss, encouraging self-monitoring, targeting specific calorie or other macronutrient goals, and providing specific plans for increasing physical activity should be a part of any prescribed weight management program.

6 Cross-References

- Bariatric Surgery
- Brain Regulation of Feeding and Energy Homeostasis
- Carbohydrate, Fat, and Protein Metabolism in Obesity
- Diet and Obesity (Macronutrients, Micronutrients, Nutritional Biochemistry)
- Global, National, and Community Obesity Prevention Programs
- Obesity and Cardiac Disease
- Pharmacotherapy of Obesity and Metabolic Syndrome
- Prevention and Treatment of Childhood Obesity and Metabolic Syndrome
- Principles of Energy Homeostasis
- Reproductive Disorders and Obesity in Males and Females and Focus on the Polycystic Ovary Syndrome
- Social and Community Networks and Obesity
- The Built Environment and Obesity
- Type 2 Diabetes: Etiology, Epidemiology, Pathogenesis, Treatment

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Pharmacotherapy of Obesity and Metabolic Syndrome

44

Rexford S. Ahima

Contents

Abstract

The management of metabolic syndrome requires a healthy low-calorie diet, increased physical activity, and other behaviors that promote the maintenance of weight loss. Medications for obesity, diabetes, hypertension, and dyslipidemia may be necessary for the treatment of components of metabolic syndrome and to reduce the risk of cardiovascular disease. This chapter describes current medications available for treatment of obesity and metabolic syndrome.

Keywords

Obesity • Metabolic syndrome • Diabetes • Hypertension • Lipid • Cardiovascular

1 Introduction

The prevalence of metabolic syndrome has increased worldwide mainly due to the obesity epidemic (Flegal et al. 2010; Schmidt et al. 2013; Allison et al. 2008; Calle et al. 2003; Jensen et al. 2014). Weight loss and long-term maintenance of weight loss have been shown to improve comorbid diseases associated with metabolic syndrome (Table 1). Diet and increased physical activity are essential for weight management. Medications or bariatric surgery may be needed to achieve and maintain a healthy weight (Cohen et al. 2012; Mingrone et al. 2012; Schauer et al. 2012; Buchwald et al. 2009; Ilanne-Parikka

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Table 1 Weight reduction improves clinical outcomes of obesity-related diseases

Disease	References
Type 2 diabetes	Cohen et al. 2012; Mingrone et al. 2012; Schauer et al. 2012; Buchwald et al. 2009
Hypertension	Ilanne-Parikka et al. 2008; Phelan et al. 2007; Zanella et al. 2006
Dyslipidemia	Ilanne-Parikka et al. 2008; Phelan et al. 2007; Zanella et al. 2006
Cardiovascular disease	Wannamethee et al. 2005
NAFLD	Andersen et al. 1991; Huang et al. 2005; Palmer and Schaffner 1990; Ueno et al. 1997
Sleep apnea	Kuna et al. 2013
Osteoarthritis	Christensen et al. 2007; Fransen 2004; Huang et al. 2000; Messier et al. 2004; van Gool et al. 2005
Cancer	Adams et al. 2009; Sjostrom et al. 2009

et al. 2008; Phelan et al. 2007; Zanella et al. 2006; Wannamethee et al. 2005; Andersen et al. 1991; Huang et al. 2005; Palmer and Schaffner 1990; Ueno et al. 1997; Christensen et al. 2007; Fransen 2004; Huang et al. 2000; Messier et al. 2004; van Gool et al. 2005; Adams et al. 2009; Sjostrom et al. 2009; Kuna et al. 2013). For weight management to be successful, it is crucial for patients to be actively involved in their care and be monitored frequently for weight loss, comorbid disease outcomes, and adverse effects of treatment.

2 Weight Loss Medications

Medications approved for the long-term treatment of obesity include orlistat, lorcaserin, the combination of phentermine and topiramate, and liraglutide. A weight loss medication is deemed effective if it results in weight loss greater than 5 % of body weight. Unfortunately, the recidivism rate for weight management is very high, and a large proportion of patients are lost to follow up even in well-controlled clinical trials. Medications that are ineffective after 12 weeks of treatment or have adverse effects or safety concerns should be discontinued and alternative therapies considered.

Orlistat (tetrahydrolipstatin) inhibits pancreatic lipase thereby reducing intestinal digestion of fat. Orlistat is available as a prescribed dose of 120 mg three times daily before meals or over-the-counter dose of 60 mg three times daily. Orlistat decreases body weight in a dose-dependent manner. A 4-year double-blind, randomized, placebo-controlled trial showed that orlistat treatment resulted in more than 11 % reduction below the baseline weight compared to 6 % below the baseline weight in the placebo group (Torgerson et al. 2004). Orlistat treatment blunts weight regain and the conversion rate of glucose intolerance to diabetes. Orlistat is effective in adolescents (Chanoine et al. 2005). A meta-analysis of orlistat clinical trials showed that orlistat reduced body weight by -5.70 ± 7.28 kg compared to -2.40 ± 6.99 kg in the placebo group (Rucker et al. 2007). The side effects of orlistat are related to blockade of triglyceride digestion in the intestine, which causes abdominal discomfort, flatulence, and oily stools (Bray and Greenway 2007). Orlistat can decrease absorption of fat-soluble vitamins; therefore, patients require multivitamin supplementation. Very rarely orlistat therapy has been associated with liver toxicity, but the etiology is unclear (Jensen et al. 2014).

Lorcaserin is a serotonin-2C receptor (5HTR-2C) agonist which decreases food intake and body weight (Kelly et al. 2013; Smith et al. 2010; Fidler et al. 2011; O'Neil et al. 2012). Lorcaserin is prescribed as a dose of 10 mg twice daily and has been shown to be effective in many studies (Halford et al. 2007), e.g., the BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management) (Smith et al. 2010), the BLOSSOM (Behavioral Modification and Lorcaserin Second Study for Obesity) (Fidler et al. 2011) which enrolled patients with BMI $\geq$27 kg/m^2 with one comorbidity, and the BLOOM-DM (O'Neil et al. 2012) which studied diabetic patients with BMI values of 27–45 and glycated hemoglobin of 7–10 %. These studies all showed significant reductions of food intake and body weight (Martin et al. 2011). In the BLOOM-DM, lorcaserin treatment decreased the fasting glucose and glycated hemoglobin levels compared to the placebo group (O'Neil et al. 2012).

Lorcaserin was well tolerated and had mild side effects, consisting of headache, fatigue, dry mouth, nausea, dizziness, and constipation. Lorcaserin treatment did not increase the risk of valvulopathy (O'Neil et al. 2012) (Fidler et al. 2011).

The combination phentermine and topiramate is marketed as an extended-release formulation, Qsymia™, as phentermine (3.75, 7.5, or 15 mg) combined with topiramate (23, 46, or 92 mg) (Allison et al. 2012; Gadde et al. 2011). A dose titration period of 2 weeks is recommended for Qsymia™, starting at the lowest combination dose. Phentermine stimulates norepinephrine levels in the hypothalamus which has been linked to appetite suppression. Topiramate stimulates γ-aminobutyric acid (GABA) receptor activity, but it is unclear if this is directly involved in appetite suppression and weight loss. The safety and efficacy of Qsymia™ were evaluated in two randomized, placebo-controlled trials that included approximately 3,700 obese and overweight patients with and without weight-related conditions treated for 1 year. The participants received lifestyle modification consisting of a reduced calorie diet and regular physical activity. In the EQUIP study, phentermine/topiramate was administered in adults $\leq$70 years of age and with a BMI $\geq$35 kg/m^2 (Allison et al. 2012). The CONQUER study (Gadde et al. 2011) examined the effects of Qsymia™ in adults $\leq$70 years, with a BMI of 27–45 kg/m^2, and 2 or more of the following conditions: hypertension, hypertriglyceridemia, abnormal glucose metabolism (impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes), or waist circumference $\geq$40 in. in men or $\geq$35 in. in women. Results from these studies showed that after 1 year of treatment, there was a mean weight loss of 6.7 % and 8.9 % with the recommended and highest daily doses of Qsymia™, respectively, over placebo treatment. About 62 % and 69 % of the participants lost at least 5 % of their body weight with the recommended dose and highest doses of Qsymia™, compared with 20 % of placebo-treated patients. Extension of the CONQUER study for a second year, i.e., the SEQUEL study, resulted in significant weight loss (Garvey et al. 2012). Qsymia™ treatment resulted in significant improvements in blood pressure, glucose homeostasis, and lipids (Allison et al. 2012; Gadde et al. 2011; Garvey et al. 2012), and these changes were related to the degree of weight loss.

The most common side effects of Qsymia™ are paresthesia, dizziness, altered taste sensation, dry mouth, insomnia, and constipation. Qsymia™ is contraindicated in pregnancy, as are all weight loss medications. Because topiramate has been associated with fetal oral clefts, a negative pregnancy test is required before treatment is initiated. A pregnancy test must be done every month, and effective contraception is required during continued Qsymia™ treatment. If a patient becomes pregnant while taking Qsymia™, the drug should be discontinued immediately. Qsymia™ is contraindicated in patients with glaucoma, hyperthyroidism, recent monoamine oxidase inhibitor (MAOI) therapy (within 14 days), recent or unstable heart disease or stroke (within the 6 months), hypersensitivity to topiramate or phentermine, or kidney stones. The US FDA approved Qsymia in 2012 with a Risk Evaluation and Mitigation Strategy (REMS), consisting of safety information for prescribers and patients, prescriber training, and pharmacy certification. The REMS is aimed toward educating prescribers and patients about the increased risk of birth defects associated with first trimester exposure to Qsymia™, the requirement for pregnancy prevention, and the discontinuation of therapy if pregnancy occurs. Qsymia™ is only dispensed through specially certified pharmacies. The manufacturer, Vivus Inc., is required to conduct post-marketing studies, including a long-term cardiovascular outcomes trial to assess the risk for major cardiovascular events.

Bupropion is approved for the treatment of depression, seasonal affective disorder, and smoking cessation. Bupropion also acts on adrenergic and dopaminergic receptors in the hypothalamus to suppress feeding and reduce body weight (Greenway et al. 2009). Naltrexone is an opioid receptor antagonist approved for the treatment of alcohol or opioid dependence. Naltrexone has minimal effect on body weight if given alone; however, it potentiates the effect of α-melanocyte-stimulating hormone (α-MSH) to

inhibit food intake (Greenway et al. 2009). Contrave™ is a combination of naltrexone and bupropion administered as an extended-release formulation (Greenway et al. 2010; Wadden et al. 2011). The effectiveness of Contrave™ was evaluated in clinical trials involving about 4,500 obese and overweight participants with and without significant weight-related conditions treated for 1 year (Greenway et al. 2010; Wadden et al. 2011). The participants received lifestyle modification consisting of a reduced calorie diet and regular physical activity. The results showed that patients without diabetes had a mean weight loss of 4.1 % over placebo treatment at 1 year. About 42 % of participants treated with Contrave™ lost at least 5 % of their body weight compared to 17 % to placebo-treated patients. Among the participants with type 2 diabetes had an average weight loss of 2 % better than placebo treatment at 1 year. About 36 % of patients treated with Contrave™ lost at least 5 % of their body weight compared to 18 % in the placebo-treated group.

Patients on maintenance doses of Contrave™ should be evaluated after 12 week, and the drug should be discontinued if they have not lost at least 5 % of baseline body weight. The most common adverse effects of Contrave™ include nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea. The bupropion component of Contrave™ increases the risk of suicidal thoughts. Contrave™ can cause seizures and increase blood pressure and heart rate and must not be used in patients with poorly controlled hypertension. Contrave™ should not be used in patients with eating disorders (e.g., bulimia or anorexia nervosa), in those on opioids or treatments for opioid dependence, or in those experiencing acute opiate withdrawal or undergoing discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs. Contrave™ is contraindicated in pregnancy. The US FDA requested the following post-marketing studies for Contrave™: assessment of cardiovascular risk, efficacy, safety, and clinical pharmacology studies in children; toxicity studies in young animals with a focus on growth, development, behavior, learning, and memory; investigation of the effect of Contrave™ on cardiac conduction; clinical trials to evaluate the dosing of Contrave™ in patients with hepatic or renal impairment; and a clinical trial to evaluate interactions between Contrave™ and other drugs.

Liraglutide is an acylated GLP-1 analogue that shares 97 % amino acid sequence homology to endogenous GLP-1 (7–37) (Scott 2014). Liraglutide has a prolonged plasma half-life compared with endogenous GLP-1 (13 h vs. 2 min). Liraglutide activates the GLP-1 receptor and triggers several responses, including glucose-dependent insulin secretion, inhibition of pancreatic glucagon secretion, and reduction of appetite and body weight (Muscogiuri et al. 2014; Holst 2013; Madsbad 2014; Iepsen et al. 2014). Saxenda containing liraglutide at a dose of 3 mg has been approved for weight loss. The safety and efficacy of Saxenda were evaluated in clinical trials that included about 4,800 obese and overweight patients with or without comorbid conditions (Astrup et al. 2009; Wadden et al. 2013; Lean et al. 2014). The patients received lifestyle counseling consisting of a reduced calorie diet and regular physical activity. Saxenda treatment resulted in an average weight loss of 4.5 % from baseline compared to placebo at 1 year, and 62 % of patients on Saxenda lost at least 5 % of their body weight compared to 34 % of placebo-treated patients. Among patients with type 2 diabetes, Saxenda treatment resulted in an average weight loss of 3.7 % from baseline compared to placebo at 1 year, and 49 % of patients treated with Saxenda lost at least 5 % of their body weight compared to 16 % of patients treated with placebo.

The most common side effects observed in patients treated with Saxenda are nausea, diarrhea, constipation, vomiting, and hypoglycemia. Although Saxenda causes thyroid C-cell tumors in rodents, it is unknown whether the drug causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans. Saxenda is contraindicated in patients with a personal or family history of MTC or in patients with MEN2. Serious adverse effects of Saxenda include pancreatitis, cholecystitis, renal impairment, and suicidal thoughts. Saxenda can induce tachycardia

and should be discontinued in patients who experience a sustained increase in resting heart rate. The US FDA approved Saxenda with a REMS consisting of a plan to educate health-care professionals and patients about the risks associated with the drug. The US FDA requested post-marketing clinical trials to evaluate dosing, safety, and efficacy of Saxenda in children; a study to investigate the effects on growth, sexual maturation, and CNS development and function in young rats; a case registry of at least 15 years duration to evaluate the risk of MTC; and an evaluation of the risk of breast cancer with Saxenda in ongoing clinical trials.

Benzphetamine, diethylpropion, phendimetrazine, and phentermine are sympathomimetic drugs approved by the US FDA for short-term weight loss treatment, i.e., 12 weeks (Ryan et al. 2010; Addy et al. 2009; Kim et al. 2006). Phentermine and diethylpropion are classified by the US DEA as schedule IV drugs, and benzphetamine and phendimetrazine are classified as schedule III drugs (Bray and Greenway 2007). Phentermine was approved in 1959 for short-term treatment, and studies have demonstrated a modest dose-related weight loss in phentermine-treated patients (Ryan et al. 2010; Addy et al. 2009; Kim et al. 2006). The side effects of the sympathomimetic drugs include insomnia, nervousness, dry mouth, tachycardia, and elevated blood pressure. These drugs should not be prescribed to patients with a history of cardiovascular disease.

Table 2 Effects of medications on body weight

Disease	Drugs associated with weight gain	Drugs that are weight neutral or cause weight loss
Diabetes	Insulin Sulfonylureas Glitinides Thiazolidinediones	*Weight neutral* Acarbose Miglitol DPP-4 inhibitors *Weight loss* Metformin Pramlintide Exenatide Liraglutide
Hypertension	Alpha-blocker Beta-blocker	ACE inhibitors ARB Calcium channel blockers
Depression	Citalopram Escitalopram Fluvoxamine Lithium Tricyclic antidepressants Monoamine oxidase inhibitors Mirtazapine Paroxetine Venlafaxine	Bupropion Nefazodone Fluoxetine Sertraline
Psychosis	Clozapine Risperidone Olanzapine Quetiapine	Ziprasidone Aripiprazole
Epilepsy	Valproate Carbamazepine Gabapentin	Zonisamide Topiramate Lamotrigine

3 Treatment of Diabetes

Obesity is closely linked to type 2 diabetes in regard to etiology, pathogenesis, and management (Knowler et al. 2002; Diabetes Prevention Program Diabetes Prevention Program Research Group et al. 2009; Tuomilehto et al. 2001; Buchwald et al. 2004). Several drugs used for the treatment of diabetes produce weight gain, e.g., insulin, sulfonylurea drugs (glipizide and glibenclamide), and thiazolidinediones (rosiglitazone and pioglitazone) (Leslie et al. 2007) (Table 2). It is important to use medications that are weight neutral or cause weight loss (Bray and Ryan 2012) (Table 2).

Metformin is a biguanide that increases hepatic insulin sensitivity and reduces glucose production. Metformin typically causes weight loss. For example, in the Diabetes Prevention Program, the patients receiving metformin lost more weight than placebo, and the weight loss persisted for 8 years of follow-up (Diabetes Prevention Program Research Group 2012). Bushe et al. (2009) reported that metformin may prevent weight gain and metabolic syndrome during treatment with antipsychotic drugs.

Pramlintide is an analog of amylin, a peptide secreted along with insulin by pancreatic β cells. Pramlintide lowers blood glucose and produces weight loss (Aronne et al. 2010). GLP-1 agonists stimulate insulin secretion (Edwards et al. 2001), inhibit glucagon secretion, slow gastric emptying, and reduce food intake (Gutzwiller et al. 1999; Turton et al. 1996). Because endogenous GLP-1 is rapidly inactivated by dipeptidyl peptidase-4 enzyme, synthetic GLP-1 receptor agonists with prolonged action have been developed for treatment of type 2 diabetes (Meier 2012). Liraglutide is appropriate for the treatment of obese diabetics because it reduces hyperglycemia, enhances insulin sensitivity, and reduces body weight (Meier 2012).

The kidney regulates glucose homeostasis through reabsorption of glucose from the glomerular filtrate via SGLT-1 and SGLT-2 (Gerich 2010). SGLT-2 inhibitors block 90 % of glucose reabsorption in the proximal tubule of the nephron, leading to urinary glucose excretion and reduction in blood glucose levels (DeFronzo et al. 2012). The US FDA approved SGLT-2 inhibitors, i.e., canagliflozin, empagliflozin, and dapagliflozin, for diabetes treatment. In addition to lowering glucose levels (List et al. 2009; Strojek et al. 2011), SGLT-2 inhibitor treatment results in loss of calories in the urine and weight loss (Ferrannini and Solini 2012). SGLT-2 inhibitors may decrease blood pressure (Ferrannini et al. 2010; Henry et al. 2012), increase HDL cholesterol, and decrease triglyceride levels (Bailey et al. 2010; Nauck et al. 2011; Rosenstock et al. 2012). SGLT-2 inhibitors may also decrease serum uric acid levels (List et al. 2009; Henry et al. 2012), suggesting multiple benefits in metabolic syndrome (Jung et al. 2014).

3.1 Treatment of Atherogenic Dyslipidemia

Statins are effective in reducing total and LDL cholesterol levels (Charlton-Menys and Durrington 2008; Baigent et al. 2005). The role of statins in reducing cardiovascular risk is well established (Baigent et al. 2005). Prospective studies such as the COmparative study with rosuvastatin in subjects with METabolic Syndrome (COMETS) and the Measuring Effective Reductions in Cholesterol Using Rosuvastatin TherapY I (MERCURY I) showed that statins improved atherogenic dyslipidemia in patients with metabolic syndrome (Stalenhoef et al. 2005; Stender et al. 2005; Deedwania et al. 2005). A meta-analysis showed that statin therapy reduced the risk of cardiovascular disease (Cholesterol Treatment Trialists et al. 2012). Statin treatment consistently reduces cardiovascular and all-cause mortality in patients at high risk of cardiovascular disease (LaRosa et al. 2005; Pyorala et al. 2004). Statins also reduce oxidative stress and inflammation, improve endothelial function, and decrease cardiovascular morbidity (Liao 2002; Meyer-Sabellek and Brasch 2006; Goff et al. 2014). Statin therapy has been associated with insulin resistance (Preiss et al. 2011; Sattar et al. 2010; Kanda et al. 2003). However, the risk of statin-mediated insulin resistance should be balanced against the benefits in reducing cardiovascular risks (Lim et al. 2013b).

