Shamim I. Ahmad
Syed Khalid Imam
Editors

Obesity

A Practical Guide

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The editor (SIA) wishes to dedicate this book to his wife Riasat Jan for her patience, love and persistent encouragement during the production of this book and to his children, Alisha Ahmad and Arsalan Mujtaba Ahmad, who have been giving him so much pleasure with their innocent interceptions and resulting recovery from the loss of energy. Also dedication goes to those obese subjects, who may not be fully aware about the seriousness of this disease and hence may be suffering from various complications and bravely fighting them. Also to the caregivers, nurses and medics who painstakingly look after them throughout their suffering period.

The editor (SKI) wishes to dedicate this book to his parents, Ahmad Imam and Mah Jabeen, for their constant support, patronage and guidance in his career; his children, Abdullah, Maham and Ebadullah, whose voices and gestures were never boring and from them he has learned a love and enjoyed flavour of life; his wife, Uzma, the key family member, who lifted his heart and encouraged him a lot because of her spiritual wholeness, inexhaustible hope and strong personality. Lastly, to all patients who have been suffering from various kind of illnesses and fight against the ailment with great courage and hope.

Preface

Although obesity is an age-old problem, existing probably ever since the humans came into existence, recent studies show that this problem is on increase with an alarming rate, especially in the industrialised and affluent countries. The reasons put forward for this increase include the life style, over-eating, consumption of commercially processed food especially with high-caloric value and high levels of sugar and fat, addiction for fast food, lack of exercise and sedentary life style. Also genetic makeup has been associated with the obesity.

It is estimated that currently in industrialised countries, about 20–40 % of the population is obese and by 2030, if the trend will continue, this may increase up to 50 %. Current studies show that in the USA around 1 in 3 persons is obese, and by 2040 it is predicted that obesity in most industrialised and oil producing countries may reach to the pandemic level if no serious control measures are taken.

We do not know when the word *obesity* was coined but whenever was, it was defined as a condition and a manifestation of consumer society. In 2007, the World Health Organization (WHO) has recognised obesity as a disease, and the recognition is mainly based on several important developments including epidemiological data, progress in pathological concept and increase in health expenditure due to obesity, as well as obesity-associated health problems.

In the past, obesity was considered to be a disease of the middle- to late-aged groups of the people, but in the last one or two decades, obesity among children has been increasing with an alarming rate. Sedentary life style and consumption of high amount of sugar and fast food may be the two most important reasons for this increase. Interestingly in a recent research report, it has been shown that in developing countries such as in Middle East and North Africa, the gender difference in obesity is prevailing, in that there are more obese women than men. Several reasons including consumption of food, laden with sugar, among women is greater there. Also the cultural values favouring larger body size among women is considered as a sign of fertility; healthfulness and prosperity are the additional reasons for increased obesity in women than men.

Obesity on its own is not a lethal disease, but it can give rise to a number of lethal and non-lethal ailments. Coronary heart disease and stroke, dyslipidemia contributing to a number of metabolic syndromes, high blood pressure and hypertension, certain cancers and insulin resistance in diabetes are

some of the important examples. These diseases account to highest number of human death amongst all other causes. Amongst non-lethal conditions are included osteoarthritis, pancreatitis, diseases of digestive organs, sleep apnoea, gout, asthma, dementia, increased stress, loss of intelligentsia, effect on human sexual development, difficulty in management in pregnancy and premature birth. Chronic and low-grade inflammation is also associated with obesity due to high-level accumulation of adipose tissue. In other words, obesity not only can lead to premature death but the quality of life of the obese people, for various reasons, may be significantly less pleasurable than their counterpart with normal body weight. Whereas, at present, little can be done if obesity is due to genetic makeup such as a reduction in brown adipose tissue, for other reasons effective measures are required to be taken to eradicate or at least reduce obesity. If not, the prediction is that the disease soon may reach to the pandemic levels.

In recent years, media have been playing important roles in highlighting the importance of damage caused by the obesity including premature death; nevertheless, little or no significant effects can be seen in the population and the obesity remains on increase, especially amongst children. Hence it is important that more education, campaign and research are needed to stop this increasing curse.

The editors believe that obesity is one of the most important health problems of the twenty-first century, yet money spent on obesity research is notoriously low in comparison to those diseases where drug companies can make substantial profits. If serious measures not taken, as soon as possible, this disease not only will become a huge burden over the health services but a huge number of population will suffer due to the lack of knowledge. The editors believe that *gaining knowledge about obesity is indeed a treatment*.

Although the CONTENTS in the book do not show the chapters sectionalized, it may not be inappropriate for the reader's guidance to divide them in sections.

Section 1 includes the Chaps. 1, 2, 3, 4 and 5 describing the basic biochemistry including enzymes and hormones assisting in driving the biochemical reaction, functional impairment, the consequences and the pathophysiology of obesity. Emphasis has been given on hormones playing key roles in obesity such as white and brown adipose tissues, long-chain omega-3 polyunsaturated fatty acids, and leptin. These have been addressed employing up-to-date research data for the readers to fill any gap left in their knowledge.

Section 2 includes genetic aspects of obesity and the oxidative stress which play equally important roles in determining the diseases as well other syndromes (as shown above).