Fibrates are useful for the treatment of hypertriglyceridemia and low HDL cholesterol levels. Fibrates also modulate fibrinogen, IL-1, IL-6, and hsCRP levels (Zambon et al. 2006; Keech et al. 2005). Studies have shown that fibrates reduce triglycerides (Aguilar-Salinas et al. 2001; Klosiewicz-Latoszek and Szostak 1991) and increase HDL cholesterol (Packard et al. 2002). Fenofibrate decreases fibrinolysis inhibitor levels and improves endothelial function in patients with metabolic syndrome (Kilicarslan et al. 2008). Some metabolic syndrome patients may need a combination of statin and fibrate for the treatment of atherogenic dyslipidemia and cardiovascular risk reduction (Lim et al. 2013a).

3.2 Treatment of Hypertension

The pathogenesis of hypertension in metabolic syndrome is thought to be mediated by various factors including activation of the SNS, increased renal tubular sodium reabsorption, and

dysregulation of the renin-angiotensin-aldosterone system (RAAS). Thiazide diuretics are the first-line agent in the treatment of hypertension within the general population (Chobanian et al. 2003; ALLHAT 2002). However, thiazides tend to raise blood glucose levels and may convert prediabetes to diabetes (Rapoport and Hurd 1964; Amery et al. 1978; Hoskins and Jackson 1978; Plavinik et al. 1992; Harper et al. 1995).

The RAAS is functionally linked to insulin resistance and endothelial dysfunction in patients with metabolic syndrome and obesity-related hypertension (Watanabe et al. 2005; Henriksen and Prasannarong 2013). Angiotensin II inhibits insulin signaling, induces oxidative stress, and exacerbates hyperglycemia and atherogenesis (Shatanawi et al. 2011). In contrast, ACE inhibitors reduce blood pressure as well as glucose levels, inflammation, oxidative stress, and endothelial dysfunction (Chin et al. 2003; Manabe et al. 2005; Edwards et al. 2007). A recent analysis with Cardiovascular Health Study showed that RAAS blocking agents reduced cardiovascular events in patients with metabolic syndrome (Zreikat et al. 2014). In the prospective, multicenter, double-blind TROPHY study, obese hypertensive patients were treated with hydrochlorothiazide (12.5, 25, or 50 mg) or lisinopril (10, 20, or 40 mg), with a target diastolic blood pressure less than 90 mmHg. About 60 % of the obese patients receiving lisinopril achieved the blood pressure goal compared to 43 % of patients treated with hydrochlorothiazide (HCTZ), and the patients receiving HCTZ had significantly higher plasma glucose and lower plasma potassium levels compared to lisinopril treatment (Reisin et al. 1997; Reisin and Jack 2009). Treatment with irbesartan alone or in combination with HCTZ was more effective in decreasing blood pressure and also led to improvements in HDL cholesterol, triglyceride levels, fasting blood glucose, and waist circumference in both men and women (Kintscher et al. 2007). To determine whether RAAS inhibition had beneficial metabolic effects, a clinical study compared HCTZ monotherapy, valsartan monotherapy, or HCTZ/valsartan combination therapy in patients with metabolic syndrome. The results showed patients on HCTZ therapy had increased hemoglobin A1c or triglyceride levels, while those on valsartan alone or valsartan/HCTZ combination had a favorable metabolic outcome (Zappe et al. 2008). A sub-analysis of diabetic patients in the Captopril Prevention Project (CAPPP) revealed that ACE inhibitor treatment reduced the total and cardiovascular mortality risk and the risk of fatal and nonfatal myocardial infarction compared to diuretic/beta-blocker treatment (Niskanen et al. 2001).

Calcium channel blockers can be given alone or in combination with an ACE inhibitor or ARB for hypertension treatment. In the ACCOMPLISH clinical trial, the patients on HCTZ/benazepril had a higher incidence of cardiovascular morbidity than patients on amlodipine/benazepril (Jamerson et al. 2008; Bakris et al. 2010, 2013). However, a sub-analysis of patients classified as normal weight, overweight, and obese based on BMI criteria found no difference in the rates of the primary cardiac endpoint between obese patients taking HCTZ versus amlodipine (Weber et al. 2013).

The use of beta-blockers for hypertension treatment has been associated with the development of glucose intolerance, dyslipidemia, and weight gain (Ripley and Saseen 2014; Messerli and Grossman 2004). Older beta-blockers, e.g., propranolol, metoprolol, and atenolol act via beta-1 and beta-2 adrenergic receptors to regulate cardiac and vascular responses and metabolism (Deedwania 2011). The International Verapamil-Trandolapril Study (INVEST), the Losartan Intervention for Endpoint Study (LIFE), and the Atherosclerosis Risk in Communities Study (ARIC) all showed higher rates of diabetes in patients treated with older beta-blockers, e.g., atenolol, compared to other medications (Pepine et al. 2003; Dahlof et al. 2002; Gress et al. 2000). Newer beta-blockers have an additive alpha-adrenergic receptor blocking component (e.g., carvedilol, labetalol) or increased nitric oxide synthesis (e.g., carvedilol, nebivolol) that promotes vasodilation. These beta-blockers often have neutral or favorable effects on body weight compared to older beta-blockers (Reisin and Owen 2015).

4 Conclusions

Weight management using diet, increased physical activity, and behavior modification is essential for patients with metabolic syndrome. Patients unable to successfully lose and maintain weight reduction may be eligible for medications. Weight loss enhances insulin sensitivity, cardiopulmonary function, and overall health status. Medications approved by the US FDA for weight reduction include phentermine, extended-release phentermine/topiramate, lorcaserin, orlistat, and sustained release bupropion/naltrexone and the glucagon like peptide-1 (GLP-1) agonist liraglutide. In patients with type 2 diabetes, metformin and other drugs that cause weight loss or are weight neutral are preferred. Lipid-lowering medications such as statins and fibrates are needed for treatment of atherogenic dyslipidemia. RAAS and calcium channel blockers are effective for treatment of hypertension and reduction of cardiovascular risk. As much as possible, physicians managing patients with obesity or metabolic syndrome should avoid prescribing medications for hypertension, dyslipidemia, and other diseases that increase body weight and predispose to adverse metabolic outcomes.

5 Cross-References

- Adipokines and Metabolism
- Bariatric Surgery
- Diet and Obesity (Macronutrients, Micronutrients, Nutritional Biochemistry)
- Diet, Exercise, and Behavior Therapy in the Treatment of Obesity and Metabolic Syndrome
- Genetics of Obesity
- Overview of Metabolic Syndrome
- Prevention and Treatment of Childhood Obesity and Metabolic Syndrome
- Principles of Energy Homeostasis

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Bariatric Surgery

45

Rexford S. Ahima and Hyeong-Kyu Park

Contents

Abstract

Bariatric surgery is the most effective and durable treatment for obesity. This review will describe the historic and current bariatric surgical procedures; outcome data focusing on weight loss, diabetes, and other obesity-related diseases; complications; and putative mechanisms underlying the effects of bariatric surgery on body weight and metabolism.

Keywords

Bariatric surgery • Obesity • Diabetes • Metabolism • Lipids • Hypertension • Cardiovascular

1 Introduction

Obesity is a major public health problem worldwide (Shields et al. 2011; Lobstein and Brinsden 2014). Studies have shown that bariatric surgery is the most effective and durable treatment for individuals with severe obesity and those at the highest risk for obesity-related comorbidity and mortality (Kraschnewski et al. 2010; Bray 2008; Sandoval 2011). The use of bariatric surgery as a treatment for obesity has increased due to various factors: (i) the prevalence of obesity in the adult population is very high and has doubled over the past three decades, and the prevalence of severe obesity (class III; body mass index [BMI] >40) has quadrupled (Sturm 2007); (ii) obesity-related comorbidities have led to more severely obese patients seeking bariatric surgery treatment; and

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(iii) behavioral and pharmacologic treatments of obesity may be successful in the short-term but do not translate into longer-term weight loss in most patients (Vetter et al. 2010). Other factors that have contributed to the increasing use of bariatric procedures include laparoscopic techniques that have improved safety and decreased the length of hospital stays (Santry et al. 2005; Reoch et al. 2011; Lo Menzo et al. 2015), increased information concerning the efficacy and safety of bariatric procedures among patients and physicians, media coverage of celebrity patients who have undergone bariatric surgery, and coverage of costs by insurance companies and other healthcare payers (Linkov et al. 2014).

2 Bariatric Procedures

Jejunoileal bypass surgery (JBS) was described in the 1960s–1970s as a method for weight loss. Massive weight loss was accomplished in patients undergoing this procedure in which a short bowel was created by bypassing >90 % of the small intestine and creating a long blind loop (Fig. 1). Because 90–95 % of the total small intestine is excluded from nutrients absorption as a result of end-to-end or end-to-side connections of intestinal segment, the JBS resulted in severe malabsorption and other systemic complications. The procedure was abandoned due to severe perioperative and long-term complications including hypokalemia, hypocalcemia, hypomagnesemia, liver failure, and kidney stones.

These problems with intestinal bypass led to the development of gastric partitioning procedures designed to decrease the reservoir for ingested food, thereby reducing energy intake (Pace et al. 1979). Gastric partitioning was done by applying a double-row stapling across the upper stomach and leaving a gap in the staple lines to allow passage of nutrients into the body of the stomach. Unfortunately, the failure rate of gastric partitioning was very high due to disruption of the staple line or dilation of the connection between the upper and lower gastric compartments, abrogating the retention of food in the upper compartment.

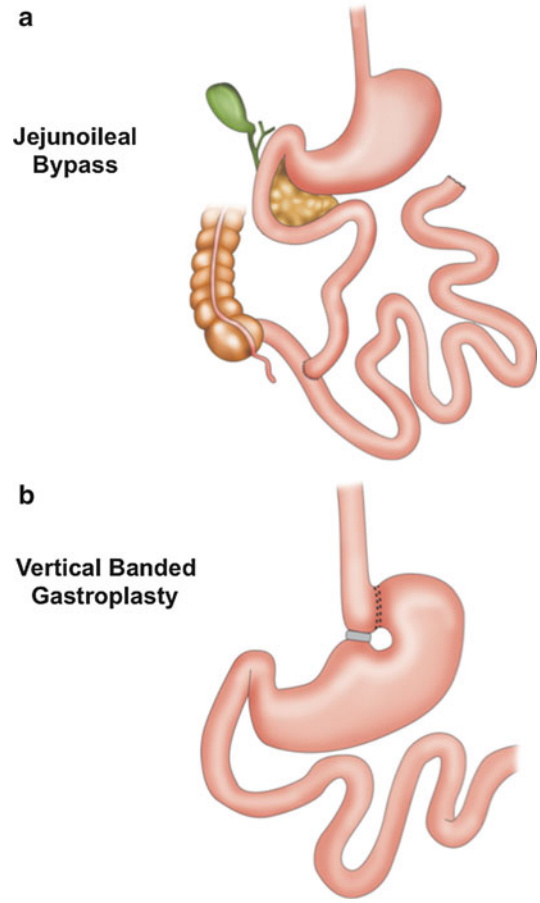

Fig. 1 (**a**) Jejunoileal bypass; (**b**) vertical banded gastroplasty (Figures are reproduced from Elder and Wolfe (2007) and Ahima and Sabri (2011), with the permission of Elsevier Publishers)

The vertical banded gastroplasty (VBG) procedure was developed to address the problems of gastric partitioning (Fig. 1). The stomach was partitioned with staples, and the opening (stoma) between the upper gastric pouch and body of the stomach was reinforced with a band of prosthetic mesh or a silicon rubber tubing to prevent dilation of the stoma (Mason 1982). VBG was the main bariatric procedure in the 1980s, but its use declined due to failure to achieve or maintain weight loss, intractable vomiting and gastroesophageal reflux disease (GERD), band erosion into the stomach, and stricture formation in some patients.

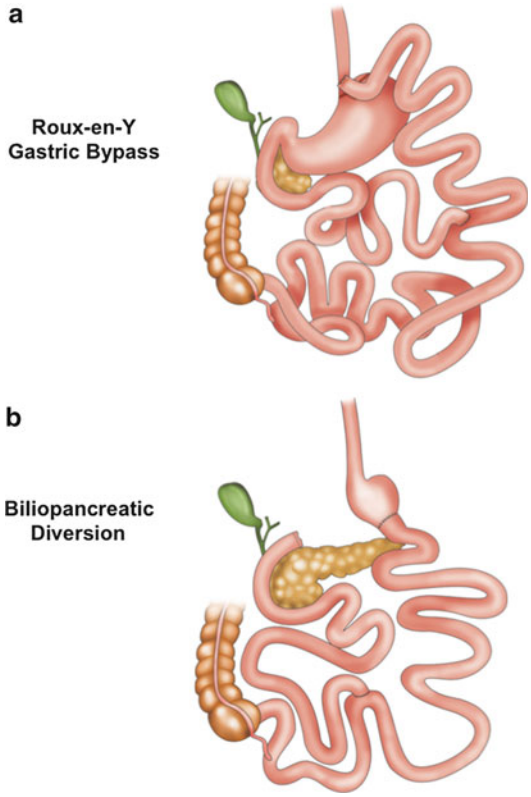

Fig. 2 (**a**) Roux-en-Y gastric bypass; (**b**) biliopancreatic diversion (Figures are reproduced from Elder and Wolfe (2007) and Ahima and Sabri (2011), with the permission of Elsevier Publishers)

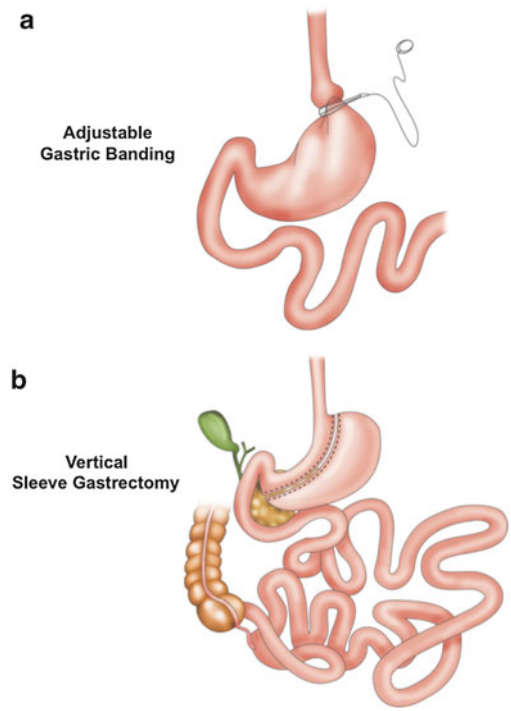

Fig. 3 (**a**) Adjustable gastric banding; (**b**) vertical sleeve gastrectomy (Figures are reproduced from Elder and Wolfe (2007) and Ahima and Sabri (2011), with the permission of Elsevier Publishers)

The gastric bypass procedure was developed in the 1970s and initially involved a horizontal partitioning of the upper stomach to create a small gastric pouch and gastrojejunostomy to establish gastrointestinal outflow. However, the latter was soon replaced with a Roux-en-Y reconstruction (RYGB) due to a high incidence of bile reflux associated with the loop procedure (Griffen et al. 1977). In the current procedure, the size of the gastric pouch is 20–30 mL capacity, an alimentary limb, i.e., jejunal Roux-en-Y limb, is anastomosed to the stomach, and the biliopancreatic limb drains bile and pancreatic secretions to the jejunojejunostomy where the mixing of ingested food and digestive juices occurs (Fig. 2).

The biliopancreatic diversion (BPD) was developed as a method for inducing malabsorption and weight loss but avoiding the intestinal stasis by maintaining the flow of bile and pancreatic juice. Malabsorption is thought to be related to the length of the common channel, varying from 50 to 125 cm above the ileocecal valve, and the original procedure was combined with a subtotal gastrectomy. BPD has been modified by adding a duodenal switch procedure (Scopinaro et al. 1979; Marceau et al. 1993; Hess and Hess 1998).

Adjustable gastric banding (AGB) procedures are often done using a laparoscopic approach (LAGB) (Belachew et al. 1994). A saline-filled collar is placed around the upper stomach 1–2 cm below the gastroesophageal junction, creating an upper gastric pouch whose volume can be adjusted by modifying the amount of saline injected into a subcutaneous port linked to a balloon (Fig. 3).

Vertical sleeve gastrectomy (VSG) was introduced as a first-stage procedure in extremely obese patients, or those at high operative risk,

undergoing duodenal switch or biliopancreatic diversion procedures (Frezza 2007). VSG was found to lead to profound weight loss and has emerged as a stand-alone procedure (Gluck et al. 2011). VSG involves the removal of 80 % or more of the stomach including the fundus and greater curvature and preserving the pylorus (Berende et al. 2012; Brethauer 2011) (Fig. 3).

3 Clinical Indications for Bariatric Surgery

Obesity is associated with increased morbidity and mortality. Unfortunately, current medical treatment does not achieve sustained weight loss or improve obesity-related comorbidities, including T2DM, hypertension, NAFLD, and cardiovascular diseases in the majority of patients. The results of clinical trials have demonstrated potent effects of bariatric procedures to induce sustained weight loss and improve or normalize obesity-related comorbidities, including T2DM (Sjostrom et al. 2004, 2012; Chakravarty et al. 2012). The most commonly performed bariatric procedures are RYGB, AGB, and VSG (Buchwald and Oien 2013). BPD with or without duodenal switch is rarely performed (Smith et al. 2011). Patient selection for bariatric surgery is based mainly on the BMI, i.e., those with a BMI of at least 40 kg/m^2 or at least 35 kg/m^2 and obesity-associated comorbidity (2006; NIH conference. Gastrointestinal surgery for severe obesity. Consensus Development Conference Panel 1991) (Table 1). Emerging evidence showing that bariatric surgery improves metabolic outcomes

Table 1 Indications, contraindications, and preoperative assessment of bariatric patients

Indications	Contraindications	Preoperative assessment
• Adults with BMI $\geq$40 kg/m^2 without comorbid illness • Adults with BMI = 35.0–39.9 kg/m^2 with at least one serious comorbidity (e.g., type 2 diabetes, obstructive sleep apnea, obesity hypoventilation syndrome, GERD, NAFLD, debilitating arthritis)	• Bariatric procedures should not be performed solely for diabetes or lipid treatment or for cardiovascular risk reduction independent of BMI parameters • Psychiatric disorders: bulimia, untreated major depression or psychosis, or binge eating disorders • Inability to understand the type and risks of bariatric procedure and the behavioral changes that are necessary for effective weight loss • Inability to comply with long-term management, e.g., vitamin replacement, and postoperative follow-up • Current alcohol or drug abuse • Severe cardiac disease • Severe coagulopathy	• Comprehensive assessment by a medical specialist, dietitian, psychologist or psychiatrist, nurse specialist, and bariatric surgeon • Psychological assessment (i) to determine whether the patient is able and willing to make lifestyle changes needed for long-term weight; (ii) to identify bipolar disorder, major depression, or antisocial personality disorder, which should be treated in order to improve compliance and weight loss outcome • Diet and eating behavior (total calories, food portions, diet composition, binge eating, grazing, overeating, nighttime eating, stress-related eating) • Physical activity (exercise and non-exercise) • Previous attempts at weight loss (diet, lifestyle modification, medication, bariatric procedures, success, or failure) • Substance abuse (past and present) • Life stressors (e.g., loss of job, discord at home, divorce, bereavement); coping skills, family and social support • Motivation and expectations (extent of weight loss and health goals) • Medical assessment: history and physical examination to evaluate comorbid diseases, e.g., hypertension, diabetes, obstructive sleep apnea, hyperlipidemia, coronary artery disease, NAFLD • Laboratory tests: plasma chemistry, HbA1c, blood count, hemoglobin. TSH, polysomnography, abdominal ultrasound, and cardiac stress test if needed

has led to suggestions that the BMI threshold be lowered to 30 kg/m^2 in patients with coexisting diseases, e.g., in patients with T2DM who are not responding to medical treatment (Dixon et al. 2011).