Section 3 embraces the consequences of obesity which includes fatal diseases leading to premature deaths such as coronary heart disease and diabetes. Among non-fatal syndromes, include sleep apnoea, gastroesophageal reflux disease, and gastrointestinal disorder in children which may be taken relatively easily in the medical field. Other consequences of obesity include non-alcoholic fatty liver disease and chronic kidney disease, which can become fatal and require more research. Polycystic ovary syndrome develop-

ing due to obesity is another medical condition usually leading to infertility. Obesity can also lead to certain types of cancer including thyroid cancer which has been described in detail in this book. A non-fatal but equally important effect of obesity is suffering from depression. This is another important consequence of obesity, and guidance has been provided in the chapter on how to handle this syndrome.

Section 4 explains the technologies available in the assessment and treatment of obesity including orthopaedic and trauma surgery, obstetrical risk in obesity and bariatric surgery including its underlying physiological mechanisms. Surgeons specialised in the field have been participating to update the readers from the current technology and most popular methods employed in the processes.

Section 5 covers another set of important subject associated with obesity, namely, the infant nutrition, their caloric importance and the formulae which can contribute towards the development of obesity. The section also discuss the roles of eating disorders, specially consumption of high- calorie food and sugar enriched drinks, plays in obesity.

Nottingham, UK — Shamim I. Ahmad
Jubail, Saudi, Arabia — Syed Khalid Imam

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The editors cordially acknowledge the various authors of this book for their contribution of the chapters with in-depth knowledge and highly skilled presentation. Without their input, it would not have been possible to produce this book on such an important subject and common endocrine dysfunction. We would also like to acknowledge the hard work, friendly approach and patience of the staff, especially of Ms Julia Megginson, of Springer Publications for efficient and highly professional handling of this project.

About the Editors

Shamim I Ahmad after obtaining his Master's degree in botany from Patna University, Bihar, India, and his PhD in Molecular Genetics from Leicester University, England, joined Nottingham Polytechnic as grade 1 lecturer and subsequently promoted to SL post. Nottingham Polytechnic subsequently became Nottingham Trent University where after serving for about 35 years, he took early retirement yet still serving as a part-time lecturer. He is now spending much of his time producing/writing medical books. For more than three decades he researched on different areas of molecular biology/genetics including thymineless death in bacteria, genetic control of nucleotide catabolism, development of anti-AIDs drug, control of microbial infection of burns, phages of thermophilic bacteria, and microbial flora of Chernobyl after the nuclear accident. But his main interest which started about 30 years ago is DNA damage and repair specifically by near ultraviolet light specially through the photolysis of biological compounds, production of reactive oxygen species, and their implications on human health including skin cancer. He is also investigating NUV photolysis of nonbiological compounds such as 8-metoxypsoralen, mitomycin C, and their importance in psoriasis treatment and in Fanconi anemia. In research collaboration with the University of Osaka, Japan, he and his co-workers had discovered a number of important enzymes that play important roles in health and diseases. In 2003, he received a prestigious "Asian Jewel Award" in Britain for "Excellence in Education". He has been editor for the following books published by Landes Bioscience/ Springer publication: *Molecular Mechanisms of Fanconi Anemia*, *Molecular*

Mechanisms of Xeroderma Pigmentosum, *Molecular Mechanisms of Cockayne Syndrome*, *Molecular Mechanisms of Ataxia Telangiectasia*, *Diseases of DNA repair*, *Neurodegenerative Diseases*, and *Diabetes: An Old Disease, a New Insight.* Also a co-author for the book *Diabetes: A Comprehensive Treatise for Patients and Caregivers.*

Dr. Syed Khalid Imam is an Assistant Professor of Medicine and Consultant Endocrinologist. He acquired Fellowship in Internal Medicine from College of Physicians and Surgeons Pakistan (CPSP) and Fellowship in Endocrinology from American College of Endocrinology (FACE). He was trained as a Clinical Fellow in Endocrinology at Liaquat National Hospital and Medical College, Karachi-Pakistan, one of the biggest private tertiary care hospitals of the country.

He affiliated with the abovementioned institute for more than fifteen years and accomplished postgraduate training, professional and career growth from this renowned health care industry. He fulfilled his responsibilities for several years as Head of Department of Diabetes, Endocrinology and Metabolism, Program Director of Internal Medicine Residency Training, and Chairman of Research and Ethics Committee. He is also a supervisor of Endocrinology Fellowship of CPSP.

He is a member of American Association of Clinical Endocrinologists and Pakistan Chapter of American Association of Clinical Endocrinologists, an executive member of Pakistan Endocrine Society, and served as the General Secretary of the society as well. He also serves as a member of an executive advisory panel of International Foundation for Mother and Child Health (IFMCH).

He has published several review articles in national and international journals and participated in many conferences as an invited speaker. Obesity and diabetes are his areas of special interest and research.