Table 2 shows examples of retrospective and prospective studies in large cohorts of patients. Long-term follow-up in the Swedish Obese Study (SOS) showed that the incidence of T2DM was halved at 10 years (Sjostrom et al. 2004). After 6 years of follow-up, 62 % of RYGB patients had a glycosylated hemoglobin (HbA1c) <6.5 %, a fasting glucose <7 mmol/L, and did not require antidiabetic therapy (Adams et al. 2012). Retrospective data at 9 years demonstrated that >65 % of T2DM patients did not require therapy after RYGB (MacDonald et al. 1997). However, it is important to note that the participants in these studies were not enrolled specifically to examine the question of T2DM remission with bariatric surgery (Adams et al. 2012; MacDonald et al. 1997; Pournaras et al. 2012). The metabolic phenotypes of participants and T2DM duration may confound the clinical outcomes of bariatric surgery. A longer duration of T2DM, higher HbA1c levels, use of insulin therapy, and reduced weight loss after bariatric surgery are all associated with failure of T2DM remission following RYGB and VSG procedures (Jimenez et al. 2012).

Few randomized controlled trials (RCT) have compared the effects of bariatric procedures and medical therapy (Schauer et al. 2012; Mingrone et al. 2012; Dixon et al. 2008) (Table 2). Over a 2-year period in patients with BMI 30–40 kg/m^2 and a duration of T2DM less than 2 years, AGB resulted in >70 % of T2DM patients achieving a HbA1c of <6.2 % compared to <15 % in patients receiving medical therapy (Dixon et al. 2008). Weight loss was significantly greater in the AGB T2DM patients compared to the medical therapy group. Glycemic responses to RYGB or BPD or medical therapy have been compared in patients with BMI ≥35 kg/m^2 and T2DM duration of at least 5 years. The results showed that 95 % of BPD T2DM patients achieved HbA1c ≤6.5 % compared to 75 % of RYGB and none of the medically treated T2D patients after 2-year follow-up (Mingrone et al. 2012). The medical therapy patients lost 5 % of their baseline weight compared with 30 % in the RYGB and BPD patients. Schauer et al. examined the effects of intensive medical therapy versus RYGB or VSG in obese patients with a mean BMI >35 kg/m^2 and T2D duration of 8 years (Schauer et al. 2012). The HbA1c target of 6 % was achieved by 42 % of the RYGB patients, 37 % of the VSG patients, and 12 % of the medical therapy patients. These data are exciting, but the samples sizes are relatively small, and previous studies have shown that glycemic control tends to worsen at 2 years after bariatric surgery (Sjostrom et al. 2004; Dixon et al. 2011). Therefore, longer follow-up studies in larger cohorts are needed to evaluate whether the benefits of bariatric surgery in T2DM can be sustained over longer periods.

The effects of bariatric surgery on microvascular complications of T2DM have been studied. Bariatric surgery decreased kidney damage in T2DM over 5 years follow-up as measured by albumin/creatinine ratio (Heneghan et al. 2013). RYGB improved kidney function as measured by the glomerular filtration rate (GFR) (Navaneethan and Yehnert 2009), creatinine clearance, and urinary cystatin C/creatinine ratio (Saliba et al. 2010). Furthermore, RYGB decreased proteinuria for up to 2 years in patients with T2DM (Amor et al. 2013).

In addition to improving glycemia, bariatric surgery affects other components of the metabolic syndrome, i.e., waist circumference, dyslipidemia, and hypertension (Sjostrom et al. 2004; Picot et al. 2009; Buchwald et al. 2004). After 10 years, bariatric surgery decreased the rates of hypertension and hypertriglyceridemia and increased HDL cholesterol levels, compared to a matched control group (Sjostrom et al. 2004). These changes may decrease cardiovascular mortality (Sjostrom et al. 2012). Some reports indicate that bariatric surgery may decrease cardiovascular risk in patients with a BMI <35 kg/m^2 by reducing blood pressure and improving glucose and lipid metabolism (Shah et al. 2010b; Sjoholm et al. 2013). However, others have reported inconsistent effects of bariatric surgery on lipid profiles (Li et al. 2012).

Table 2 Long-term outcome studies (retrospective or prospective)

(Sjöström et al. 2004, 2007, 2009, 2012; Carlsson et al. 2012)	Prospective observational study, Swedish Obese Subjects Study (SOS), duration 10–20 years, compared 2,010 surgical cases (13 % RYGB; 19 % banding; 68 % VBG) vs. 2,037 matched controls. Bariatric surgery reduced overall mortality, T2DM myocardial infarction, stroke, and cancer
Adams et al. (2007)	Retrospective observational study in Utah, USA, mean duration 7.1 years, compared 7,925 RYGB cases vs. 7,925 weight-matched controls. Bariatric surgery reduced mortality rates (all-cause, cardiovascular, and T2DM)
Adams et al. (2012)	Prospective observational study in Utah, USA, duration 6 years, compared 418 RYGB cases vs. 417 patients seeking bariatric surgery but who did not undergo surgery vs. 321 population-based matched controls. RYGB group lost more weight and had greater T2DM remission rates compared to control groups. Bariatric surgery was associated with greater improvements in blood pressure, cholesterol, and quality of life
Maciejewski et al. (2011, 2012)	Retrospective observational studies in 6.7 years, in the US Department of Veterans Affairs patients, compared 847 surgical cases vs. 847 matched controls. Bariatric surgery was associated with reduced mortality in unadjusted analysis
Courcoulas et al. (2013)	Prospective observational study, Longitudinal Assessment of Bariatric Surgery, USA, duration 3–5 years, studied 2,458 bariatric surgery cases (70.7 % RYGB vs. 24.8 % AGB vs. 5 % other procedures). Weight loss and remission of T2DM, dyslipidemia, and hypertension were significantly greater in RYGB compared with AGB
Arterburn et al. (2013)	Retrospective observational study in a Health Maintenance Organization Network in the USA, median duration 3.1 years, studied 4,434 RYGB cases with T2DM. 68 % of patients had T2DM remission within 5 years after RYGB, but 35.1 % of patients with T2DM remission redeveloped T2DM within 5 years
Carlin et al. (2013)	Prospective observation study, Michigan Bariatric Surgery Collaborative, USA, 3 years duration, studied 8,847–35,477 bariatric surgery patients. Complication rates: AGB < VSG < RYGB. Weight loss: RYGB > VSG > AGB
Randomized control trials	
Schauer et al. (2012)	Stampede I Trial; Cleveland Clinic, USA; 1 year duration; unblinded RCT in 150 patients; BMI, 27–43 with T2DM, randomized to medical therapy vs. medical therapy+RYGB vs. medical therapy+VSG. The primary end point of HbA1c $\leq$6.0 % was achieved in 12 % medical group, 42 % RYGB, and 37 % VSG. Excess weight loss was 13 % in medical group, 88 % in RYGB, and 81 % in VSG. Serious adverse events occurred in 9 % of medical group, 22 % RYGB, and 8 % VSG
Mingrone et al. (2012)	Teaching hospital in Italy; 2 years duration, unblinded RCT in 80 patients; BMI>35; T2DM duration $\geq$5 years; HbA1c $\geq$7.0 %; randomized to medical therapy vs. RYBG vs. BPD. The primary end points of FPG <100 mg/dL and HbA1c <6.5 % were achieved in 75 % RYGB and 95 % BPD. Bariatric surgery patients discontinued diabetes medications within 15 days after surgery
Ikramuddin et al. (2013)	Diabetes Surgery Study; four teaching hospitals in the USA and Taiwan; 1-year duration; unblinded RCT in 120 patients with HbA1c $\geq$8.0 %; BMI 30.0–39.9; C-peptide >1.0 ng/mL; T2DM duration $\geq$6 months; patients randomized to intensive medical treatment vs. medical treatment + RYGB. The primary end points of HbA1c <7.0 %, LDL cholesterol <100 mg/dL, and systolic blood pressure <130 mmHg were achieved by 49 % RYGB and 19 % medical patients. RYGB required less medications and lost 26.1 % body weight, compared with 7.9 % in the medical group. Serious adverse events requiring hospitalization (22 cases) occurred in RYGB

4 Complications of Bariatric Surgery

Although bariatric procedures are effective for weight loss, there are adverse consequences besides typical complications resulting from abdominal surgery (Table 3). As with any treatment, patients and clinicians must carefully balance the benefits of bariatric surgery against long-term potential complications, such as dumping syndrome, severe hypoglycemia, gastroesophageal reflux (GERD), and nutritional deficiencies.

Table 3 Complications of bariatric procedures

Bariatric procedure	Complications
Gastric bypass surgery	Gastric remnant distension
	Stomal stenosis
	Marginal ulcer
	Cholelithiasis
	Internal hernia
	Ventral (incisional hernia)
	Dumping syndrome
	Severe hypoglycemia
	Malodorous flatulence
	Change in bowel movement
	Nutritional deficiencies
Sleeve gastrectomy	Stenosis
	Gastric leakage
	GERD
Gastric banding	Band slippage or erosion
	Port blockage or infection
	Stomal obstruction
	Esophageal dilation
	Esophagitis
	Hiatal hernia
Vertical banded gastroplasty	Staple line disruption
	Erosion of mesh band
	Obstruction
	GERD
	Vomiting
Biliopancreatic diversion/ jejunoileal bypass	Severe malabsorption
	Electrolyte imbalance
	Impaired renal function
	Impaired liver function

(i) ***Dumping syndrome*** has been reported after RYGB and other bariatric procedures involving partial gastrectomy and/or vagotomy. The prevalence of dumping syndrome may be as high as 40 % in RYGB patients (Banerjee et al. 2013). Studies have also reported that up to 40 % of VSG patients develop symptoms of dumping syndrome 6–12 months after the procedure (Tzovaras et al. 2012; Papamargaritis et al. 2012). Early dumping is characterized by gastrointestinal symptoms (abdominal pain, bloating, nausea, diarrhea, and borborygmi) and vasomotor symptoms (flushing, palpitations, sweating, dizziness), occurring soon after meal ingestion. Early dumping is thought to be triggered by a rapid passage of hyperosmolar nutrients into the small bowel and a shift of fluids from the circulation into the gastrointestinal tract. Gut peptides, including vasoactive intestinal peptide, peptide YY, pancreatic polypeptide, and neurotensin, may mediate the symptoms of early dumping. Late dumping occurs 1–3 h after a meal and is often characterized by mild hypoglycemia, associated with hunger sensation, palpitations, and sweating. Late dumping has been linked to rapid gastric emptying after bariatric surgery which increases glucose in the intestinal lumen, triggers insulin release, and induces mild hypoglycemia (Tack et al. 2009).

Dumping syndrome is evaluated using symptom-based questionnaires, e.g., Sigstad's score or Arts' dumping questionnaire (Tack et al. 2009; Arts et al. 2009; Tzovaras et al. 2012). Patients with dumping syndrome are instructed to ingest small frequent meals, avoid sugars, and limit drinking with meals (Tack et al. 2009). Food additives such as pectin may increase food viscosity, slow gastric emptying, and reduce the frequency of dumping symptoms.

(ii) ***Severe hypoglycemia*** may develop after RYGB and pose major safety risks. Unlike mild hypoglycemia associated with late dumping, a more severe hypoglycemia associated with loss of consciousness, seizures,

and accidents is rare and occurs 1–3 years after RYGB. Hypoglycemic symptoms are classified as autonomic, e.g., palpitations, lightheadedness, and sweating, or neuroglycopenic, e.g., confusion, seizure, and loss of consciousness. The prevalence of severe hypoglycemia is uncertain due to underreporting, but documented cases of severe hypoglycemia occur in 0.2–1 % of gastric bypass patients (Marsk et al. 2010). The diagnosis is established by confirming that symptoms are directly related to hypoglycemia and associated with venous blood glucose values <70 mg/dL (3.9 mmol/L) and inappropriately elevated plasma insulin levels. Unlike insulinoma, post-RYGB hypoglycemia is not associated with fasting hyperinsulinemia (Mala 2014).

The etiology of post-RYGB hyperinsulinemic hypoglycemia is not well understood. It has been postulated that a rapid emptying of the gastric pouch triggers a rapid and excessive rise in glucose, which triggers insulin secretion, and subsequently rapidly suppresses glucose levels. A potential candidate mediator of post-RYGB hyperinsulinemic hypoglycemia is GLP-1, an incretin that is markedly increased postprandially after RYGB (Goldfine et al. 2007). To test the role of GLP-1, Salehi et al. performed studies in controls and two groups of post-RYGB patients: those with severe recurrent hypoglycemia, defined as neuroglycopenia with documented glucose levels <50 mg/dL (2.8 mmol/L), or asymptomatic post-RYGB patients (Salehi et al. 2011). The patients with a history of hypoglycemia had lower postprandial glucose nadir, as well as higher glucose-stimulated insulin secretion in response to a meal tolerance test. Using tracer methods, the investigators found that hypoglycemic patients had increased rate of glucose appearance after meals compared with controls, while hepatic glucose production was not different in the two groups. As expected, blockade of exendin$_{9–39}$ decreased insulin levels and increased the fasting and postprandial plasma glucose concentrations in control and RYGB patients. Notably, the ability of exendin$_{9–39}$ to increase glycemia and suppress insulin secretion was much greater for in RYGB patients prone to hypoglycemia than in RYGB patients without hypoglycemia (Salehi et al. 2014). These data suggest that GLP-1 is an important contributor to insulin secretion and hypoglycemia in post-RYGB patients with neuroglycopenia.

Given the marked individual variability in the incidence of post-RYGB hypoglycemia, it is possible that genetic differences in GLP-1 receptor-mediated signaling pathways or other modifiers of GLP-1 signaling effects on insulin and glucose are also important. Differences in insulin sensitivity from other mechanisms could alter the risk of insulin-induced hypoglycemia. Also, inadequate liver glycogen stores and impaired secretion of glucagon and other counter-regulatory hormones may predispose to hypoglycemia (Laferrere et al. 2011). Other factors, including gut microbiota (Liou et al. 2013), bile acid composition (Patti et al. 2009), and intestinal adaptation (Hansen et al. 2013), could influence brain-gut-liver interactions, resulting in differences in susceptibility to post-RYGB hypoglycemia (Mussig et al. 2010). Pancreatic islet hyperplasia has been observed in the few pathologic specimens available from patients with post-RYGB hypoglycemia, but it is unclear whether this is adaptive or plays a causal role in hypoglycemia (Service et al. 2005; Patti et al. 2005; Meier et al. 2006).

Therapeutic approaches to post-RYGB hypoglycemia include nutrition therapy aimed at reducing sugars and glycemic index carbohydrates (Kellogg et al. 2008) and premeal treatment with acarbose, an alpha-glucosidase inhibitor (Valderas et al. 2012), which attenuates rapid postprandial glucose surges and insulin secretion. Continuous glucose monitoring may be necessary in patients with hypoglycemia

unawareness (Halperin et al. 2011). In case the hypoglycemic episodes do not improve in response to changes in diet and acarbose treatment, octreotide can be administered to decrease the secretions of incretins and insulin (Myint et al. 2012). Other treatment options include diazoxide or calcium channel blockers to reduce insulin secretion (Spanakis and Gragnoli 2009; Moreira et al. 2008). Gastric restriction surgery or placement of a gastrostomy tube into the bypassed duodenum may be used to alter intestinal nutrient loading and decrease the frequency of hypoglycemic episodes (Fernandez-Esparrach et al. 2010; McLaughlin et al. 2010). In rare cases, partial pancreatectomy may be necessary for patients with life-threatening neuroglycopenia (Service et al. 2005; Patti et al. 2005).

(iii) ***Gastroesophageal reflux*** has been associated with bariatric surgery. Most studies show improvement of GERD after RYGB surgery (De Groot et al. 2009; Tai et al. 2009). RYGB decreases lower esophageal sphincter pressure, esophageal contractile amplitude, and acid exposure (Madalosso et al. 2010; Herbella et al. 2011). However, there are variable effects of VBG and ABG on GERD (Di Francesco et al. 2004; De Groot et al. 2009; Angrisani et al. 1999; de Jong et al. 2004). Sleeve gastrectomy increased GERD symptoms in some patients, while others had no symptoms (Chiu et al. 2011; Mahawar et al. 2013). VSG may increase intragastric pressure leading to postprandial regurgitation (Del Genio et al. 2014). A large study has suggested a less favorable outcome of VSG patients with preexisting GERD symptoms (DuPree et al. 2014). These results require further studies to ascertain the effects of bariatric surgery on GERD.

(iv) ***Malnutrition***. Bariatric surgery reduces food intake in the postoperative period, and this may be associated with poor intake of micronutrients which predisposes to further deficiencies. Preexisting micronutrient deficiencies can exacerbate postoperative deficiencies; hence, weight loss management prior to bariatric surgery should include adequate supplementation of micronutrients (Saltzman and Karl 2013; Hammer 2012; Levinson et al. 2013). The type of bariatric procedure is also a factor in determining nutritional deficiencies. Since AGB is mainly restrictive, it does not predispose to malabsorption. VSG is also less frequently associated with nutritional deficiencies. In contrast, BPD carries the highest risk for nutritional deficiencies (Saltzman and Karl 2013; Hammer 2012). RYGB causes fat and protein malabsorption. Fat malabsorption after RYGB is related to the length of the common intestinal channel which determines the contact of nutrients with digestive enzymes. A longer biliopancreatic limb in RYGB promotes bacterial overgrowth and decreases fat digestion (Hammer 2012).

Malabsorption should be suspected after bariatric surgery if patients develop abdominal symptoms, e.g., persistent diarrhea, distension, flatulence, and discomfort, or general symptoms, e.g., excessive weight loss, anemia, night blindness, xerophthalmia, peripheral neuropathy, fatigue, amenorrhea, or impotence (Hammer 2012). Recommended screening tests include blood cell count, lipids, albumin, alkaline phosphatase, calcium, phosphorus, magnesium, zinc, iron, ferritin, prothrombin time, serum vitamin A, parathyroid hormone, serum vitamin D, folic acid, and vitamin B12, preoperatively, and 3-month, and 6-month intervals for 2 years, and then annually, after malabsorptive procedures, e.g., BPD and RYGB (Hammer 2012; Levinson et al. 2013). Dietary adjustments are needed in the early postoperative period with protein supplementations (60 g) to avoid loss of body protein (Saltzman and Karl 2013; Levinson et al. 2013). For RYBG, more than 1 g/kg of the ideal body weight/day is the recommended long-term protein intake. In addition, patients who undergo malabsorptive bariatric procedures should receive multivitamin supplements with double the daily recommended doses or more, containing 18 mg of

elemental iron and 400 ug of folic acid, as well as vitamin A, copper, and zinc. A daily intake of 2 g of calcium, 1,000 ug of vitamin B12, and 1,000–2,000 IU of vitamin D orally is recommended after malabsorptive bariatric procedures (Levinson et al. 2013). Specific micronutrient deficiencies resulting from bariatric surgery are discussed next.

Vitamin B1 (thiamine) deficiency has been reported in 29 % of bariatric patients (Saltzman and Karl 2013; Hammer 2012; Levinson et al. 2013) and may lead to serious neurological manifestations. Vomiting, poor food intake, and lack of vitamin supplement intake are all predisposing factors (Galvin et al. 2010). Rarely, intravenous glucose administration may trigger acute thiamine deficiency, characterized by Wernicke's encephalopathy, peripheral neuropathy, nystagmus, and ocular palsy. This can be avoided by prophylactically administering thiamine 100 mg intravenously when starting intravenous fluids in at-risk patients. Symptomatic thiamine deficiency with neurological signs is treated with 100–500 mg thiamine daily administered intravenously. Prophylactic daily intake of a multivitamin preparation with 3 mg of thiamine is recommended after malabsorptive procedures, i.e., BPD and RYGB, and this is increased to 50 mg thiamine daily in patients at risk for Wernicke's encephalopathy (Levinson et al. 2013).

Vitamin B12 deficiency may occur in 18 % of patients or more presenting for bariatric surgery. Measurement of serum methylmalonic acid concentrations is a more sensitive marker for vitamin B12 deficiency. Factors predisposing to vitamin B12 deficiency include reduced intake of meat, diminished contact of food and gastric acid, and decreased intrinsic factor levels. Vitamin B12 deficiency leads to megaloblastic anemia, myelopathy, and neuropathy. A prophylactic oral vitamin B12 dose of 500 ug daily or more after bariatric surgery is recommended (Levinson et al. 2013). Weekly intramuscular injection of 1,000 ug for 8 weeks may be necessary for severe vitamin B12 deficiency, and daily intramuscular administrations and lifelong monthly injections are recommended for patients with neurological deficits. Folate deficiency can occur after gastric bypass surgery and lead to megaloblastic anemia. Folate deficiency is prevented with oral intake of 1 mg of folate daily. Patients with proven folate deficiency should be treated with 5 mg daily.

Vitamin D deficiency has been reported in 25–75 % of bariatric patients (Saltzman and Karl 2013; Hammer 2012). Vitamin D deficiency decreases intestinal calcium absorption, which is also reduced by reduced gastric acidity as a result of bypassing the duodenum. Clinical manifestations of vitamin D deficiency include osteopenia, osteoporosis, and osteomalacia. Measurements of calcium, vitamin D, and parathyroid hormone levels and postoperative bone mineral density may be indicated after bariatric surgery (Heber et al. 2010). Vitamin D intake of 800–2,000 IU of cholecalciferol (vitamin D3) is recommended postoperatively. In case of deficiencies, administration of 50,000 IU of ergocalciferol (vitamin D2) weekly, either orally or intramuscularly for 8 weeks, is recommended. In patients with decreased gastric acid secretion, calcium citrate may be better absorbed at doses of up to 2 g daily (Levinson et al. 2013).

Vitamin A deficiency may occur in 11 % of bariatric patients (Levinson et al. 2013). The symptoms include dry eyes and impaired night vision. Confirmed cases of vitamin A deficiency should be treated with doses of 10,000–25,000 IU of vitamin A daily until clinical improvement is noted.

Iron deficiency occurs in 5–44 % of bariatric patients. Factors predisposing to iron deficiency include reduced meat intake and diminished gastric acid and intestinal absorption (Saltzman and Karl 2013; Hammer 2012). An oral dose of 35–100 ug of elemental iron is recommended for prevention, and oral supplementation of 300 ug elemental iron daily is sufficient for iron deficiency anemia treatment. If the latter fails, an intravenous iron administration should be given. Zinc deficiency may occur in about 30 % of patients prior to bariatric surgery. In cases of zinc deficiency, the recommended dose is 60 mg of elemental zinc given orally twice a day. Zinc treatment may deplete copper stores; hence, the doses of these trace metals need careful adjustments. Copper deficiency is present in up to 18 %

of patients after bariatric surgery (Levinson et al. 2013) and leads to anemia, leucopenia, neuropathy, and myelopathy. Copper deficiency is treated with 1 week of 6 mg of elemental copper orally daily, then a week of 4 mg daily, and then 2 mg daily as the maintenance dose (Levinson et al. 2013).

5 Mechanisms of Bariatric Surgery

Weight loss from diet, exercise, and drug therapy is accompanied by a decrease in energy expenditure that makes it difficult to sustain the reduced body weight over long periods (Schwartz and Doucet 2010). In contrast to conventional weight loss therapies, bariatric procedures produce sustained weight loss (Bray 2008). Bariatric surgery decreases food intake, alters taste perception, blunts hedonic responses to food, and prevents the fall in energy expenditure associated with weight loss (Sandoval 2011). Studies in bariatric patients and animal models have provided new insights into gut and central nervous systems' pathways underlying the effects of bariatric procedures on hunger, eating, satiety, and metabolism.

A popular theory is that bariatric surgery causes weight loss by restricting gastric volume and inducing satiety signals (Stefater et al. 2012). Consistent with this hypothesis, malfunction of LAGB leads to weight regain (Suter et al. 2006; Boza et al. 2011). Contrary to this theory, weight loss after VSG is comparable to RYGB, and yet the stomach volume in VSG is significantly larger than in RYGB (Chapman et al. 2004). Gastric dilatation following VSG does not affect weight loss in humans, and VSG-mediated weight loss in rats is not dependent on the stomach size (Abu-Jaish and Rosenthal 2010). Gastric emptying has been suggested as a mechanism for bariatric surgery-mediated weight loss by altering nutrient, endocrine, and neural signaling in the upper intestine. Enteroendocrine cells are stimulated by increased nutrient delivery and signal via vagal afferent nerves to the brain stem to regulate gastric emptying (Cummings et al. 2004).

Structural changes in the gastrointestinal tract following RYGB, VSG, and AGB may differentially alter gastric emptying and delivery of nutrients to enteroendocrine cells in the intestine, leading to changes in feeding and glucose and lipid metabolism (Sandoval 2011). However, this view is not supported by various studies. LAGB may increase the rate of gastric emptying above the restriction but does not affect total gastric emptying rate, and there is no significant association of gastric emptying, satiety, or weight loss after LAGB (Burton et al. 2011; Usinger et al. 2011). The rate of emptying of the gastric pouch may be delayed in RYGB despite the absence of a pylorus; however, the intestinal transit time is increased (Suzuki et al. 2005; Dirksen et al. 2013). VSG increases gastric emptying as well as intestinal transit time (Shah et al. 2010a; Melissas et al. 2013), arguing against a causal role of gastric emptying in weight loss.

Another explanation for the dramatic effects of gastric bypass surgery is based on gut hormones. Postprandial GLP-1 levels are markedly increased after RYGB or VSG surgery, but the evidence for a causal link between GLP-1 and weight loss and glucose homeostasis is variable (Salehi and D'Alessio 2014). Administration of a GLP-1 receptor antagonist is well known to attenuate the insulin response to a mixed nutrient liquid meal (Johnson et al. 2011); however, GLP-1 receptor antagonists do not consistently alter glucose tolerance or insulin sensitivity in patients undergoing RYGB or VSG (Chambers et al. 2011; Jorgensen et al. 2013). Moreover, mice lacking GLP-1 receptor exhibit weight loss and improved glucose tolerance after bariatric surgery similar to normal mice (Wilson-Perez et al. 2013; Mokadem et al. 2014). Furthermore, the weight loss effect of long-acting GLP-1 agonists is much less compared to RYGB and VSG procedures (Fujishima et al. 2012; Jimenez et al. 2014).

The level of peptide YY (PYY), a gut hormone that inhibits feeding and increases insulin sensitivity (Vrang et al. 2006), is increased after gastric bypass surgery and has been linked to weight loss (Chambers et al. 2011; Peterli et al. 2009; Shin et al. 2010). Plasma PYY levels are increased

during weight regain in RYGB patients (Meguid et al. 2008), and RYGB-induced weight loss is blunted in PYY knockout mice (Chandarana et al. 2011). Ghrelin is produced mainly in the stomach and has been proposed as a mediator of gastric bypass surgery. Ghrelin levels decrease after VSG (Basso et al. 2011; Bohdjalian et al. 2010; Wang and Liu 2009). In contrast, some reports indicate a reduction in ghrelin levels after RYGB (Cummings et al. 2002), while others show no change in ghrelin (Tymitz et al. 2011). However, ghrelin-deficient mice responded appropriately in weight loss and showed similar improvement in glucose tolerance after VSG, raising doubts about a causal role of ghrelin in the response to gastric bypass surgery (Chambers et al. 2013).

Bile acids have been implicated in the effects of gastric bypass surgery. Primary bile acids are produced in the liver through oxidation of cholesterol and conjugated with a glycine or taurine to form bile salt which serves as a detergent for lipid hydrolysis. Primary bile acids are also secreted into the intestine and undergo dehydroxylation to form secondary bile acids which are then conjugated to form bile salts. Bile acids enhance digestion and absorption of lipids and signal via membrane and nuclear receptors in the intestine and liver to regulate lipid and glucose metabolism (Parks et al. 1999; Kohli et al. 2010; Cummings et al. 2010). Studies show that RYGB results in higher plasma bile acid levels compared to AGB (Kohli et al. 2013a). An increase in circulating bile acids and bile salts after RYGB induces weight loss, improves glucose tolerance, and increases GLP-1 secretion (Kohli et al. 2013b). In rodents, ileal interposition surgery increases bile acid levels, improves glucose tolerance, and increases GLP-1 secretion (Strader et al. 2005).

Recent studies have suggested that FXR, a nuclear transcription factor that binds bile acids, plays an important role in weight loss after bariatric surgery (Kuipers and Groen 2014). Mice lacking FXR display less weight loss after VSG and also increase their food intake to compensate for weight loss (Ryan et al. 2014). Bile acids also bind to TGR5 (also known as G protein-coupled bile acid receptor 1, GPBAR1), and activation of TGR5 by bile acid increases GLP-1 (Thomas et al. 2009). These mediators provide plausible functional connections between TGR5 signal pathways and metabolic effects of bariatric surgery.

The gut microbiota are responsive to changes in body weight and dietary composition (Karlsson et al. 2013). Studies indicate that gastric bypass surgery results in a significant change in the composition of the gut microbiome (Sweeney and Morton 2013). RYGB changes the gut microbiome of obese individuals to patterns seen in normal weight individuals (Zhang et al. 2009; Li et al. 2011). Germ-free mice fed the microbiota from RYGB mice are resistant to obesity (Liou et al. 2013). The gut microbiota are correlated with bile acid levels in RYGB mice and may require FXR signaling to produce weight loss and improvement in glucose metabolism (Lutz and Bueter 2014).

Neuronal circuits in the hypothalamus control feeding and energy expenditure (Blouet and Schwartz 2010). The arcuate nucleus (ARC) contains pro-opiomelanocortin (POMC)-producing neurons that produce α-MSH, a peptide whose role is to inhibit food intake and decrease body weight via melanocortin 4 (MC4) receptor (MC4R). Neurons expressing neuropeptide Y (NPY) and agouti-related peptide (AGRP) are also present in ARC. AGRP is a competitive antagonist/inverse agonist of MC4R. AGRP blocks the action of α-MSH, resulting in stimulation of feeding and weight gain. POMC and NPY/AGRP neurons project to the paraventricular nucleus (PVN), a key center for integration of metabolic signals mediating feeding, energy expenditure, and neuroendocrine function (Kim et al. 2014). Studies show that expression of POMC, AGRP, and NPY in the hypothalamus is not different in VSG versus sham-operated obese rats (Stefater et al. 2010). RYGB induces weight loss in individuals with loss-of-function mutations in MC4R (Aslan et al. 2011). One study reported that individuals with MC4R mutations were prone to LAGB failure (Elkhenini et al. 2014); yet another study did not confirm this finding (Valette et al. 2012). Further studies are needed to determine whether other

hypothalamic or extra-hypothalamic circuits are involved in the regulation of hunger, satiety, and hedonic aspects of feeding after RYGB, VSG, and LABG.

6 Cross-References

- Body Composition Assessment
- Brain Regulation of Feeding and Energy Homeostasis
- Carbohydrate, Fat, and Protein Metabolism in Obesity
- Diet, Exercise, and Behavior Therapy in the Treatment of Obesity and Metabolic Syndrome
- Gut Hormones and Obesity
- Gut Microbiome, Obesity, and Metabolic Syndrome
- Insulin Resistance in Obesity
- Overview of Metabolic Syndrome
- Pharmacotherapy of Obesity and Metabolic Syndrome

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Prevention and Treatment of Childhood Obesity and Metabolic Syndrome

46

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Contents

Abstract

Obesity remains a significant public health issue in the United States with nearly one-fifth of children and one-third of adults being obese. Particularly in the pediatric population, much emphasis is placed on prevention in addition to treatment of obesity. Lifestyle modifications remain the first line of intervention both for prevention and treatment of pediatric obesity. Numerous studies indicate that risk factors for obesity develop prior to conception and continue throughout childhood. Prenatally, parental weight, maternal smoking, and mode of delivery all influence later obesity risk. Feeding style during infancy, including both breastfeeding and the timing of complementary feeds, is associated with differential risk for later obesity. Furthermore, the presence or lack of appropriate nutrition, exercise, and intervention programs at school impact risk for obesity. Unlike in the adult population, there is evidence for sustained positive effects from lifestyle interventions for treatment of obesity in the pediatric population. Many intervention studies have been performed to study the effects of dietary changes, increased physical activity, behavioral, and family centered interventions on pediatric overweight and obesity. When conventional strategies for weight management are insufficient, pharmacologic and surgical options are appropriate for the treatment of both obesity and the associated metabolic

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syndrome. Orlistat remains the only FDA-approved treatment option in childhood obesity, but several other options have been and continue to be investigated in research trials. Bariatric surgery is recommended cautiously at this time in only a subset of adolescents, and when pursued, a multidisciplinary team approach is recommended.

Keywords
Obesity • Metabolic syndrome • Pediatrics • Lifestyle modification • Orlistat • Bariatric surgery

1 Introduction

Obesity remains a significant public health problem with over one-third of adults in the Unites States being obese (Flegal et al. 2012), and 17 % of US children are obese (Ogden et al. 2014). Given the great public health burden from obesity, much emphasis has been placed on both prevention and treatment of obesity. Body mass index (BMI) is currently accepted as the international standard for defining overweight and obesity. In children over the age of 2 years, a BMI greater than or equal to the 85th percentile but less than the 95th percentile for age and sex is considered *overweight*, and a BMI greater than or equal to the 95th percentile for age and sex is diagnosed as *obese*. In children under the age of 2 years, the utility of BMI as a measure of adiposity is uncertain. The 85th percentile and 95th percentile for BMI at age 18 years corresponds to an approximate BMI of 25 and 30 kg/m^2, respectively.

Metabolic syndrome is defined by abdominal obesity along with two or more of the following: hypertension, glucose intolerance, and dyslipidemia (low HDL cholesterol or elevated triglycerides) (Zimmet et al. 2007). In this chapter, we describe the role of lifestyle modifications on prevention of obesity and metabolic syndrome, followed by the role of pharmacologic agents and bariatric surgery on prevention and treatment of these conditions.

2 Prevention of Pediatric Obesity Through Lifestyle Modifications

Preventing pediatric obesity before it occurs is of utmost importance. Many studies have recently emerged, demonstrating key areas of intervention throughout all stages of development that can help prevent obesity. Maternal prepregnancy obesity has been implicated as a risk factor for later childhood obesity (Salsberry and Reagan 2005; Whitaker 2004; Eriksson et al. 2003). A population-based prospective cohort study of over 5,000 subjects in the Generation R Study in the Netherlands indicated that prepregnancy maternal BMI compared to paternal BMI had a stronger impact on childhood BMI; however, the odds of overweight at age 4 years was 6.5 times higher in children in whom both parents were obese compared to those in whom parental BMI was normal, indicating that paternal BMI may also impact later childhood obesity risk (Durmus et al. 2013).

Furthermore, maternal smoking during pregnancy has also been associated with later childhood obesity risk (Salsberry and Reagan 2005; von Kries et al. 2002; Al Mamun et al. 2006). The mechanism whereby maternal smoking results in later childhood obesity has not been fully elucidated, although preliminary studies suggest that nicotine-induced vasoconstriction compromising the placental vasculature along with impaired oxygen uptake from carbon monoxide toxicity affects fetal growth. Indeed, data for over 5,000 subjects from the 1958 British birth cohort indicated lighter birth weight, yet an increasing risk for obesity with time and higher odds of obesity at age 33 years in subjects whose mother smoked in pregnancy (Power and Jefferis 2002).

The mode of delivery (cesarean section versus vaginal delivery) has also been shown to affect later obesity risk in offspring. A meta-analysis of 28 studies identified that children delivered by cesarean section have a higher risk of childhood obesity than those born by vaginal delivery (Kuhle et al. 2015). These data indicate that

prevention of childhood obesity requires interventions even prior to conception.

2.1 Infancy Factors

Breastfeeding during infancy has been positively associated with decreased risk of overweight and obesity. In a large survey study of over 9,500 subjects, Gillman et al. found that infants who were fed more breast milk than formula and those with longer duration of breastfeeding had lower risk for overweight in older childhood and adolescence (Gillman et al. 2001). A meta-analysis of 17 studies also supported an association between longer breastfeeding duration and decreased risk of overweight (Harder et al. 2005). Numerous other studies, including a study of sibling pairs, also support the protective role of breastfeeding on risk of overweight and obesity (Hediger et al. 2001; Nelson et al. 2005).

Timing of introduction of complementary foods has been identified as another determinant of later obesity risk. A large prospective, observational study from the Danish National Birth Cohort identified that in infants who breastfed for fewer than 20 weeks, the introduction of complementary foods prior to 4 months of age was associated with greater infancy weight gain (Baker et al. 2004). Another large prospective study of over 800 infants also supported these findings, demonstrating that introduction of solid foods prior to age 4 months in formula-fed infants (but not in breastfed infants) was associated with a significantly higher odds of obesity at age 3 years (Huh et al. 2011). A prospective, observational cohort study of over 97,000 infants in the Jiaxing Birth Cohort of Southeast Asia specifically identified that introduction of fish liver oil prior to 4 months of age was associated with higher BMI in childhood and higher risk of overweight at 4–5 years of age (Zheng et al. 2015). However, the data on exact timing of complementary feeding and obesity risk remains unclear. A systematic review of 23 studies found no clear association, although supporting the notion that very early timing of complementary food introduction at less than 4 months of age may be associated with higher BMI in childhood (Pearce et al. 2013).

2.2 Childhood Factors

In a systematic review of 39 school-based obesity prevention studies with a minimum follow-up period of 12 months, 40 % of the 33,852 children studied demonstrated benefits from obesity prevention measures; none of the studies demonstrated negative effects from these prevention strategies. Some of the prevention measures included heath education for children, parents, and teachers; smoking prevention; nutrition education and dietary changes; and physical activity measures (Flodmark et al. 2006). Another meta-analysis of 19 randomized clinical trials and clinical controlled trials of school-based intervention programs with a minimum of a 1-year follow-up period demonstrated that school-based interventions to decrease consumption of high-fat and high-sugar foods and increase moderate-to-vigorous physical activity led to a decrease in the prevalence of overweight (OR 0.81, 95 % CI 0.68–0.92) and obesity (OR 0.59, 95 % CI 0.37–0.94). In contrast, there was no significant difference in the prevalence of overweight or obesity between those in intervention programs lasting less than 6 months versus the control group (Gonzalez-Suarez et al. 2009). Collectively, these studies indicate that, at least in the short-term, school-based intervention programs to modify lifestyle can help prevent later obesity.

Interventions targeted toward either nutrition or physical activity appear to have the greatest effect on preventing obesity. A Cochrane Review of 22 obesity prevention trials showed that studies focusing on either a dietary intervention or a physical activity intervention had a positive impact on BMI while studies combining these approaches did not significantly affect BMI (Summerbell et al. 2005). The authors consider that the lack of an effect in the combined studies might be from an insufficient intervention period or from underpowered studies.