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White Adipose Tissue: Beyond Fat Storage

1

Syed Khalid Imam

Introduction

Adipose is a loose connective tissue that fills up space between organs and tissues and provides structural and metabolic support. In humans, adipose tissue is located beneath the skin (subcutaneous fat), around internal organs (visceral fat), in bone marrow (yellow bone marrow) and in the breast tissue. Apart from adipocytes, which comprise the highest percentage of cells within adipose tissue, other cell types are also present, such as preadipocytes, fibroblasts, adipose tissue macrophages, and endothelial cells. Adipose tissue contains many small blood vessels as well. In the skin it accumulates in the deepest level, the subcutaneous layer, providing insulation from heat and cold.

White adipocytes store lipids for release as free fatty acids during fasting periods; brown adipocytes burn glucose and lipids to maintain thermal homeostasis. A third type of adipocyte, the pink adipocyte, has recently been characterized in mouse subcutaneous fat depots during pregnancy and lactation [1].

Pink adipocytes are mammary gland alveolar epithelial cells whose role is to produce and secrete milk. Emerging evidence suggests that they are derived from the transdifferentiation of subcutaneous white adipocytes. All mammals possess both white and brown adipose tissues. White adipocytes contain a single large lipid droplet occupying about 90 % of the cell volume. The nucleus is squeezed to the cell periphery and the cytoplasm forms a very thin rim. The organelles are poorly developed; in particular mitochondria are small, elongated and have short, randomly organized cristae. Because of these ultrastructural characteristics, these cells are also called unilocular adipocytes [2].

Brown adipose fat cells are smaller in size and quantity and derive their color from the high concentration of mitochondria for energy production and vascularization of the tissue. These mitochondria contain a unique uncoupling protein 1 (UCP1), that supports the thermogenic function of brown adipocytes These cells are also called multilocular adipocytes [3].

The lipid in brown fat is burned to provide high levels of energy as heat in animals who hibernate and infants who may need additional thermal protection. The concept of white adipose tissue as an endocrine organ originated in 1995 with the discovery of leptin and its wide-ranging biological functions [4]. Adipose tissue was traditionally considered an energy storage organ, but over the last decade, it has emerged as an endocrine organ. It is now recognized that adipose tissue produces multiple bioactive peptides, termed ‘adipokines’, which not only influence adipocyte function in an autocrine and paracrine fashion but also affect more than one metabolic pathway [5–7].

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To maintain normal body functions, each adipocyte secretes diverse cytokines and bioactive substances into the surrounding environment which act locally and distally through autocrine, paracrine and endocrine effects. Although each adipocyte produces a small quantity of adipocytokines, as adipose tissue is the largest organ in the human body, their total amount impacts on body functions. Furthermore, as adipose tissue is supplied by abundant blood stream adipocytokines released from adipocytes pour into the systemic circulation. In obesity the increased production of most adipokines impacts on multiple functions such as appetite and energy balance, immunity, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism and haemostasis, all of which are linked with cardiovascular disease. Obesity, associated with unfavourable changes in adipokine expression such as increased levels of Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), resistin, Plasminogen Activator Inhibitor (PAI-1) and leptin, and reduced levels of adiponectin affect glycemic homeostasis, vascular endothelial function and the coagulation system, thus accelerating atherosclerosis. Adipokines and a 'low-grade inflammatory state' may be the link between the metabolic syndrome with its cluster of obesity and insulin resistance and cardiovascular disease.

Table 1.1 Important adipokines

Adipokines	Metabolic functions
Leptin	Improves insulin sensitivity, inhibits lipogenesis, increases lipolysis, satiety signals
Adiponectin	Improves insulin sensitivity, increases fatty acid oxidation, inhibits gluconeogenesis
Adipsin	Inhibits lipolysis, increases fatty acid re-esterification, triglyceride storage in adipose cells
IL-6	Impairs appetite, inflammation, insulin resistance, increases hepatic fatty acid synthesis
TNF	Inflammation, insulin resistance, reduces adiponectin synthesis
PAI-1	Inhibits activity of tissue type plasminogen activator
Resistin	Insulin resistance, endothelial dysfunction?
Angiotensinogen	Significantly correlated with hypertension
Aromatase	Driving fat to subcutaneous and breast tissues by converting androstenidione to estrone
11Beta HSD	Synthesizes cortisol from cortisone

Adipokines and Their Metabolic Function

See Table 1.1.

Leptin

Leptin, a 16-kDa adipocyte-derived cytokine is synthesized and released from fat cells in response to changes in body fat. It is encoded by a gene called *ob* (from obesity mice), and was named leptin from the Greek word meaning thin. Leptin circulates partially bound to plasma proteins and enters the CNS by diffusion through capillary junctures in the median eminence and by saturable receptor transport in the choroid plexus. In the hypothalamus, leptin binds to receptors that stimulate anorexigenic peptides such as proopiomelanocortin and cocaine- and amphetamine-regulated transcript and inhibits orexigenic peptides, e.g. neuropeptide Y and the agouti gene-related protein [8].

Leptin reduces intracellular lipid levels in skeletal muscle, liver and pancreatic beta cells, thereby improving insulin sensitivity. There is strong evidence showing that the dominant action of leptin is to act as a 'starvation signal'. Leptin declines rapidly during fasting, and triggers a rise in glucocorticoids, and reduction in thyroxine (T4), sex and growth hormones [9]. Moreover, the characteristic decrease in thermogenesis during fasting and postfast hyperphagia is mediated, at least in part, through a decline in leptin. Therefore, leptin deficiency could lead to hyperphagia, decreased metabolic rate and changes in hormone levels, designed to restore energy balance [10].