Importantly, intervention studies to prevent obesity, thus far, appear more beneficial in mid-childhood rather than in adolescence. A follow-up Cochrane Review in 2011 incorporating 55 studies determined that there is evidence for a positive effect from short-term school-based behavioral intervention programs in children aged 6–12 years and that further studies should focus on children aged 0–5 years and adolescents. Furthermore, this more recent Cochrane Review emphasized the importance of more long-term studies to evaluate sustainability and of studies that compare intervention approaches (Waters et al. 2011). A systematic review and meta-analysis of 34 studies indicated that prevention measures in children can have significant positive impacts on diet and physical activity, with better effects noted from reduction of unhealthy behaviors (decreasing sedentary behaviors and fats in diet) compared to endorsement of healthier behaviors (increasing physical activity and fruit/vegetable consumption). This review also noted a greater reduction in sedentary activity in children compared to adolescents from these interventions (Kamath et al. 2008).

Many specific interventions have been proposed (Barlow and Expert 2007) to help prevent childhood and adolescent obesity including eating a daily breakfast (Antonogeorgos et al. 2012); minimal consumption of food from restaurants, but particularly fast foods (Mistry and Puthussery 2015); limited consumption of sugar-sweetened beverages (Kosova et al. 2013); increasing intake of fruits and vegetables in diet (Natale et al. 2014); a practice of eating family meals together (Berge et al. 2015); limited portion sizes and decreased consumption of high-energy foods (Pourshahidi et al. 2014); restriction of screen time to no more than 2 h per day (McCarthy 2013); and vigorous physical activity for at least 1 h per day (Strong et al. 2005) of which at least 30 min should be undertaken while at school for school-going children. Other supplemental interventions suggested to help prevent excessive weight gain with minimal known risks include (Barlow and Expert 2007) a high-calcium diet according to the US Department of Agriculture (USDA) recommendations, a high-fiber diet, and an age-specific diet balanced in macronutrients (carbohydrates, proteins, and fats).

Technology is also being utilized to impact health outcomes, as studies are trialing web- and mobile-based applications to promote changes in the diets and physical activity levels of children (Delisle et al. 2015). The impact of these technology-based programs on preventing overweight and obesity remains to be determined.

3 Treatment of Pediatric Obesity Through Lifestyle Modifications

Lifestyle interventions are the first-line treatment recommended for all overweight and obese children and adolescents (August et al. 2008). Many intervention studies have been performed to study the effects of dietary changes, increased physical activity, and family centered interventions on overweight and obesity. While long-term efficacy of obesity intervention studies in adults is questionable, there is evidence for sustained positive effects in the pediatric population.

3.1 Dietary and Physical Activity Interventions for Treatment of Pediatric Obesity

Studies indicate positive benefits from dietary restriction and modifications in overweight and obese children. A 2009 Cochrane Review of pediatric obesity treatment studies found improvements in BMI from dietary intervention studies both for children under 12 years and children over age 12 years (Oude Luttikhuis et al. 2009). A meta-analysis of 37 randomized controlled trials of dietary interventions (with or without physical activity or behavioral modifications) in overweight or obese children and adolescents (<18 years) found that a relative weight loss does occur with these interventions. Many different dietary intervention techniques were studied in the various trials, including the Stoplight/Traffic Light diet in 16 studies in which foods are labeled as “green” (acceptable foods), “yellow” (caution

needed in consuming these foods), and "red" (unacceptable foods); food or calorie exchange programs in five studies; and low fat versus low carbohydrate comparison in one study (Collins et al. 2006). This meta-analysis along with the 2009 Cochrane Review primarily demonstrated, however, the paucity of high-quality studies with adequate follow-up to assess efficacy of dietary intervention programs in youth (Collins et al. 2006; Oude Luttikhuis et al. 2009).

There is no consistent evidence at this time for low glycemic index or low glycemic load diets in the treatment of pediatric obesity. The glycemic index captures the ability of a food to increase blood glucose 2 h postprandially; glycemic load describes carbohydrate intake both qualitatively and quantitatively as it is the glycemic index multiplied by the amount of carbohydrates in grams. A systematic review evaluating the effects of glycemic index and glycemic load on pediatric obesity noted controversial effects from intervention and cohort studies, showing a lack of a significant difference with the glycemic index diet in some studies and improvement in BMI in others, although many limitations were noted in several of these positive studies, including low sample size and lack of inclusion of physical activity level in the analyses (Rouhani et al. 2014). Notably, the 2009 Cochrane Review of interventions for treating pediatric obesity indicated two dietary intervention studies in children 12 years and older showing improvements in BMI and fat mass at 12 months with reduced glycemic index diets compared to low-fat diets (Oude Luttikhuis et al. 2009). More studies are needed to clarify the role of the low glycemic index diet in treating pediatric obesity.

Large meta-analyses of randomized clinical trials demonstrate mixed and inconsistent results from physical activity interventions as the only modality. In one meta-analysis, the 17 of 20 trials with complete data had inconsistent results, thought due to an outcome-treatment interaction, with modest treatment effects seen in studies measuring the effect of activity on adiposity but with no treatment effect seen in studies measuring the effect of activity on BMI (McGovern et al. 2008). In contrast, combination intervention studies involving both dietary and physical activity modifications show a modest effect on BMI compared to either dietary or physical activity interventions alone (McGovern et al. 2008).

3.2 Behavioral and Family Based Interventions for the Treatment of Pediatric Obesity

Importantly, many successful obesity intervention programs have a clear behavioral or family based component as well. Childhood obesity intervention studies performed by Epstein and colleagues have identified behavioral predictors of success in treating childhood obesity, including self-monitoring, modifying eating behavior, praise, and change in parental percent overweight (Epstein et al. 1990). Self-help groups and commercial weight loss programs are two specific forms of behavioral intervention programs. A 2-year multicenter randomized controlled trial was conducted to compare the efficacy of self-help groups versus the largest provider of commercial weight loss services in the United States (Weight Watchers©) with regard to change in body weight. The study found that the self-help group maintained a 1.3–1.4 kg weight loss for the first year but that weights returned to baseline by the 2-year follow-up period. In contrast, the commercial weight loss group had a continued weight loss of 4.3–5 kg at the end of the first year and remained 2.7–3 kg below baseline weight by the 2-year follow-up period (Heshka et al. 2003).

While most behavioral intervention programs are conducted outpatient, immersion programs, such as summer camps and boarding school programs, are another form of behavioral intervention. By definition, immersion programs involve at least 10 consecutive days and nights of active participation (Kirschenbaum and Gierut 2013). A systematic review of 22 studies of pediatric obesity immersion programs found that compared to results of a meta-analysis of outpatient treatment results (Wilfley et al. 2007), immersion programs led to an average of 191 % greater reduction in percent overweight posttreatment and 130 % improved reduction at follow-up, along with

significantly lower mean attrition rates (Kelly and Kirschenbaum 2011).

Family based involvement is an important component of pediatric obesity treatment. A randomized controlled trial of 135 overweight children (ages 8–16 years) found that those randomized to an intensive family based program (incorporating exercise, nutrition, and behavioral modification) for 6 months with bimonthly follow-up until 12 months had significant improvements in BMI, body fat, and homeostasis model assessment of insulin resistance (HOMA-IR) at 6 and 12 months than those randomized to a traditional weight management counseling sessions (Savoye et al. 2007). Furthermore, a meta-analysis of 33 obesity intervention studies demonstrated that the effective intervention programs had a family component, particularly noting that the family involvement is most important for intervention studies involving children less than 12 years of age (Ho et al. 2012). Other large meta-analyses of randomized clinical trials have similarly concluded that the largest effects of lifestyle intervention studies result from involvement of parents in delivering the intervention (McGovern et al. 2008; Young et al. 2007). Based on the many studies indicating the positive impact of family based intervention studies for pediatric overweight and obesity, a few organizations, including the American Dietetic Association (Position of the American Dietetic Association: individual-, family-, school-, and community-based interventions for pediatric overweight 2006) and a joint committee of the Centers for Disease Control and Prevention and the American Medical Association (Spear et al. 2007), have formally encouraged incorporation of the family in pediatric overweight and obesity treatment programs.

3.3 Long-Term Efficacy of Lifestyle Interventions for the Treatment of Pediatric Obesity

A landmark analysis published in 1990 by Epstein and colleagues on 10-year outcomes of behavioral and family based treatments for childhood obesity provided the first long-term data on the effects of various types of childhood obesity intervention studies, each lasting 8–12 weeks with a monthly follow-up period for 6–12 months. The group found a significant improvement in percentage overweight both in a study targeting a joint intervention for both parent and child (vs. targeting the child alone) and for subjects in a study who were given lifestyle or aerobic exercise (vs. calisthenics). Notably, in a study randomizing families to either a diet and lifestyle exercise group or a diet-only group versus a no-treatment control group, both intervention groups experienced a decrease in long-term percentage overweight, but there was no significant difference between these groups (Epstein et al. 1994).

Since this landmark Epstein study, several other intervention studies have emerged, many investigating 1-year outcomes; however, 5–10-year long-term outcomes of these more recent intervention studies still remain to be determined. A meta-analysis was performed of 33 pediatric studies evaluating effects of lifestyle intervention on weight and cardiometabolic outcomes (Ho et al. 2012). All studies were randomized controlled trials of modifications for treatment of overweight and obesity in children and adolescents less than or equal to 18 years of age. Specific dietary interventions studied included the Traffic Light diet (a color-coded calorie-controlled diet) (Jiang et al. 2005; Janicke et al. 2008; Reinehr et al. 2010; Diaz et al. 2010; Hughes et al. 2008; Kalarchian et al. 2009; Johnston et al. 2007; Epstein et al. 1984; Saelens et al. 2002), a calorie-restricted diet (Nemet et al. 2005, 2008), or dietary interventions via a dietician (Park et al. 2007; Rooney et al. 2005; Diaz et al. 2010; Hughes et al. 2008; Kalavainen et al. 2007; Nemet et al. 2005, 2008; Sabet Sarvestani et al. 2009; Estabrooks et al. 2009; Weigel et al. 2008; Becque et al. 1988; Botvin et al. 1979; Rocchini et al. 1988). The exercise intervention programs provided 1.5–2 h of training per week on average, although they varied in intensity and duration of activities. Compared to control arms with no treatment intervention, lifestyle interventions resulted in a significant improvement in both BMI and BMI Z-score. Furthermore, significant cardiometabolic improvements were noted,

specifically improved low-density lipoprotein (LDL) cholesterol, triglycerides, fasting insulin, and blood pressure up to 1 year following the baseline measurement (Ho et al. 2012).

It is unclear at this time whether the setting of the lifestyle intervention impacts the long-term efficacy of pediatric obesity interventions. A randomized clinical trial conducted in the Netherlands determined that an inpatient treatment program for children and adolescents aged 8–18 years with severe obesity was more effective than an ambulatory treatment program. Both the inpatient and ambulatory programs delivered family based lifestyle interventions, including exercise, dietary education, and behavior modification during a 6-month period. There were significant improvements in BMI Z-score for the inpatient group, but these favorable outcomes were not sustained at 12 and 24 months following the intervention (van der Baan-Slootweg et al. 2014).

It is possible that pediatric obesity intervention programs may result in improvements in metabolic parameters in children and adolescents that persist beyond the initial weight loss. A randomized controlled study in overweight children aged 8–16 years demonstrated that maintenance programs following the initial weight loss intervention resulted in sustained improvement in body composition and insulin resistance that persisted both at 6 and at 12 months (Savoye et al. 2007). Studies of longer duration and more studies specifically in the pediatric population are needed to provide insights into the long-term weight and metabolic implications of pediatric and adolescent weight loss programs (Collins et al. 2006).

In contrast, to the preliminary positive long-term efficacy noted in pediatric intervention studies, the long-term efficacy of lifestyle modifications on weight loss in adults has been questioned, with some studies indicating that weight regain may happen soon after the intervention program concludes. An adult study using 1999–2002 National Health and Nutrition Examination Survey (NHANES) data indicated that of 1,310 individuals who had lost 10 % of their maximum weight in the year prior to the survey, one-third had regained this weight within a year (Weiss et al. 2007). Similarly, a meta-analysis of 46 adult randomized controlled trials with dietary interventions lasting at least 4 months revealed a regain of BMI (0.02–0.03 kg/m^2/month) during the maintenance phase following the intervention program, despite an initial decrease of BMI (0.1 kg/m^2/month) during the active phase of the intervention. Ultimately, 3 years following the intervention, nearly half of the initial weight loss was regained (Dansinger et al. 2007). Both of these studies demonstrated a regain in weight, despite a prior positive response to an intervention.

A few contributors to weight regain in adults have been identified. Mexican-American (vs. non-Hispanic white) ethnicity is associated with two times the odds of regaining weight (Weiss et al. 2007). The lack of continued exercise following an intervention program has been identified as a risk factor for weight regain, with twice the odds of weight regain in individuals with sedentary behaviors and a higher odds of weight regain in those with four or more daily hours of screen time (Weiss et al. 2007).

3.4 Summary of Society Recommendations

Several professional societies and groups have published expert recommendations regarding the treatment of obesity in childhood and adolescence (Kirschenbaum and Gierut 2013), including the American Academy of Pediatrics (AAP) in 2007, the Endocrine Society in 2008, the *Obesity Management* expert committee in 2009, and the US Preventive Services Task Force (USPSTF) in 2010.

The AAP put together an Expert Committee in 2007 to revise prior recommendations regarding prevention, assessment, and treatment of child and adolescent overweight and obesity. The recommendations call for a chronic care model, which will allow the integration of community resources, health care, and patient self-management to optimize care. The recommendations specifically emphasize the primary care provider's role in monitoring the BMI and weight status of all youth as well as being an advocate in local communities. An important component of

the recommendations is the prevention of unhealthy weight gain, from as early as birth. The committee recommends assessment of dietary patterns, physical activity, sedentary behaviors, and family history for obesity and related comorbidities in all children. When overweight children are identified, the committee recommends that treatment be approached with a staged method based on age of the child, BMI, comorbidities, parents' weight, and the current motivation and progress in treatment. This committee promotes provider-guided motivational interviewing to help patients and parents identify their weight concerns and identify areas they would like to improve. The primary goal of treatment is to improve long-term health with permanent healthy lifestyle routines. The four stages of treatment are (1) Prevention Plus, (2) Structured Weight Management, (3) Comprehensive Multidisciplinary Intervention, and (4) Tertiary Care (Barlow and Expert 2007). Each stage typically deserves a 3–6-month trial period and then advancing based on the specific patient, though not all will advance to Tertiary Care which is recommended for those with BMI $>$ 99 % or $>$95 % with significant comorbidities. Tertiary Care may incorporate low-calorie diets, medications, and/or surgery; this option may be limited geographically.

The Endocrine Society 2008 guidelines emphasize the importance of education on healthy eating and exercise, as modeled and taught by parents, pediatricians, and schools. The major dietary treatments recommended include limited consumption of sugary drinks and fast food, portion control, regular meals, and increased intake of fruits, vegetables, and fibers. Additionally, the Endocrine Society recommended 60 min of daily moderate-to-vigorous physical activity and a decrease in sedentary activities (August et al. 2008). Furthermore, the society supported immersion treatment programs (including camps) and emphasized the importance of a minimum of 3 months of intensive weekly counseling for obese children, ideally targeting the entire family.

The *Obesity Management* journal established a team of experts in 2009 to form the Seven-Step Model for treatment of pediatric obesity. The steps recommended by the committee included education for the family (through books, handouts, and education from the medical provider), self-help groups, outpatient lifestyle and behavioral therapy interventions, and immersion programs (including summer camps and boarding schools) (Kirschenbaum et al. 2009).

In 2010, the USPSTF advocated for education in the context of a moderate- to high-intensity comprehensive outpatient cognitive behavioral therapy program, including counseling on healthy dieting, physical activity, and behavioral management, such as self-monitoring and stimulus control. The group defined moderate- to high-intensity as at least 25 h of contact with the child and family in order to effect positive change in BMI in a 12-month period (Barton 2010).

The goal of treatment, in children with significant height gain potential, is not necessarily weight reduction but rather can focus on prevention of further weight gain or slowing in the rate of weight gain to achieve a normal adult BMI $<$25. A specific target adult weight should be provided to each patient/family. This can be calculated using a target BMI of $<$25, as well as the midparental target height of the child. Once the target adult weight is calculated, the patient/family can be given the number of pounds per year that the child can afford to gain.

4 Pharmacologic Treatment of Obesity and Metabolic Syndrome

It is well recognized that many obese youth become obese adults (Whitaker et al. 1997) and are at increased risk of having cardiovascular disease and other metabolic dysfunction. Lifestyle interventions alone frequently fail for a variety of reasons, which is why other options are sought after (Boland et al. 2015). While there is no current role for the use of pharmacologic therapy in the prevention of pediatric obesity, pharmacologic therapy may be an option in treatment of severe or morbid obesity, particularly in those facing comorbidities associated with obesity.

While there may be some difficulty in deciding at what point, and in which patients, pharmacologic treatment should be considered, the Endocrine Society has facilitated the decision-making process with their Clinical Practice Guidelines, which recommend that therapy be considered in (1) obese children after failure in a formal program of intensive lifestyle modification and (2) overweight children with persistence of severe comorbidities despite intensive lifestyle modifications (August et al. 2008). Even with such guidance, many providers may limit the use of pharmacotherapy in children due to the absence of US Federal Drug Administration (FDA) approval in preadolescents and the lack of long-term efficacy and safety studies in this population.

4.1 Pharmacologic Treatment of Obesity

At the present time, orlistat is the single pharmacologic agent which is FDA-approved for pediatric obesity. Previously approved, sibutramine was taken off the market in 2010. Other medications offering potential for weight reduction in adolescents include metformin and topiramate which are approved for type 2 diabetes mellitus (T2DM) and forms of epilepsy, respectively. Some medications used in the treatment of adult obesity have undergone studies in pediatrics (exenatide), whereas others are currently undergoing studies in youth (topiramate, lorcaserin).

4.1.1 Orlistat

Now approved for over-the-counter (OTC) use for adults with obesity, orlistat has been the only pharmacologic agent approved by the FDA for children aged 12–16 years. It is a reversible inhibitor of gastric and pancreatic lipases, leading to reduced absorption of dietary fat. Several studies have examined the efficacy and safety of orlistat in randomized control trials in youth. In these trials as well as open-label trials, the dose of orlistat used was 120 mg three times daily and given in combination with lifestyle modification. While they have shown BMI reduction ranging from -0.55 to -2 kg/m^2 in youth (McDuffie et al. 2002a, 2004; Chanoine et al. 2005; Maahs et al. 2006), the adverse side effects and uncertain long-term benefit may offset the observed benefit. The largest study was a randomized clinical trial of 539 adolescents aged 12–16 years with BMI $\geq$2 points above the 95th percentile, who were monitored over 54 weeks (Chanoine et al. 2005). BMI reduction occurred in both placebo and orlistat groups at 12 weeks, but BMI then rose in the placebo group while remaining stable in the orlistat group with a final BMI reduction of -0.55 kg/m^2 in the orlistat group and an increase of +0.31 kg/m^2 in the placebo group. 26.5 % of participants in the orlistat group compared to 15.7 % in the placebo group had 5 % or more reduction in BMI at the end of the study (Chanoine et al. 2005). One meta-analysis of several randomized control trials (RCTs), specific to children and adolescents treated with nonsurgical obesity interventions, showed a pooled effect of BMI reduction of -0.7 kg/m^2 in those using orlistat (McGovern et al. 2008). Overall, the results have been modest. In all the studies examined, side effects reported were primarily gastrointestinal in nature, including increased defecation, fatty/soft stools, abdominal pain, increased flatus, and fecal incontinence (McDuffie et al. 2004; Chanoine et al. 2005; Maahs et al. 2006). Decreased vitamin D levels have been reported (McDuffie et al. 2002a), though there may be potential for other fat-soluble vitamin deficiencies.

4.1.2 Metformin

Approved for treatment of children aged 10 years and above with type 2 diabetes and often used in adolescents with polycystic ovarian syndrome (PCOS), metformin has been used as an adjunct in the treatment of obesity. Metformin reduces hepatic glucose production and plasma insulin, inhibits lipogenesis, increases peripheral insulin sensitivity, and increases satiety by increasing levels of glucagon-like peptide (Freemark 2007; August et al. 2008), but the exact mechanism of action for weight loss is uncertain. More than ten randomized, blinded studies have been done comparing metformin to placebo in children and adolescents with obesity. Dosing varied among metformin trials, with the typical dose prescribed

being 1,500 mg/day and ranging between 500 and 1,000 mg twice daily. While individual studies have been promising with BMI reduction ranging between −0.16 and −1.8 kg/m^2 (Atabek and Pirgon 2008; Clarson et al. 2009; Wilson et al. 2010; Wiegand et al. 2010; Rezvanian et al. 2010; Yanovski et al. 2011; Kendall et al. 2013; Love-Osborne et al. 2008), there have been two meta-analyses showing less overall benefit. McGovern et al. reviewed three metformin studies and showed a small insignificant change in BMI of −0.17 (CI = −0.62 to 0.28) kg/m^2 among obese youth treated with metformin monotherapy (McGovern et al. 2008). McDonagh reviewed 14 RCTs and showed a significant mean reduction in BMI by −1.16 kg/m^2 with metformin use, with subgroup analysis showing better outcomes in younger children (≤12 years) and those with a higher baseline BMI (>35 kg/m^2) (McDonagh et al. 2014). A critical review highlights the finding that the observed effect was more robust in short-term studies (i.e., 6 months or less) compared to studies lasting 1 year or longer, which is concerning for decreased effectiveness over time (Metformin in obesity 2014). Extended release (XR) metformin has been examined in obese children 13–18 years with similar results. Wilson reports mean (SE) BMI reduction of −0.9 kg/m^2 in the XR group compared to a mean (SE) gain of +0.2 kg/m^2 in the placebo group after 48 weeks of treatment; however at 48 weeks of follow-up, the mean (SE) BMI increased by +0.5 kg/m^2 in the former XR-treated group yet decreased in the former placebo group by mean (SE) −0.8 kg/m^2 (Wilson et al. 2010). At least one study shows that metformin may be more useful in obese adolescents prescribed atypical antipsychotic medications (Morrison et al. 2002). However, rebound weight gain and hyperinsulinemia may still occur when metformin is discontinued (August et al. 2008), and this hypothesis remains to be tested in a randomized clinical trial.

Compared to other agents, the safety profile of metformin is better known given its extensive use in T2DM and PCOS. Generally, it is well tolerated, but the most common complaints are gastrointestinal in nature and include diarrhea, abdominal discomfort, and nausea (Boland et al. 2015). However, in at least one study, the gastrointestinal symptoms were similar among those receiving metformin and those receiving placebo (Wiegand et al. 2010). While there is concern for possible liver and kidney toxicity, this was not found in a meta-analysis (McDonagh et al. 2014).

4.1.3 Exenatide

Exenatide is a GLP-1 agonist approved for use in adults with T2DM, and favorable effects on weight have been reported (Boland et al. 2015; Standards of medical care in diabetes – 2012 (2012)). The mechanism of action is thought to result from delayed gastric emptying and appetite reduction due to the diminished hyperactivation in appetite-reward regions within the brain (Ioannides-Demos et al. 2011; van Bloemendaal et al. 2014). Studies in pediatrics are limited. In the RCT performed by Kelly et al., 26 obese adolescents (12–19 years, BMI > 1.2 times 95th percentile or >35 kg/m^2) were randomized to exenatide 10 mcg twice daily (titrated up from 5 mcg twice daily) or placebo in addition to lifestyle modification counseling. They found a reduction in BMI of −1.13 kg/m^2, which was −2.7 % compared to placebo after 3 months (Kelly et al. 2013). The most common side effects were nausea, vomiting, headache, abdominal pain, and diarrhea (Kelly et al. 2013).

4.1.4 Octreotide

Octreotide is a somatostatin agonist, acting upon somatostatin receptors including beta cells where it leads to decreased insulin secretion in response to glucose. Octreotide has been associated with mild-to-moderate weight loss in adults and a special population of children. Lustig et al. completed a placebo-controlled RCT in 172 adults with baseline BMI ranging between 30 and 65 kg/m^2 and evidence of insulin hypersecretion. Those treated with 40 and 60 mg had mean BMI reduction of −0.73 and −0.79 kg/m^2, respectively, whereas the placebo-treated group had an overall gain in mean BMI compared to baseline (Lustig et al. 2006a). Post hoc analysis showed that efficacy correlated with the degree of insulin

hypersecretion (Lustig et al. 2006a). While these adult subjects did not have hypothalamic obesity, children who have been included in the octreotide studies do have central nervous system (CNS) insults and suspected hypothalamic obesity. One theory to explain why hypothalamic obesity occurs in response to certain CNS insults is that increased insulin secretion results from neural dysregulation of beta cells with weight gain resulting from insulin's anabolic function (Bereket et al. 2012). Octreotide has been used in children with hypothalamic obesity based on this principle (Lustig et al. 2006b; Bereket et al. 2012). In a small study of 18 subjects (mean age 14 years) with hypothalamic obesity demonstrating annual weight gain over +2SD for their age, those treated with octreotide for 6 months showed BMI change −0.2 kg/m^2 compared to +2.2 kg/m^2 in placebo group (Lustig et al. 2003). The degree of response to octreotide relies on hypersecretion and insulin sensitivity (Lustig et al. 2006b). While octreotide may be a promising therapeutic modality for hypothalamic obesity, it has only been examined in small studies; further, it has not been evaluated in obese hyperinsulinemic children without CNS injury. Common side effects include diarrhea, headache, cholelithiasis, nausea, and abdominal pain (Lustig et al. 2006a), though other side effects from octreotide have been reported including gallstones, edema, sterile abscess at the injection site, B12 deficiency, thyroid-stimulating hormone suppression, growth hormone suppression, and hyperglycemia (Tauber et al. 1994).

4.1.5 Leptin

Only a few dozen cases of leptin deficiency have been described. They present with hyperphagia from birth with obesity beginning as early as 6 months of age. Such individuals have hyperphagia with increased energy intake. Leptin therapy in these individuals leads to significantly improved health with reduced obesity, improved immune function, and normalization of puberty (Farooqi et al. 2002). While leptin may be used in youth with leptin deficiency, there have been no studies of leptin in common obesity of children or adolescents. Leptin has been studied for this indication in adults. Heymsfield evaluated leptin in lean and obese adults in a dose-escalating trial and found mean weight reduction of −7 kg in the highest leptin dose (0.3 mg/kg/day) compared to −1.5 kg in placebo, after 24 weeks (Heymsfield et al. 1999). A long-acting leptin (leptin A-200) was later evaluated to find more meaningful reduction in weight in one adult study. The 30 subjects treated with 20 mg daily of leptin A-200 had a mean reduction in weight of −0.6 kg (Liu et al. 2013). With lack of clinically significant improvement in weight profile, leptin replacement is not indicated in common obesity.

4.1.6 Topiramate

Topiramate is a sulfamate-substituted monosaccharide, FDA-approved for treatment of epilepsy and migraine headache. It has been associated with weight loss in 10–40 % of children treated for seizures. The mechanism of action in regard to weight reduction relates to an increase in serum adiponectin and reduction in leptin to adiponectin ratio (Fruebis et al. 2001) but may also be related to dysgeusia (Boland et al. 2015). A placebo-controlled RCT in adults demonstrated weight reduction ranging from −4.8 % to −6.3 % in those treated with topiramate (64–384 mg/day) compared to −2.6 % in the placebo group (Bray et al. 2003). Another large RCT in adults favored topiramate to placebo in weight reduction, but sponsors ended the study early to develop a new controlled-release formation to improve tolerability (Wilding et al. 2004). No pediatric trials have been done to date, but are currently underway according to clinicaltrials.gov. Adverse effects of topiramate include parasthesias, cognitive dysfunction, somnolence, fatigue, and nervousness. Cognitive effects are worrisome as there is some evidence that these effects may be long term even with dose reduction (Aarsen et al. 2006).

4.1.7 Phentermine/Topiramate and Lorcaserin

Approved by the US FDA for adult use in 2012 as an adjunct to lifestyle modification in adults with BMI greater than 30 or 27 kg/m^2 with obesity-related comorbidities, lorcaserin and phentermine/topiramate are the only other US

FDA-approved medications for treatment of obesity in adults beyond orlistat (Fleming et al. 2013). In this combination of phentermine/topiramate, topiramate is formulated as extended release. Results of several studies show a majority (i.e., up to 75 %) of patients treated achieve 5 % or greater weight loss. Side effects were infrequent, but included blurry vision, headache, irritability, dizziness, insomnia, depression, and anxiety (Fleming et al. 2013). This combination has not been studied in children or adolescents.

Lorcaserin is a serotonin 5HT2c receptor agonist studied in obese adults with comorbidities. In the BLOSSOM trial, adults with BMI between 30 and 45 kg/m^2 or BMI between 27 and 29.9 kg/m^2 with obesity-related complications were randomized to lorcaserin 10 mg daily, 10 mg twice daily, or placebo in addition to lifestyle modification. Mean BMI changes were −5.8 and −4.7 kg/m^2 in twice daily and daily dosing, respectively, versus −2.8 kg/m^2 in placebo (Fidler et al. 2011). Headache, nausea, and dizziness were the most cited side effects in this particular study, while other side effects reported include nasopharyngitis, upper respiratory infection, back pain, and fatigue (Boland et al. 2015). Lorcaserin is not yet approved in children or adolescents, but a safety and tolerability study is in progress according to clinicaltrials.gov.

There are few pharmaceutical treatment options for adults with obesity and even fewer for children with obesity. Orlistat remains the only US FDA-approved treatment option in 12–16-year-old obese adolescents, which has shown modest short-term efficacy with less certain long-term benefit. Metformin is often used as an adjunct, though the long-term benefit remains elusive. Current research is testing the safety and efficacy of topiramate and lorcaserin in adolescents, which may increase the breadth of treatment options for childhood obesity.

4.2 Pharmacologic Treatment of Metabolic Syndrome

Metabolic syndrome encompasses a variety of obesity-related comorbidities including dyslipidemia, hypertension, and increased plasma glucose. We will discuss the effect of orlistat and metformin in the treatment and prevention of these comorbidities in children and adolescents and briefly discuss specific treatment of abdominal obesity and dyslipidemia.

4.2.1 Orlistat

Many of the studies evaluating orlistat in the treatment of obesity included secondary outcomes including waist circumference, lipid profiles, and glucose regulation. The small, open-label trials done by McDuffie et al. showed reduction of waist circumference, total cholesterol, low-density lipoprotein (LDL), and insulin levels but no improvement in high-density lipoprotein (HDL) or glucose parameters in adolescents receiving orlistat in addition to participation in a behavioral weight loss program (McDuffie et al. 2002b, 2004). In the large Chanoine study (an RCT of 539 adolescents aged 12–16 years with BMI ≥2 units above 95th percentile, who were monitored over 54 weeks), least squares mean of waist circumference was reduced by −1.55 cm in the orlistat group compared to a gain of +0.12 cm in the placebo group. However, they found no significant difference in blood pressure, insulin, glucose, or lipid parameters (Chanoine et al. 2005). A large meta-analysis of pharmacologic agents used in the treatment of obesity in children adolescents, including orlistat, found no significant difference in lipids, glucose, or insulin in those treated with orlistat compared to placebo (Viner et al. 2010).

4.2.2 Metformin

In obese adults with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) with risk factors, metformin is recommended by the American Diabetes Association (ADA) as it has been shown to be effective in prevention of diabetes. As the risk of T2DM is highest in obese patients with hyperinsulinemia, metformin is often considered an adjunct to lifestyle modification (Pacifico et al. 2011). Many studies report benefit from metformin in obese hyperinsulinemic youth with reduction of weight and improved insulin resistance in the short term (Srinivasan

et al. 2006; Love-Osborne et al. 2008; Atabek and Pirgon 2008; Wilson et al. 2010; Wiegand et al. 2010). In the MOCA trial, 8–18-year-olds with hyperinsulinemia or prediabetes with mean BMI-SDS +3.4 had a slight reduction in mean BMI when treated with metformin for 6 months; however, fasting glucose, fasting lipids, blood pressure (BP), and waist-to-hip ratio showed no significant difference compared to the placebo group (Kendall et al. 2013). One study of obese children 7–18 years addressed the effect of 6 months of metformin treatment on weight loss and markers of inflammation, thrombosis, and intrahepatic fat contents. The results showed weight loss and mean waist circumference change of −6.7 cm compared to −0.3 cm in placebo group; however, blood pressure and fasting lipids did not show significant improvement (Mauras et al. 2012). The meta-analysis done by McDonagh of obese children under age 18 years showed a slightly greater reduction in total cholesterol and triglycerides in those treated with metformin compared to placebo. Other lipid outcomes were not different between groups (McDonagh et al. 2014). Of the few studies to examine blood pressure, only four reported changes in blood pressure, with inconsistent results that did not reach statistical difference in a meta-analysis (McDonagh et al. 2014). In the RCT of metformin XR use in obese children between 13 and 18 years, there was no significant improvement in lipid, insulin, or glucose parameters (Wilson et al. 2010; Kendall et al. 2013).

4.2.3 Drug Effects on Abdominal Obesity

Reductions in waist circumference, in addition to overall obesity, may result in fewer obesity-related comorbidities as recent studies have shown abdominal obesity to be an independent risk factor for atherogenic and diabetogenic abnormalities in youth (Pacifico et al. 2011; Bacha et al. 2006). Orlistat has been shown to reduce waist circumference compared to placebo (Chanoine et al. 2005). Metformin has shown mixed results in its effect on abdominal obesity (Mauras et al. 2012; Kendall et al. 2013). Obese youth treated with exenatide demonstrated mean waist circumference change of −2 cm compared to −1 cm in controls, which was not significant (Kelly et al. 2013). Overall, the results of studies do not show profound reductions with pharmacologic agents, but orlistat may be the best choice among the available options.

4.2.4 Drug Effects on Dyslipidemia

Lipid abnormalities associated with metabolic syndrome include elevated TG and decreased HDL cholesterol. While there is a paucity of literature and lack of consensus guidelines regarding pharmacologic treatment of dyslipidemia in adolescents with metabolic syndrome (Pacifico et al. 2011), many studies cited above report the efficacy of pharmacologic agents on lipid profiles. As described previously, the majority of the orlistat and metformin studies showed little to no improvement in lipid profiles. Additionally, exenatide was not found to improve lipid profiles in obese adolescents (Kelly et al. 2013). Guidelines from the expert panel for cardiovascular health and risk reduction in children and adolescents are available and provide some treatment options (Daniels et al. 2011; Bamba 2014). While HDL-specific pharmacologic treatment is not discussed, triglyceride-lowering recommendations are addressed in these guidelines. In general, diet and lifestyle modification are the mainstay for the reduction of triglycerides. Pharmacologic treatment may be indicated for severe hypertriglyceridemia (TG $\geq$ 500 mg/dl), as it could help prevent pancreatitis – though this degree of hypertriglyceridemia is unlikely to be due to obesity and metabolic syndrome. Weight reduction is typically sufficient to improve triglyceride levels; therefore, in obesity, triglyceride management is primarily aimed at weight control (Bamba 2014). In moderate hypertriglyceridemia (TG >200–499 mg/dl), fish oil can be considered if no improvement occurs after 6–12 months of lifestyle intervention. Elevated LDL may accompany metabolic syndrome. Dietary supplements, including plant sterols and psyllium fiber, may be incorporated to help lower LDL (Bamba 2014). Psyllium fiber has modest reduction in LDL compared to placebo (Davidson et al. 1996). Pharmacologic treatment is recommended in those with persistent LDL $\geq$190 mg/dl or $\geq$130 mg/dl with

very specific risk factors after failure to improve with lifestyle changes over 6–12 months. Statins are limited to those over the age 10 years or postmenarchal (females) or beyond Tanner 2 (males) (Daniels et al. 2011; Bamba 2014).

5 Bariatric Surgery

Consideration of pediatric bariatric surgery is recommended only in a very specific population, as outlined by the Endocrine Society, the American Society for Metabolic and Bariatric Surgery (ASMBS), and the Obesity Society (Michalsky et al. 2012; August et al. 2008; Pratt et al. 2009). The Endocrine Society recommends that subjects should have attained Tanner 4 or 5 pubertal development and be near final adult height; BMI should be greater than 50 kg/m^2 or greater than 40 kg/m^2 but with significant comorbidities; morbid obesity and comorbidities persist despite a lifestyle modification program and regardless of pharmacotherapy usage; psychological evaluation demonstrates social stability and competence within the family; access to an experienced surgeon and care team exists; and importantly, the patient displays willingness and the ability to adhere to a healthy diet and active lifestyle. The BMI cutoff recommendations for bariatric surgery by the ASMBS and the Obesity Society are less stringent at 35 and 40 kg/m^2, respectively, in the presence of comorbid disease (Pratt et al. 2009; Michalsky et al. 2012). Even if the above criteria are met, bariatric surgery is highly discouraged in preadolescents, pregnant or breastfeeding adolescents and those with plans to become pregnant within 2 years, patients with eating disorders or untreated psychiatric disorders, and individuals with Prader-Willi syndrome (August et al. 2008). Given the requisite intensive lifestyle changes needed with bariatric surgery, a multidisciplinary team approach is recommended when pursuing the surgery, including the presence of a psychologist, nutritionist, physical therapist or exercise physiologist, a patient coordinator, and perhaps even a social worker in addition to the surgeon (Wulkan and Walsh 2014).

5.1 Types of Bariatric Surgery

The most commonly performed bariatric procedures for adults include laparoscopic adjustable gastric banding (LAGB), laparoscopic sleeve gastrectomy (LSG), and Roux-en-Y gastric bypass (RYGB). However, as of 2011, LAGB and LSG were not FDA-approved in adolescents, but RYGB was approved for adolescent weight loss surgery. Less commonly performed procedures include the malabsorptive bariatric surgeries, jejunoileal bypass and biliopancreatic diversion, and duodenal switch procedure (Levitsky et al. 2009; Mun et al. 2001). Malabsorptive bariatric surgeries involve anatomic rearrangements of the intestine for the purpose of decreasing the working length or effectiveness of the gut mucosa. Given the high morbidity and mortality associated with malabsorptive bariatric procedures, these procedures are not recommended in pediatric patients (August et al. 2008).

LAGB is a restrictive bariatric technique in which an adjustable prosthetic band is used to encircle the proximal stomach and separate it into a small pouch along with a large remnant (Mun et al. 2001). LSG is another restrictive bariatric technique in which resection of a part of the greater gastric curvature results in a reduced gastric volume (Broderick et al. 2014). RYGB similarly reduces the gastric volume to the size of a small pouch via staples, which is then reconnected to a segment of the inferior jejunum; thus, the lower stomach, duodenum, and proximal jejunum are bypassed. RYGB, thus, results in dumping physiology in addition to restrictive physiology (Mun et al. 2001).

5.2 Outcomes of Bariatric Surgery

Bariatric surgery has had favorable results with regard to the reduction in insulin resistance, hypertension, and dyslipidemia in numerous adult studies, and these positive results are starting to become apparent in adolescent surgeries as well. Bariatric surgery is thought to result in improvements in insulin resistance secondary to

the weight loss, although the specific mechanisms are unclear (Coppini et al. 2006). In a meta-analysis of 11 studies (one of which included adolescents) with nearly 800 obese individuals, bariatric surgery led to greater improvement in body mass and increased remission rates of type 2 diabetes along with metabolic syndrome within a 2-year follow-up period (Gloy et al. 2013).