In patients with lipodystrophy and leptin deficiency, leptin replacement therapy improved glycemic control and decreased triglyceride levels. In a recent study, nine female patients (age range, 15–42 years; eight with diabetes mellitus) with lipodystrophy and serum leptin levels under 4 ng/ml (0·32 nmol/ml) received r-metHuLeptin (recombinant leptin) subcutaneously twice a day for 4 months at escalating doses, in order to achieve low, intermediate and high physiological leptin replacement levels. During treatment, serum leptin levels increased and glycosylated haemoglobin decreased in the eight patients with diabetes. Four months therapy reduced average triglyceride levels by 60 % and liver volume by a mean of 28 % in all nine patients and led to suspension of, or to a substantial reduction in, antidiabetes medication. Self-reported daily caloric intake and resting metabolic rate also decreased significantly [11]. Similar results were observed in three severely obese children with no functional leptin [12]. LEPR null humans are hyperphagic, morbidly obese and fail to undergo normal sexual maturation [13]. Furthermore, these patients did not respond to thyrotropin-releasing hormone and growth hormone releasing hormone testing, suggesting leptin also plays a critical role in neuroendocrine regulation [13].

Leptin Resistance Syndrome

The concept of 'leptin resistance' was introduced when increased adipose leptin production was observed in obese individuals who were not leptin-deficient. Apart from mutations in the leptin receptor gene, the molecular basis of leptin resistance has yet to be determined [14, 15].

A large prospective study – the West of Scotland Coronary Prevention Study (WOSCOPS) – showed, for the first time, that leptin might be an independent risk factor for coronary heart disease. At baseline, plasma leptin levels were significantly higher in 377 men (cases) who experienced a coronary event during the 5-year follow-up period than in 783 male controls, matched for age and smoking history who did not suffer a coronary event and who were representative of the entire WOSCOPS cohort [16].

Leptin and Neuroendocrine Functions

In addition to its effects on energy homeostasis, leptin regulates neuroendocrine function and traditional endocrine systems. Leptin deficiency in Lepob/Lepob mice is associated with activation of the hypothalamic-pituitary-adrenal (HPA) axis and suppression of the hypothalamic-pituitary-thyroid and -gonadal axes. Leptin decreases hypercortisolemia in Lepob/Lepob mice, inhibits stress-induced secretion of hypothalamic CRH in mice, and inhibits cortisol secretion from rodent and human adrenocortical cells *in vitro*. The role of leptin in HPA activity in humans *in vivo* remains unclear. Leptin also normalizes suppressed thyroid hormone levels in leptin-deficient mice and humans, in part via stimulation of TRH expression and secretion from hypothalamic TRH neurons [14, 17]. Leptin replacement during fasting prevents starvation-induced changes in the hypothalamic-pituitary-gonadal and –thyroid axes in healthy men [18]. Leptin accelerates puberty in normal mice and restores normal gonadotropin secretion and reproductive function in leptin-deficient mice and humans as well has direct effects via peripheral leptin receptors in the ovary, testis, prostate, and placenta [19].

Several other important endocrine effects of leptin include regulation of immune function, hematopoiesis, angiogenesis, and bone development. Leptin normalizes the suppressed immune function associated with malnutrition and leptin deficiency [20].

It also promotes proliferation and differentiation of hematopoietic cells, alters cytokine production by immune cells, stimulates endothelial cell growth and angiogenesis, and accelerates wound healing [21, 22].

Adiponectin

Adiponectin is highly and specifically expressed in differentiated adipocytes and circulates at high levels in the bloodstream [23]. Its expression is higher in subcutaneous than visceral adipose tissue [24]. Adiponectin is an approximately

30-kDa polypeptide containing an Nterminal signal sequence, a variable domain, a collagen-like domain, and a C-terminal globular domain [25–28]. It shares strong sequence homology with type VIII and X collagen and complement component C1q, termed adipocyte complement-related protein because of its homology to complement factor C1q. A strong and consistent inverse association between adiponectin and both insulin resistance and inflammatory states has been established [23, 29]. Plasma adiponectin declines before the onset of obesity and insulin resistance in nonhuman primates, suggesting that hypoadiponectinemia contributes to the pathogenesis of these conditions [30]. Adiponectin levels are low with insulin resistance due to either obesity or lipodystrophy, and administration of adiponectin improves metabolic parameters in these conditions [28, 31]. Conversely, adiponectin levels increase when insulin sensitivity improves, as occurs after weight reduction or treatment with insulin-sensitizing drugs [23, 29].