RYGB is an approved weight loss surgery for adolescent patients in the United States. In 78 adolescent subjects, RYGB was shown to reduce the proportion with insulin resistance from 70 % to 3 % at 2 years postoperatively (Olbers et al. 2012). In the same study, LDL decreased from 2.61 to 1.99 mmol/L (100.8–76.8 mg/dL), with similar reduction in triglycerides. Mean blood pressure was lowered from 125/77 to 117/70 after 2 years (Olbers et al. 2012). A multicenter study from the Pediatric Bariatric Study Group found that mean BMI decreased from 56.5 kg/m^2 preoperatively to 35.8 kg/m^2 1-year postoperatively in subjects who had RYGB compared to a nonsignificant decrease in BMI from 47.2 to 46 kg/mg^2 in nonsurgical patients. Furthermore, significant improvements in triglycerides, total cholesterol, fasting blood glucose, and fasting insulin levels were also noted in postoperative RYGB patients (Lawson et al. 2006). A retrospective evaluation of 11 adolescent patients in the United States who had undergone RYGB found no mortalities and improvement in self-esteem, productivity, and social functioning from survey data in 9 of the 11 patients (Collins et al. 2007).

In preliminary pediatric studies, LAGB has resulted in improvements in both weight and metabolic complications (Horgan et al. 2005). In a study of 73 obese adolescents, percent of excess weight loss was over 55 % both at the 1- and 2-year follow-up periods. Mean baseline BMI was 48 ± 7 kg/m^2, and mean BMI at 1 and 2 years was 34 ± 8 and 32 ± 6 kg/m^2, respectively. Of the 51 presurgical comorbidities, 44 were either completely resolved or improved following surgery (Nadler et al. 2008). In another study of 50 Austrian adolescent patients receiving LAGB, mean BMI decreased from 45 ± 8 kg/m^2 at the time of surgery to 33 ± 7 kg/m^2 after 1.5 years, and two-thirds of preoperative comorbidities resolved (Silberhumer et al. 2006). A study of 60 Swedish adolescents receiving gastric banding also showed an improvement in BMI from a mean of 43 kg/m^2 preoperatively to 30 kg/m^2 at nearly 40 months postoperatively with no serious safety concerns (Yitzhak et al. 2006).

Preliminary studies indicate that LSG may actually be more efficacious and safe than LAGB although prospective and long-term studies are needed to fully assess this. A head-to-head comparison of LSG with LAGB in morbidly obese adolescents found that those undergoing LSG had greater improvements in BMI 2 years postoperatively than those undergoing LAGB (percent preoperative BMI loss 32.3 ± 11.0 versus 16.4 ± 12.7, $P = 0.004$). Furthermore, more postoperative complications were noted in patients receiving LAGB than in those who received LSG (Pedroso et al. 2015). In another study of 291 obese children and adolescents who underwent laparoscopic sleeve gastrectomy (LSG), mean BMI preoperatively was 48.3 ± 10 kg/m^2, and mean BMI change was -19.6 ± 6.4 kg/m^2 48 months postoperatively. Minor complications occurred in 12 patients (4.1 %), including emesis, wound infections, gastroesophageal reflux disease (GERD), bleeding, and metabolic neuropathy that improved with injections of vitamin B_1 and B_{12} (Alqahtani and Elahmedi 2015). Compared to the control group who received weight management alone who had less than a 30 % reduction in comorbidities over a 4-year period, those who received bariatric surgery experienced more than a 90 % resolution of comorbidities, with substantial improvements in obstructive sleep apnea, dyslipidemia, hypertension and prehypertension, along with diabetes and prediabetes (Alqahtani and Elahmedi 2015).

Adult studies indicate that bariatric surgery is more effective than nonsurgical treatments both for weight loss and for metabolic improvements in patients with BMI ≥ 40 kg/m^2 with less than a 1 % mortality rate (Maggard et al. 2005); however, long-term data on pediatric patients is scarce. Preliminary pediatric data, however,

indicates the following: both LAGB and RYGB result in effective and significant pediatric weight loss (August et al. 2008). Furthermore, moderate evidence demonstrates that no operative or postoperative deaths occurred with LAGB (after a follow-up period of 1–85 months) or in RYGB (after a follow-up period of 2 weeks to 6 years) (August et al. 2008). However, nearly 8 % of patients receiving LAGB required reoperation for various complications, and complications following RYGB ranged from mild to severe complications (including severe malnutrition, pulmonary embolism, and gastrointestinal obstruction).

More long-term data on outcomes of pediatric bariatric surgery is needed. An ongoing multicenter study, the Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study, is prospectively investigating outcomes of adolescent bariatric surgery and is expected to provide information on the types of surgeries best suited for adolescent patients while also giving information on safety and efficacy of the procedures (Michalsky et al. 2014).

6 Cross-References

- Adipokines and Metabolism
- Childhood Environment and Obesity
- Diet, Exercise, and Behavior Therapy in the Treatment of Obesity and Metabolic Syndrome
- Genetics of Obesity
- Global, National, and Community Obesity Prevention Programs
- Overview of Metabolic Syndrome
- Pharmacotherapy of Obesity and Metabolic Syndrome

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Global, National, and Community Obesity Prevention Programs

47

Regien Biesma and Mark Hanson

Contents

Abstract

Although some high-income countries have managed to flatten the rate of increase in their (already high) obesity rates, no country in the world has been able to reverse the obesity epidemic. Obesity prevention is not an easy task because it requires multiple population-wide policy interventions targeted at global, national, and community settings. Public health strategies must be comprehensive and multisectoral and range from improving individual behavior to modifying the obesogenic environment, from promoting an individual responsibility to changing health policy, and from targeting adults to adopting a life-course approach. The latter approach has recently been recognized in global strategies as critical to curb the obesity prevention. It stresses the importance of early intervention during the life cycle to preventing obesity in the population. Interventions targeting the preconception period aim to assist parents-to-be in the best shape as possible, preferably resulting in women with a healthy prepregnancy BMI, lower gestational weight gain, and postpartum weight retention. Interventions in the postnatal phase aim to ensure the provision of sufficient and nutritious food to infants, children and adolescents to promote healthy growth. Comprehensive food policies are needed to create an enabling environment for infants and children so that they can acquire healthy food preferences and targeted actions to enable

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disadvantaged populations to overcome barriers to meeting healthy preferences. We argue that a focus on these so-called early life risk factors is essential in obesity prevention and could be the missing link in stopping the vicious cycle of obesity begetting obesity.

Keywords
Early life • Life course • Prevention strategies • Obesity

1 Introduction

Obesity is now one of the most important public health threats worldwide and is a major risk factor of noncommunicable diseases (NCDs) (Organization WH 2014). The worldwide prevalence of obesity has more than doubled since 1980, with 1.9 billion adults aged 18 years and older overweight in 2014 (World Health Organization 2014). A particular concern is childhood obesity. More and more children are becoming obese, especially in low- and middle-income countries, and these children are more likely to stay obese in adult life (Nader et al. 2006).

The obesity epidemic is a complex multifactorial health problem, affecting society as well as individuals, and single, isolated interventions are unlikely to work (World Health Organization 2012). Interventions need to address behavioral, cultural, social, political, economic, environmental, and physiological factors and their interrelationships throughout the life course. Governments, health-care organizations, schools, work settings, neighborhoods, communities, individuals, and families need to work together to create an environment where the healthy option is the default choice (Friel et al. 2007). Prevention starting early in life, even before birth, is likely to be the most cost-effective and feasible approach for many countries (Baidal and Taveras 2012; Darnton-Hill et al. 2004; Gluckman and Hanson 2008; Muller et al. 2001). This chapter provides an overview of promising strategies for obesity prevention at global, national, and community levels. First, we outline the life-course approach with a focus on early prevention of obesity. Then, we describe the guiding principles for the development of a global NCD prevention strategy, followed by national approaches for population-based obesity prevention. In the last section we will look at community-based interventions in early life.

2 Life-Course Approach

Evidence is accumulating that obesity should be prevented using a life-course approach, beginning in early life and continuing throughout every stage of the life course (Garmendia et al. 2014; Uauy et al. 2010; Hanson et al. 2012; Perez-Escamilla and Kac 2013). Perez-Escamilla and Kac (2013) described two evidence-based cycles that help to understand the need for an early focus of the life-course approach (Perez-Escamilla and Kac 2013). The first cycle in the life-course approach is the "maternal" cycle when prepregnancy overweight (especially primiparous) women are more likely to gain and retain excessive weight during pregnancy and after delivery. The second or "offspring" cycle indicates that the children of prepregnancy overweight women have an increased risk for storing excessive fat themselves, especially if the mother gained excessive weight during pregnancy, and the infant is not (exclusively) breastfed for the first 6 months and is introduced early to solids and sugar-sweetened beverages. Such infants are then more likely to grow rapidly in the first year of life, which in itself is an important risk factor for the development of obesity in early childhood. If during the toddler and preschool period exposure to an obesogenic environment is continued, the child is more likely to remain overweight or obese during the primary school and adolescent years and indeed as an adult.

Socioeconomic status (SES) is an important mediator in this intergenerational cycle. Young low-SES mothers are less likely to breastfeed, and if they do, for a shorter duration, they are more likely to start early with formula and cow's milk consumption (Puhl et al. 2013). These mothers are more likely to be overweight and obese and less likely to adhere to lifestyle guidelines. This all implies a vicious cycle of "obesity begetting obesity": a girl born to an overweight or

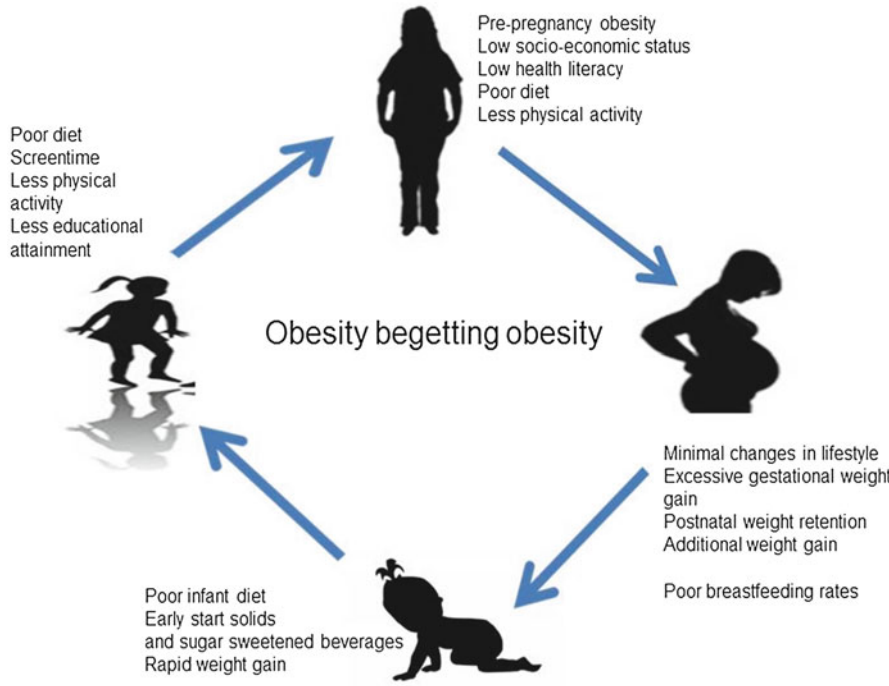

Fig. 1 Life-course approach to obesity

obese low-SES mother is very likely that she herself will enter her first pregnancy being overweight and obese (see Fig. 1). The pattern of "obesity begetting obesity" in low-SES mothers has been mostly apparent in high-income countries but is now rapidly emerging in low- and middle-income countries affected by globalization, urbanization, and economic development. These countries are now faced with a double burden of over- and undernutrition which both have major implications for the obesity epidemic (Perez-Escamilla and Kac 2013; Barker et al. 1993).

3 Obesity: A Global Problem Requires a Global Strategy

There are several reasons why a global view of obesity prevention is helpful. The first is that obesity is genuinely a global problem, because the prevalence of overweight and obesity is static or increasing in every country so far examined. National, regional, and global trends in body mass index (BMI) since 1980, from systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants from 199 countries and territories, showed large variations in the rates of overweight and obesity globally. 19 countries showed a non-significant decrease since 1980 while at the other extreme, the mean BMI increased at the rate of 2.0 kg/m^2 per decade over this period in adults over the age of 20 years (Finucane et al. 2011). The global trend between 1980 and 2008 was 0.4 kg/m^2. Recent analyses have indicated the impact of these trends and emphasized the need for global action (Ng et al. 2014).

A second reason is that the increase in overweight and obesity is associated with increases in NCDs in every country. However, these global trends mask substantial regional differences in risk. Some Asian populations show large increases in prevalence of NCDs such as metabolic syndrome at much lower levels of BMI or waist-hip ratio than Caucasian populations (McKeigue et al. 1991). Asian Americans have greater prevalence of metabolic syndrome despite lower BMI (McKeigue et al. 1991). In part, this appears to be due to greater

abdominal fat and less skeletal muscle in the former, constituting two risk factors for type 2 diabetes which starts in early development (the "thin-fat" Indian baby syndrome) (Lakshmi et al. 2012). A further complication is that, at a similar BMI, ethnic groups in the same country can show different patterns of disease (Goff et al. 2013).

A third reason is that both basic and clinical research indicate that there are fundamental developmental reasons for the increase in obesity globally. They include the effects of "mismatch" which occurs when aspects of the developmental environment such as nutrition, which induce adaptive changes in the phenotype of the offspring, are not met by similar aspects in the postnatal environment (Gluckman and Hanson 2006). The changes in body composition and physiological control mechanisms in individuals exposed to a poor nutritional level prenatally leave them "mismatched," i.e., unprepared to meet the challenges of the contemporary, urban obesogenic environment. This mismatch is an important feature of populations going through socioeconomic and nutritional transitions and of vulnerable groups such as economic migrants and ethnic minority groups (Drewnowski and Popkin 1997; Kalhan et al. 2001). The underlying mechanisms are beginning to be elucidated (Haugen et al. 2005), revealing how the human species appears to have evolved a propensity to deposit body fat during prenatal development, perhaps to protect brain growth postnatally (Kuzawa et al. 2011). The fact that these processes appear to be common to members of our species to different degrees in different settings and that their operation may be identified in early life through the use of biomarkers (especially epigenetic changes) (Godfrey et al. 2007) provides a mechanistic basis for believing that global interventions may be feasible.

3.1 Need for Early Life Interventions Now Recognized in Global NCD Strategies

These insights have become clearer over the first decade of the twenty-first century. The greater health problem posed by NCDs than by communicable disease, accidents, and other causes of mortality in both men and women globally was not identified in the Millennium Development Goals (MDGs), despite some related to maternal and child health. Nonetheless, the challenge posed by obesity and associated NCDs, in particular in developing countries and other deprived populations, was clearly evident from the Global Strategy for the Prevention and Control of NCDs 2000 and the Global Strategy on Diet, Physical Activity, and Health 2004 (Organization WH 2004). In 2008, the need for population-based prevention and a multisectoral approach as being vital to addressing rising levels of noncommunicable diseases was translated into concrete action in the World Health Organization (World Health Organization) Action Plan for the Global Strategy for the Prevention and Control of NCDs 2008–2013 (World Health Organization 2008) and endorsed at the Sixty-First World Health Assembly in May 2008. In September 2011, the High-Level Meeting of the United Nations General Assembly convened a summit to address the issue, resulting in the Political Declaration of the Prevention and Control of Noncommunicable Diseases of September 2011. There are several new elements in the UNGA Political Declaration, of which one of the most striking refers to the need to recognize the part played by early developmental origins of conditions such as obesity in the problem. Phrased in this way, it is clear that interventions can share common elements globally and that a life-course approach is needed to take them forward. This theme is very much taken up in subsequent World Health Organization recommendations, for example, the Global Action Plan for the Prevention and Control of NCDs 2013–2020 (World Health Organization 2008). This Action Plan identified life-course approach as an overarching principle and recognized that interventions in early life often offer the best chance for primary prevention.

In parallel, a range of nongovernmental organizations (NGOs), civil society organizations (CSOs), and other organizations have produced reports on the global obesity crisis, for example,

the International Obesity Task Force (IOTF) (Swinburn et al. 2005) and the US Institute of Medicine (IOM) (Medicine Io 2012). These draw attention to the multifactorial basis for the epidemic, from international, national, societal, community, family, and personal components, each of which has to be addressed simultaneously, albeit with differing emphases in different countries, if the problem is to be effectively addressed. A picture therefore emerges of a truly integrated approach to the problem across both temporal (life course) and spatial (from personal to public) domains. The economic benefits of intervention have been calculated (Dobbs et al. 2014) and make a strong case for interventions. This is strengthened still further by the clear perception that obesity and associated NCDs are associated with social inequalities in health (Marmot 2005) and thus raise rights and ethical issues.

The life-course aspect of obesity prevention focuses attention on starting early, for example, in childhood. In 2014, The Director-General of World Health Organization established a Commission on Ending Childhood Obesity (ECHO), which has met several times, consulted widely, and aims to report in mid-2016. The Commission's Interim Report in 2015 identified key issues including the need to tackle the obesogenic environment in which children and adolescents grow and develop and the importance of a life-course approach to address the risk factors for childhood obesity (World Health Organization 2015). One of the thorny issues with which the ECHO Commission will have to engage, as will the architects and actors of the SDGs at all levels, is the role of the private sector, especially the food companies. The global multinational food companies have been pilloried repeatedly, "big food" being likened to "big pharma" in terms of conflicts of interest (Swinburn et al. 2011; Beaglehole et al. 2011). Many proposals to restrict their influence through legislation, taxation of unhealthy products, have been made (Cecchini et al. 2010), although questions have been raised about whether such fiscal measures may merely widen inequalities in health (Swinburn 2008) and they may not be compatible with trade agreements, UN member state financial policies, etc. Some successes in this respect have been achieved (e.g., Mexico's soft drink tax has been effective in reducing soda consumption and in turn had an effect on the rate of obesity). It seems likely that a more inclusive approach to collaboration to address the problem with "as appropriate" the private sector as suggested in the UNGA Political Declaration of 2011 will be needed. New frameworks for public-private partnerships with the food industry, to provide transparency and control of conflicts of interest, are now being discussed (Alexander et al. 2015).

4 National Obesity Prevention: Focusing on the Obesogenic Environment

Traditionally, public health strategies to promote healthy lifestyles have targeted the individual (Belay and Dietz 2009). However, recently this paradigm is shifting toward the environment in which individuals make choices on food consumption and physical activity. Creating supportive environments requires the use of policy instruments, such as laws and regulations, taxation and subsidies, and advocacy to the public and private sector and other jurisdictions (World Health Organization 2012). They involve shifting the responsibility of healthy behavior from individual to the national level and typically target the so-called social determinants of health (Bambra et al. 2009).

Although there are several key players in obesity prevention at the national level, such as the government, the private sector, and civil society/nongovernmental organizations (NGOs), governments generally lead and drive policy changes (World Health Organization 2012). Ministries of Health play a leading role in developing and implementing health policies and bringing together other ministries, the private sector, health professional bodies, academics, and NGOs that are needed to effectively address obesity and NCD risk in subpopulations (Swinburn et al. 2013). However, the determinants of obesity are complex, and a key challenge for governments is to make the most appropriate and effective mix of multiple policy-based obesity prevention

interventions, across different settings, levels, and sectors. Strategies are usually combined so as to complement each other.