Several mechanisms for adiponectin's metabolic effects have been described. In the liver, adiponectin enhances insulin sensitivity, decreases influx of NEFAs, increases fatty acid oxidation, and reduces hepatic glucose output. In muscle, adiponectin stimulates glucose use and fatty acid oxidation. Within the vascular wall, adiponectin inhibits monocyte adhesion by decreasing expression of adhesion molecules, inhibits macrophage transformation to foam cells by inhibiting expression of scavenger receptors, and decreases proliferation of migrating smooth muscle cells in response to growth factors. In addition, adiponectin increases nitric oxide production in endothelial cells and stimulate angiogenesis. These effects are mediated via increased phosphorylation of the insulin receptor, activation of AMPactivated protein kinase, and modulation of the nuclear factor B pathway [23, 29]. Taken together, these studies suggest that adiponectin is a unique adipocyte-derived hormone with antidiabetic, anti-inflammatory, and anti-atherogenic effects. Adiponectin also has antiatherogenic properties, as shown *in vitro* by its inhibition of monocyte adhesion to endothelial cells, macrophage transformation to foam cells (through down-regulation of scavenger receptors and endothelial cell activation (through reduced production of adhesion molecules and inhibition of tumour necrosis factor α (TNF-α) and transcriptor factor nuclear factor kappa beta (NF-κβ) [32, 33]. Insulin resistance in lipoatrophic mice was fully reversed by a combination of physiological doses of adiponectin and leptin, but only partially by either adiponectin or leptin alone [34]. This suggesting that adiponectin and leptin work together to sensitize peripheral tissues to insulin. However, because globular adiponectin improves insulin resistance but not obesity in *ob*/*ob* leptin-deficient mice, adiponectin and leptin appear to have distinct, albeit overlapping, functions [35]. Two receptors for adiponectin have been cloned. Adipo R1 and Adipo R2 are expressed predominantly in muscles and liver. Adiponectin-linked insulin sensitization is mediated, at least in part, by activation of AMPK in skeletal muscles and the liver, which increases fatty-acid oxidation and reduces hepatic glucose production [33]. Interleukin (IL) 6 and TNF-α are potent inhibitors of adiponectin expression and secretion in human white adipose tissue biopsies or cultured adipose cells [36, 37]. Unlike most adipokines, adiponectin expression and serum concentrations are reduced in obese and insulin-resistant states. *In vivo*, high plasma adiponectin levels are associated with reduced risk of myocardial infarction (MI) in men as demonstrated in a case control study that enrolled 18,225 subjects without cardiovascular disease who were followed up for 6 years [38]. Although further studies are needed to clarify whether adiponectin independently predicts coronary heart disease events, in men with Type 2 diabetes, increased adiponectin levels are associated with a moderately decreased risk of coronary heart disease. The association seems to be mediated in part by the effects of adiponectin on high-density lipoprotein (HDL) cholesterol, through parallel increases in both. Although many mechanisms have been hypothesized, exactly how adiponectin affects HDL cholesterol remains largely unknown. In American Indians, who are particularly at risk of obesity and diabetes, adiponectin does not correlate with the incidence of coronary heart disease [39, 40]. Two case control studies in

obesity-prone Pima Indians and in Caucasians suggest that individuals with high adiponectin concentrations are less likely to develop Type 2 diabetes than those with low concentrations [41, 42].

Tumor Necrosis Factor- α

TNF-α is a 26-kDa transmembrane protein that is cleaved into a 17-kDa biologically active protein that exerts its effects via type I and type II TNF-α receptors. Within adipose tissue, TNF α is expressed by adipocytes and stromovascular cells [24]. TNF-α, a multipotential cytokine with several immunologic functions, was initially described as a cause of tumour necrosis in septic animals and associated with cachexia-inducing states, such as cancer and infection [43]. In 1993 it was the first product from adipose secreted tissue to be proposed as a molecular link between obesity and insulin resistance [44–47]. Several potential mechanisms for TNF- α's metabolic effects have been described. First, TNF- α influences gene expression in metabolically important tissues such as adipose tissue and liver. In adipose tissue, TNF-α represses genes involved in uptake and storage of NEFAs and glucose, suppresses genes for transcription factors involved in adipogenesis and lipogenesis, and changes expression of several adipocyte secreted factors including adiponectin and IL-6. In liver, TNF-α suppresses expression of genes involved in glucose uptake and metabolism and fatty acid oxidation and increases expression of genes involved in *de novo* synthesis of cholesterol and fatty acids. Second, TNF α impairs insulin signaling. This effect is mediated by activation of serine kinases that increase serine phosphorylation of insulin receptor substrate-1 and −2, making them poor substrates for insulin receptor kinases and increasing their degradation [46]. TNF-α also impairs insulin signaling indirectly by increasing serum NEFAs, which have independently been shown to induce insulin resistance in multiple tissues [45].

A recent elegant hypothesis suggested that in obese rats TNF-α production from the fat cuff around the arteriole origin inhibits insulin-stimulated nitric oxide synthesis and results in unopposed vasoconstriction - a mechanism termed 'vasocrine' signalling [48]. These findings suggest a homology between vasoactive periarteriolar fat and visceral fat, which may explain relationships among visceral fat, insulin resistance and vascular disease. Several mechanisms could account for the effect of TNF-α on obesity-related insulin resistance such as increased release of FFA by adipocytes, reduced adiponectin synthesis and impaired insulin signalling. *In vitro* and *in vivo* studies show TNF-α inhibition of insulin action is, at least in part, antagonized by TZD, further supporting the role of TNF-α in insulin resistance [49]. Acute ischemia also increases TNF-α level. A nested case control study in the Cholesterol and Recurrent Events (CARE) trial compared TNF-α concentrations in case and control groups. Overall, TNF-α levels were significantly higher in cases than controls. The excess risk of recurrent coronary events after MI was predominantly seen among patients with the highest TNF-α levels [50].