4.1 National Policies for Obesity Prevention

There are different public health strategies for risk reduction available at the national level. These are usually categorized as (i) "upstream" policies which are broad social and economic conditions (socio-ecological approach) that are indirectly influencing population behavior, (ii) "midstream" or behavioral policies which are directly influencing population behaviors, and (iii) "downstream" policies which support health service and clinical interventions (typically individual based) (Sacks et al. 2008). The upstream (socio-ecological) approach aims to influence the underlying determinants of health in society and represents the greatest potential for obesity prevention by creating environments that support healthy diets and physical activity (Cecchini et al. 2010; Sacks et al. 2009; Dobe 2013). This approach is in line with Geoffrey Rose's original idea of "population-based prevention approaches" which focus on changing the contextual conditions of risk rather than the individual risk per se (Rose 1994). Upstream policies target the food environments, physical activity environments, and the broader socioeconomic environments (such as taxation, employment, education, housing, and welfare) and can improve outcomes across all socioeconomic groups, both adults and children, and often with greater cost-effectiveness than individual interventions (World Health Organization 2012).

The midstream policy approach aims at influencing directly the behavior of subpopulations to improve eating and physical activity. In order to influence behavior directly, interventions need to take place in settings where people eat and/or can be physically active, such as schools, workplaces, households, hospitals, prisons, and military establishments (Swinburn et al. 1999). Government policy instruments to influence behavior directly are almost exclusively based on education- and campaign-based programs. Downstream policy approaches supporting health services and medical interventions are predominantly focused on obesity management rather than prevention. These are typically individual based rather than population based. Both downstream investments (individualized health care) and upstream investments (high-level policy and legislation) are both needed to alter obesogenic environments by providing incentives for healthy eating and physical activity (Walls et al. 2011). In addition, integrated healthy living strategies (healthy eating, active living, and mental health) are needed to address common risk factors associated with obesity and related chronic diseases (Flynn et al. 2006). In the next section, we will focus on population-based prevention strategies with specific emphasis on childhood and discuss the most important "upstream" and "midstream" interventions: policies influencing the food environment, policies influencing physical activity environment, and social marketing campaigns.

4.1.1 Population-Wide Policies Influencing the Food Environment

The aim of these policies is to alter the food environment so that the *healthy choice will become the easy choice*. They are based on national nutrition guidelines, food selection guides, and policies relating to breastfeeding and infant nutrition (World Health Organization 2012; Institute of Medicine 2012). For example, the Institute of Medicine (IOM) in the United States offers detailed recommendations, strategies, and action steps for implementation by key stakeholders and sectors for accelerating progress in obesity prevention (Institute of Medicine 2012). Evidence suggests that a number of policy interventions in food environments are cost-effective and have the potential to prevent obesity in the population (Lehnert et al. 2012). These are related to combined efforts to reduce unhealthy food and beverage options and to increase the availability and reduce the prices of healthier food and beverage options (Williams and Mummery 2013). Examples are regulations to reduce food marketing to children, "nutrition labeling" to encourage consumers to make healthy food choices, and

increased taxation on obesogenic food and price subsidies or production incentives for foods that are encouraged (Organization WH 2004; World Health Organization 2012; Bodker et al. 2015).

Hawkes, Smith, et al. (2015) went one step further and claimed that food policies could be more effective and sustainable in preventing obesity if focused on the interaction between human food preferences and the early life environment in which those preferences are learned, expressed, and reassessed (Hawkes et al. 2015). Comprehensive food policies are needed that create an enabling environment for infants and children to learn healthy food preferences and targeted actions that enable disadvantaged populations to overcome barriers to meeting healthy preferences. This is an important addition to the literature as antenatal and infant determinants of appetite and food preference persist through adult life (Belsky 2014; Cripps et al. 1979; Bachmanov et al. 2009). It is well known that unhealthy behavior is highly habitual, evolves in early life, and, once established, is not easy to change. Again, this suggests that the most effective time to instigate new interventions to prevent obesity is early in life, before appetite control, food preference, and fat cell number are established, to make sure that *the healthy choice* is not the easy choice but also *the preferred choice* (Hawkes et al. 2015).

4.1.2 Population-Wide Policies Influencing Physical Activity Environment

Physical activity is important for healthy growth and development of young children. It is recommended that children and adults accumulate at least 60 min of moderate to vigorous physical activity every day (World Health Organization 2012). National policies should include the encouragement of physical activity in early life as it can help reduce stunting and encourage healthy linear growth.

Furthermore, there is a need for multifaceted physical activity policies to increase active and safe methods of transport, to encourage physical activity in school settings, and to provide sport and recreation facilities available for all (World Health Organization 2012). A Cochrane systematic review found that school-based physical activity interventions can be effective in increasing duration of physical activity, reducing time per day spent watching television, and increasing physical fitness levels of children (Dobbins et al. 2009). The evidence also suggested that children exposed to school-based physical activity interventions are approximately three times more likely to engage in moderate to vigorous physical activity during the school day than those not exposed. These are discussed further in the section on community-based interventions.

4.1.3 Mass Media or Social Marketing Campaigns

Mass media or social marketing campaigns are tools, based on commercial marketing approaches, to increase awareness and change attitudes toward diet and physical activity of the whole population (Grier and Kumanyika 2010). It is an important task of the government to use effective social marketing campaigns to motivate individuals to adopt healthy lifestyles and create healthy environments, such as educating children about selecting healthy food (Gortmaker et al. 2011). An example is the use of national health brands or logos to assist consumers in making healthy food choices. However, evidence is limited on the (long-term) effect of social marketing campaigns promoting healthy diets (Kremers et al. 2010; Lemmens et al. 2008), and some have argued that social marketing campaigns focusing on the undesirability of obesity can be harmful (Puhl et al. 2013).

It has been suggested that the promotion of a single simple message with frequent exposure to increase, for example, the consumption of low-fat milk or to promote regular physical activity is most effective (Sacks et al. 2009). Until recently, social marketing campaigns have primarily aimed to influence individual behavior (also called the "downstream approach"), but recently this has shifted toward targeting the environment as the means to bringing about desired change (the "upstream approach") (Henley and Raffin 2010). Some have argued that social marketing

campaigns should first consider the social determinants of health before attempting to persuade individuals to change their behavior (Sacks et al. 2008).

5 Community Obesity Prevention: Focusing on the Child, Families, and Communities

Community-based interventions are multicomponent interventions and programs, typically tailored to the local environment. Community-based interventions have been demonstrated to be successful when applied in multiple childhood settings, including home, schools, and neighborhoods. First, we discuss community-based obesity prevention interventions targeting the maternal cycle followed by interventions aimed at the offspring cycle.

5.1 Obesity Prevention via Addressing Maternal Factors

Maternal obesity has become a major public health issue worldwide and affects health of both the mother and her offspring (Catalano and Ehrenberg 2006). Maternal obesity may result from prepregnancy obesity or excessive weight gain. High prepregnancy BMI increases the risk of gestational diabetes mellitus (GDM) and type 2 diabetes in women (Boney et al. 2005), while excessive weight gain increases the risk of fetal macrosomia, maternal overweight, and postpartum weight retention (Scholl and Chen 2002). During the postpartum period, postpartum weight retention and additional weight gain increase the risk of becoming obese (Siega-Riz et al. 2009). Moreover, children who are exposed to an intrauterine environment of maternal hyperglycemia are at increased risk of developing obesity later in life (Catalano and Ehrenberg 2006; Whitaker 2004; Ferrara 2007). This suggests that pregnancy is a key period in shaping a healthy future of mothers and their children. However, it has not been easy to influence health-related behavior in pregnant women effectively. There is the widespread social belief that pregnant women should "eat for two" and rest physically (Catalano and Ehrenberg 2006). On the other hand, pregnancy is a time when behavior can be challenged as a woman is more likely to improve her lifestyle for her baby's health (Inskip et al. 2009).

Socioeconomic inequalities play an important role in this scenario, with the highest prevalence rates of obesity among low-SES mothers and their children (Hedley et al. 2004). Nutrition knowledge is poorest in low-SES mothers and affects intake of fruit and vegetables and overall diet quality (Beydoun and Wang 2008). This suggests that tailored interventions may be needed to improve maternal literacy in lower socioeconomic groups.

5.1.1 Pregnancy Interventions

Women who gain excessive weight during pregnancy are more likely to retain and gain weight after delivery, creating a vicious circle of increasing body weight and obesity (Linne 2004). To date, evidence on the effective pregnancy interventions on dietary habits, physical activity, and gestational weight gain has been limited and inconsistent (Oteng-Ntim et al. 2010). Some dietary and lifestyle interventions in pregnancy have been found to reduce total gestational weight gain and long-term postpartum weight retention (Guelinckx et al. 2010; Asbee et al. 2009). Specific components of these successful interventions were weight monitoring, setting weight goals, education counseling, and physical activity settings (Streuling et al. 2010; Tanentsapf et al. 2011).

Furthermore, there has been some success with antenatal lifestyle interventions in preventing excessive gestational weight gain in overweight/obese women and reducing the risk of GDM (Poston et al. 2010). However, it has been suggested that interventions in overweight/obese women need to be more intense than in normal-weight women and involve frequent contact and emphasis on caloric restriction (Tanentsapf et al. 2011). This may limit the possibility of such labor-intensive and costly

interventions being implemented at wider, national scale.

5.1.2 Preconception Interventions

Many young adults do not realize that their body weight and lifestyle during the reproductive years affect their future health and that of their children (Krummel 2007). Targeting lifestyles of adolescents and young couples before they become pregnant to reduce prepregnancy BMI would perhaps be the ideal intervention (Hanson et al. 2012; Birdsall et al. 2009). To date, there are few preconception interventions. Pregnancies are often unplanned, and even women who are planning to conceive often do not contact a health professional (Birdsall et al. 2009). As a result, it is difficult to target women before conception.

Focusing interventions on adolescents and young couples would require the promotion of health literacy for reducing risks of obesity and NCDs for the mother and her child(dren), such as the importance of appropriate weight gain before and during pregnancy and breastfeeding (Hanson et al. 2012). It is well known that parents with low literacy have less health knowledge and are more likely to negatively affect their children's health compared with parents with higher literacy (DeWalt and Hink 2009). Renkert and Nutbeam defined maternal health literacy as "the cognitive and social skills that determine the motivation and ability of women to gain access to, understand, and use information in ways that promote and maintain their health and that of their children" (Renkert and Nutbeam 2001). A systematic review on interventions to improve health literacy and child health outcomes found that education classes, clearly written instructions, and counseling for parents improved health outcomes in their children (DeWalt and Hink 2009). In improving a woman's ability and motivation to adhere to health recommendations for herself and her child, it is critical to address barriers to change, such as time limitations, social pressure, and a perceived lack of control (Hanson et al. 2012). It is therefore important in intervention design to incorporate components to tackle barriers to adhere and improve attendance (Hartman et al. 2011).

5.1.3 Postpartum Interventions

An additional approach to interventions targeting couples before pregnancy would be to target maternal weight after delivery (Birdsall et al. 2009). It is known that women in the highest BMI category are more likely to retain weight and to be insufficiently active postpartum, especially if they were less active before pregnancy, had more gestational weight gain, worked greater hours, and reported lack of childcare as a barrier (Pereira et al. 2007). Clearly it is difficult to help mothers with young children to improve aspects of their behavior.

Indeed, the number of experimental interventions for promoting physical activity and healthy eating among new mothers is limited, and attrition is very high in most of the interventions (Hartman et al. 2011). Effective intervention components targeted toward mothers aimed to promote lifestyle change including nutrition advice sessions, use of peer educators and strategies to promote targeted food choice by reducing costs, and those to overcome barriers to physical activity and healthy eating. It seems that, in particular for intervening in the postpartum period, it is essential to address the key barriers to postpartum weight loss, such as locality, childcare provision, and including the whole family in goal setting and behavior change (Uauy et al. 2010).

5.1.4 Interventions to Promote Breastfeeding and Delay Introduction of Solid Foods

The health benefits of breastfeeding for both mother and child are well documented. Babies who are not breastfed exclusively for at least 4 months are more likely to suffer health problems, such as gastroenteritis, and develop obesity. Despite that, many women chose to formula-feed their babies. The reasons are likely to be sociocultural and may include attitudes of family and close friends, attitudes towards breastfeeding in public, and employment practices (Sikorski et al. 2002). Helping and supporting women to initiate and prolong breastfeeding is therefore critical. There are a number of global strategies aimed at enabling mothers to breastfeed babies, such as

the World Health Organization/UNICEF *International Code of Marketing of Breast-Milk Substitutes* (World Health Organization 1981) and the *Baby-Friendly Hospital Initiative* (BFHI) (World Health Organization and UNICEF 1991). However, breastfeeding initiation rates are still relatively low, especially in low social class, income, and education levels and among overweight and obese women (Birdsall et al. 2009). Interventions that have shown to have an impact on breastfeeding rates typically included needs-based and informal peer support in the antenatal and postnatal period (Dyson et al. 2009; Britton et al. 2007). Peer support can also help mothers to breastfeed for longer. Furthermore, there is evidence of a positive association between antenatal care and breastfeeding among low-SES women. It seems that interventions to improve health literacy and attitudes are key to helping mothers among all population groups to make informed choices about breastfeeding and infant feeding practices.

5.2 Obesity Prevention in Children

5.2.1 Home Settings

The home and family environment have the most important and lasting influence on the development of children's health in general and eating and lifestyles in particular (Gerards et al. 2011). Parental weight has been found one of the most robust predictors of child's weight (Perez-Pastor et al. 2009). Parents determine their child's lifestyle and parenting and home life, especially in early childhood (Lloyd et al. 2014). Parenting style, parental role modeling, family lifestyle, responsive feeding, infant feeding, use of food for non-nutritional purposes, exposure to television, and sleeping habits are all risk factors in the home environment that increase the risk of childhood obesity (Gillman and Ludwig 2013; Robinson et al. 2015). Young children are dependent on parents and caregivers for food, and parents' choices on when to eat, responses to children's indication of hunger or distress, the context in which eating happens, and foods and portion sizes influence children's early learning about food and eating (Birch and Ventura 2009).

Surprisingly, few interventions have been developed that address general parenting in the prevention of childhood obesity (Gerards et al. 2011). These interventions provide evidence that suggests that the promotion of authoritative parenting is an effective strategy for the prevention and management of childhood obesity. There is some evidence that suggests that interventions promoting authoritative parenting (high demandingness, high responsiveness) are effective in improving weight-related outcomes in children (Uauy et al. 2010).

Other home- and family-based interventions have been shown to be effective in affecting child weight status. These have focused on engaging with parents to support activities in the home setting to encourage healthy eating, more physical exercise, and less screen time (Waters et al. 2011). Several studies found evidence for the association between pressure and child eating and preferences. Generally, children who are *rewarded* for eating certain types of food, such as vegetables, would eat more of that food but had a decreased preference for it. On the other hand, *pressuring* children to eat certain types of food would lead to eating less of it and having a lower preference for it (Ogden et al. 2006).

5.2.2 Preschool Settings

Given that early childhood is a period where children are developing food preferences and behavior and activity behavior, interventions and strategies to promote active living, motor development, and healthy eating should start as early as possible (Hanson et al. 2009). Preschool settings (nurseries, day care, kindergarten, preschools) provide excellent access to the young child and their families to help attain and maintain a healthy lifestyle. Even though physical activity guidelines for the preschool years in several countries are inconsistent, preschoolers (aged 3–5 years) should accumulate at least 60 min of physical activity at any intensity spread throughout the day (Skouteris et al. 2012). This would include any activity which gets them moving, such as climbing stairs or moving around the

house, playing outside and exploring the environment, and crawling, walking, running, or dancing.

However, evidence of effectiveness of obesity prevention programs at this early life stage is limited (Flynn et al. 2006; Waters et al. 2011). A systematic review and meta-analysis on the prevention of overweight and obesity in young children conducted in 2010 (Monasta et al. 2011) identified prevention programs aimed to promote healthy eating, physical activity, and reduced television viewing among preschool children. Some focused on health education or training or had a component on physical activity, while three of the preschool interventions included an educational component for parents. However, the included interventions were not able to prove an effect on weight gain or BMI, while some small effects were observed in dietary or physical activity behavior. It has been suggested that growth velocity or rapid weight gain (identified by crossing BMI centiles) (Taveras et al. 2011) or the timing of adiposity rebound (Whitaker et al. 1998) could be better indicators of overweight and obesity in children (Monasta et al. 2011).

5.2.3 School Settings

Schools are critical settings for obesity prevention programs as they can help to establish lifelong healthy habits in school-aged children (Flynn et al. 2006). Schools can play a particularly critical role by establishing a safe and supportive environment with policies and practices that support healthy behaviors such as school lunch programs. Schools also provide opportunities for students to learn about and practice healthy eating and physical activity behaviors (health education). A Cochrane systematic review of 55 published interventions found strong evidence for the effect of child obesity prevention programs on the relative reduction of BMI, especially in 6- to 12-year-old children (Waters et al. 2011). These included the following promising strategies and policies: include healthy eating, physical activity, and body image integrated into regular curriculum; include more sessions for physical activity/fundamental movement skills throughout the school week; create an environment and culture that support children eating nutritious foods and being active throughout each day; provide professional development and capacity building activities for teachers to implement health promotion strategies and activities; and educate parents in the importance of continuing these activities at home (Waters et al. 2011).

5.3 Challenges in Obesity Prevention

Even though governments are prioritizing actions to tackle obesity and NCDs, there has been insufficient progress worldwide. Obesity prevalence rates have reached a plateau in some high-income countries but are still alarmingly high. Low- and middle-income countries are catching up rapidly and are faced with a double burden of under- and overnutrition. Obesity is a complex and multifactorial problem that requires a comprehensive and multisectoral approach, but all too often the debate around obesity prevention is based on polarizing and seemingly opposing approaches (Roberto et al. 2015) such as:

- Individual behavior versus an obesogenic environment
- Lack of physical activity versus unhealthy diets
- Prevention versus treatment
- Government regulation versus industry self-regulation
- Treatment versus prevention
- Children versus adults
- Undernutrition versus overnutrition

Simplifying the problem into dichotomizing approaches will not reduce obesity at the population level. Firstly, most implemented obesity prevention strategies have targeted individual behavior rather than the wider environment in a more holistic way as part of a response to the current dominant political climate of free markets and individualism (Swinburn et al. 2015). Secondly, preventive interventions aimed at children

require a large investment in both time and resources, and the resulting health gains may not become apparent for decades (Lehnert et al. 2012). For politicians, the electoral cycle is short, and there are limited resources for competing policy priorities (Lobstein and Brinsden 2014). Thirdly, the ultra-processed food industry has been very successful in blocking government-led regulatory and fiscal measures to modify the obesogenic environment (Lehnert et al. 2012).

Obesity prevention has been challenging not only because of these problems in trying to understand its causes and solutions to obesity but also because of the lack of evidence on what policy actions are effective, sustainable, and feasible (Roberto et al. 2015). This has made it difficult for national policymakers in the obesity field to invest in the best possible package of interventions to reverse the obesity epidemic (Mongeau 2008). There has been insufficient recognition of the early origins of obesity and the life-course trajectory which is established during development: both research and prevention strategies should focus more on these concepts.

6 Summary

There is a broad range of population-level actions that governments and other organizations can take to prevent childhood obesity. A comprehensive childhood obesity prevention strategy will incorporate a variety of approaches across a range of areas that may include social marketing, obesogenic environments, government policy, legislative and fiscal measures, and wider community approaches. The concept that obesity preventions should be based on a life-course approach with an emphasis on early life is relatively new (Haugen et al. 2005). There is now extensive evidence that the mother's diet and body composition before and during pregnancy and that of her child in the first few years of postnatal life are related to increased adiposity in childhood, setting up a trajectory of risk which can be tracked into adulthood (Uauy et al. 2010). Interventions aimed very early in the life course offer most potential for reducing obesity prevalence by focusing on the early, plastic phases of development.

7 Cross-References

- ▶ Childhood Environment and Obesity
- ▶ Diet and Obesity (Macronutrients, Micronutrients, Nutritional Biochemistry)
- ▶ Fetal Metabolic Programming
- ▶ Prevention and Treatment of Childhood Obesity and Metabolic Syndrome
- ▶ Social and Community Networks and Obesity
- ▶ The Built Environment and Obesity

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Index

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