Interleukin-6

IL-6, secreted by many cell types, including immune cells, fibroblasts, endothelial cells, skeletal muscle and adipose tissue, is another cytokine associated with obesity and insulin resistance [51]. However, only about 10 % of the total IL-6 appears to be produced exclusively by fat cells [52]. Omental fat produces threefold more IL-6 than subcutaneous adipose tissue, and adipocytes isolated from the omental depot also secrete more IL-6 than fat cells from the subcutaneous depot [53]. IL-6 circulates in multiple glycosylated forms ranging from 22 to 27-kDa in size. The IL-6 receptor (IL-6R) is homologous to the leptin receptor and exists as both an approximately 80-kDa membrane-bound form and an approximately 50-kDa soluble form. A complex consisting of the ligand-bound receptor and two homodimerized transmembrane gp130 molecules triggers intracellular signaling by IL-6. Within adipose tissue, IL-6 and IL-6R are expressed by adipocytes and adipose tissue matrix [24].

Expression and secretion of IL-6 are 2 to 3 times greater in visceral relative to sc adipose tissue [24, 54]. In contrast to TNF α, IL-6 circulates at high levels in the bloodstream, and as much as one third of circulating IL-6 originates from adipose tissue. Adipose tissue IL-6 expression and circulating IL-6 concentrations are positively correlated with obesity, impaired glucose tolerance, and insulin resistance. Both expression and circulating levels decrease with weight loss. Furthermore, plasma IL-6 concentrations predict the development of type 2 diabetes and cardiovascular disease and MI [55, 56]. Weight loss significantly reduces IL-6 levels in adipose tissue and serum. While as administration of IL-6 to healthy volunteers increased blood glucose in a dose-dependent manner probably by inducing resistance to insulin action [57].

Inhibition of insulin receptor signal transduction in hepatocytes might underlie the effects of IL-6 on insulin resistance. This could be mediated, at least in part, by suppression of cytokine signalling-3 (SOCS-3), increased circulating FFA (from adipose tissue) and reduced adiponectin secretion [58, 59].

It is interesting to note the central role of IL-6 in energy homeostasis. IL-6 levels in the CNS are negatively correlated with fat mass in overweight humans, suggesting central IL-6 deficiency in obesity. Central administration of IL-6 increases energy expenditure and decreases body fat in rodents. Furthermore, transgenic mice overexpressing IL-6 have a generalized defect in growth, which includes reduced body weight and decreased fat pad weights [60]. On the other hand, mice with a targeted deletion of IL-6 develop mature-onset obesity and associated metabolic abnormalities, which are reversed by IL-6 replacement, suggesting that IL-6 is involved in preventing rather than causing these conditions [61]. Hence, IL-6 has different effects on energy homeostasis in the periphery and the CNS.

Adipocyte Trypsin

Adipocyte trypsin (ADIPSIN) is a secreted serine protease related to complement factor D. In humans, adipose tissue also releases substantial amounts of acylation-stimulating protein (ASP), a protein derived from the interactions of ADIPSIN with complement C3 and factor B. Although ASP is known to stimulate triglyceride storage in adipose cells through stimulation of glucose transport, enhancement of fatty acid re-esterification and inhibition of lipolysis the receptor and signalling pathways mediating ASP effects have not yet been characterized [62]. ASP influences lipid and glucose metabolism via several mechanisms. ASP promotes fatty acid uptake by increasing lipoprotein lipase activity, promotes triglyceride synthesis by increasing the activity of diacylglycerol acyltransferase, and decreases lipolysis and release of NEFAs from adipocytes. ASP also increases glucose transport in adipocytes by increasing the translocation of glucose transporters and enhances glucose-stimulated insulin secretion from pancreatic β cells [63]. Most, but not all studies in humans report substantial increases in plasma ASP in obese subjects although it has still to be established whether these high circulating levels reflect increased ASP activity or resistance to ASP [64]. Resistance to ASP could redirect fatty acid flux away from adipose tissue towards the liver [63].

Resistin

Human resistin (resistance to insulin) is a dimeric protein containing 108 amino acids Holocomb et al. first described the gene family and its tissue-specific distribution, identifying a protein (FIZZ1) that was up-regulated in the asthmatic lung in bronchoalveolar lavages of mice with experimentally induced asthma [65]. Found in inflammatory zone 1, FIZZ1 is also known as resistin-like molecule a (RELMα). One of two homologues, FIZZ2, also known as RELMβ, was localized in proliferating epithelia at the base of intestinal crypt. A third homologue, FIZZ3, also known as 'resistin' or adipocyte-specific secretory factor was later identified. As TZD suppresses resistin production in 3 T3-L1 adipocytes, Steppan *et al*. suggested resistin could be a link between obesity and insulin resistance [66].

Initial studies suggested that resistin had significant effects on insulin action, potentially linking obesity with insulin resistance [67]. Treatment of cultured adipocytes with recombinant resistin impairs insulin-stimulated glucose uptake whereas antiresistin antibodies prevent this effect [66, 68]. In murine models, obesity is associated with rises in circulating resistin concentrations. Resistin increases blood glucose and insulin concentrations and impairs hypoglycaemic response to insulin infusion [69].

In obese mice, antiresistin antibodies decrease blood glucose and improve insulin sensitivity [70]. All these data support the hypothesis that in obese rodents, resistin induces insulin resistance and contributes to impaired insulin sensitivity.

In humans, the physiological role of resistin is far from clear and its role in obesity and insulin resistance and/or diabetes is controversial. In humans, as resistin is primarily produced in peripheral blood monocytes and its levels correlate with IL-6 concentrations, the question of its inflammatory role has been raised [68, 71, 72]. Four genes encode for resistin in the mouse and two in humans [73]. The human resistin gene is localized on chromosome 19. Some genetic case control studies demonstrated genetic variations in the resistin gene are associated with insulin resistance and obesity in humans [74–76].

Plasminogen Activating Inhibitor (PAI)-1

Plasminogen activating inhibitor (PAI)-1, synthesized in the liver and in adipose tissue, regulates thrombus formation by inhibiting the activity of tissue-type plasminogen activator, an anticlotting factor. PAI-1 serum concentrations increase with visceral adiposity decline with caloric restriction, exercise, and weight loss and metformin treatment [77]. Visceral tissues secrete significantly more PAI-1 than subcutaneous tissues from the same subject [78]. Plasma PAI-1 levels are elevated in obesity and insulin resistance, are positively correlated with features of the metabolic syndrome, and predict future risk for type 2 diabetes and cardiovascular disease [79, 80]. Plasma PAI-1 levels are strongly associated with visceral adiposity, which is independent of other variables including insulin sensitivity, total adipose tissue mass, or age. Weight loss and improvement in insulin sensitivity due to treatment with metformin or thiazolidinediones (TZDs) significantly reduce circulating PAI-1 levels.

Proteins of the Renin Angiotensin System (RAS)

Several proteins of the classic RAS are also produced in adipose tissue. These include renin, angiotensinogen (AGT), angiotensin I, angiotensin II, angiotensin receptors type I (AT1) and type 2 (AT2), angiotensin-converting enzyme (ACE) etc. Expression of AGT, ACE, and AT1 receptors is higher in visceral compared with subcutaneous adipose tissue [81–83]. Angiotensin II mediates many of the well-documented effects of the RAS including increasing vascular tone, aldosterone secretion from the adrenal gland, and sodium and water reabsorption from the kidney, all of which contribute to blood pressure regulation. Thus, the adipose tissue RAS is a potential link between obesity and hypertension. Inhibition of the RAS, either by inhibition of ACE or antagonism of the AT1 receptor decreases weight and improves insulin sensitivity in rodents. Although several large randomized trials have shown that ACE inhibitors reduce the incidence of Type 2 diabetes, a direct effect of RAS inhibition on insulin sensitivity in humans has been observed in some studies but not others [84]. In addition to its well-known effects on blood pressure, the RAS influences adipose tissue development. Components of the RAS such as AGT and angiotensin II are induced during adipogenesis . Angiotensin II promotes adipocyte growth and differentiation, both directly by promoting lipogenesis and indirectly by stimulating prostaglandin synthesis [81]. Increased AGE production could also contribute to enhanced adipose mass because angiotensin II is believed to act locally as a trophic factor for new adipose cell formation. In human adipose tissue, aromatase

activity is principally expressed in mesenchymal cells with an undifferentiated preadipocyte phenotype [85].

Enzymes Involved in the Metabolism of Corticosteroids

Although the adrenal gland and gonads serve as the primary source of circulating steroid hormones, adipose tissue expresses a full arsenal of enzymes for activation, interconversion, and inactivation of steroid hormones [86, 87]. Several steroidogenic enzymes are expressed in adipose tissue including cytochrome P450-dependent aromatase, 3 β hydroxysteroid dehydrogenase (HSD), 3 α HSD, 11 β HSD1, 17 β HSD, 7 α hydroxylase, 17α hydroxylase, 5 α reductase, and UDP-glucuronosyltransferase 2B15.

Given the mass of adipose tissue, the relative contribution of adipose tissue to whole body steroid metabolism is quite significant, with adipose tissue contributing up to 100 % of circulating estrogen in postmenopausal women and 50 % of circulating testosterone in premenopausal women [86, 87]. The sexually dimorphic distribution of adipose tissue in humans has implicated sex steroids in the regulation of adiposity and body fat distribution. Premenopausal females tend to have increased lower body or subcutaneous adiposity, whereas males and postmenopausal females tend to have increased upper body or visceral adiposity. Expression of 17 β HSD is decreased relative to aromatase in subcutaneous adipose tissue but increased relative to aromatase in visceral adipose tissue. The ratio of 17 β HSD to aromatase is positively correlated with central adiposity, implicating increased local androgen production in visceral adipose tissue.

White adipose tissue also plays a role in glucocorticoid metabolism [88, 89].

This tissue specific glucocorticoid metabolism is primarily determined by the enzyme 11 β HSD1, which catalyzes the conversion of hormonally inactive 11 β ketoglucocorticoid metabolites (cortisone in humans and 11-dehydrocorticosterone in mice) to hormonally active 11 β hydroxylated metabolites (cortisol in humans and corticosterone in mice).

Although 11 β HSD1 amplifies local glucocorticoid concentrations within adipose tissue, it does not contribute significantly to systemic glucocorticoid concentrations. Tissue-specific dysregulation of glucocorticoid metabolism by 11 β HSD1 has been implicated in a variety of common medical conditions including obesity, diabetes, hypertension, dyslipidemia, hypertension, cardiovascular disease, and polycystic ovarian syndrome [88, 89]. In human idiopathic obesity, 11 β HSD1 expression and activity are also decreased in liver and increased in adipose tissue and are highly correlated with total and regional adiposity. Finally, pharmacological inhibition of 11 β HSD1 in humans increases insulin sensitivity suggesting a potential therapeutic role for 11 β HSD1 inhibition in the treatment of obesity and insulin resistance [90, 91].

Adipokines and Atherosclerosis

Adipokines play a significant role in the pathogenesis of atherosclerosis. TNF-α activates the transcription factor nuclear factor-κβ, with subsequent inflammatory changes in vascular tissue. These include increased expression of intracellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1, which enhances monocyte adhesion to the vessel wall, greater production of MCP-1 and M-CSF from endothelial cells and vascular smooth muscle cells and up-regulated macrophage expression of inducible nitric oxide (NO) synthase, interleukins, superoxide dismutase, etc. [92–97]. Leptin, especially in the presence of high glucose, stimulates macrophages to accumulate cholesterol [98]. IL-6 exerts proinflammatory activity in itself and by increasing IL-1 and TNF-α. Importantly, IL-6 also stimulates liver production of C-reactive protein, which is considered a predictor of atherosclerosis. IL-6 may also influence glucose tolerance by regulation of visfatin. Visfatin, a newly discovered adipocytokine in the human visceral fat, exerts insulin-mimetic effects in cultured cells and lowers plasma glucose levels in mice through activation of the insulin receptor [97]. PAI-1 concentrations,

which are regulated by the transcription factor nuclear factor-κβ, are abnormally high in hyperglycaemia, obesity and hypertriglyceridaemia, because of the increased PAI-1 gene expression [99]. PAI-1 inhibits fibrin clot breakdown, thereby favouring thrombus formation upon ruptured atherosclerotic plaques [100]. In humans, circulating PAI-1 levels correlate with atherosclerotic events and mortality, and some studies suggest PAI-1 is an independent risk factor for coronary artery disease [101]. Angiotensinogen is a precursor of angiotensin II (AngII), which stimulates ICAM-1, VCAM-1, MCP-1 and M-CSF expression in vessel wall cells [102]. AngII also reduces NO bioavailability with loss of vasodilator capacity and with increased platelet adhesion to the vessel wall [103]. Furthermore, endothelial dysfunction is indicative of the preclinical stages of atherosclerosis and is prognostic of future cardiovascular events [104, 105]. Therefore, high concentrations of proinflammatory adipokines may contribute to development of endothelial dysfunction and accelerate the process of atherosclerosis.

Conclusion

The traditional role attributed to white adipose tissue is energy storage. Now it is proven that the white adipose tissue is a major secretory and endocrine organ involved in a range of functions beyond simple fat storage. Adipose tissues secrete adipokines which perform various functions. However, the metabolic effects of adipokines are a challenging and an emerging area of research and in-depth understanding of their pathophysiology and molecular actions will undoubtedly lead to the discovery of effective therapeutic interventions. Reducing adipose tissue mass will prevent the metabolic syndrome, atherosclerosis and cardiovascular events. Despite the new findings in the field of adipokines, researchers are still led to focus back on obesity as an essential primary target in the continued effort to reduce the risk of developing the metabolic syndrome and Type 2 diabetes, challenges of this millennium, with its associated cardiovascular complications.

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Brown Adipose Tissue and Obesity

2

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Introduction

Adipose tissue is a connective tissue predominantly composed by adipocytes and is considered as a major endocrine organ. Classically it has been described the existence of two types of adipose tissue, the white adipose tissue (WAT), formed mainly by white adipocytes, and the brown adipose tissue (BAT), commonly composed by brown adipocytes. However, recently the so called "brite" or "beige" adipose tissue has been found within certain WAT depots, and appear functionally similar to classical brown adipocytes. BAT and WAT have different structure, composition and function. Adipose tissue has two types of depots, subcutaneous and visceral, and their respective amounts vary in relation to strain, age, gender, environmental and nutritional conditions [1–3].

BAT uniquely exists in mammals and presents a thermogenic function dissipating energy as heat [1]. Initially, scientific community thought that BAT was present only in newborns and children, but later, presence of BAT was discovered in adult humans exposed to cold or in pheochromocytoma where there is a hyper-adrenergic stimulation [4]. The BAT tissue was found in adult humans trying to identify metastatic cancers with ^{18}F-fluorodeoxyglucose (FDG), an intravenously administered radioactive glucose analogue, in combination with positron emission tomography (FDG-PET). Afterward, its composition was determined by combining FDG with computed tomography (FDG/CT) [5, 6].

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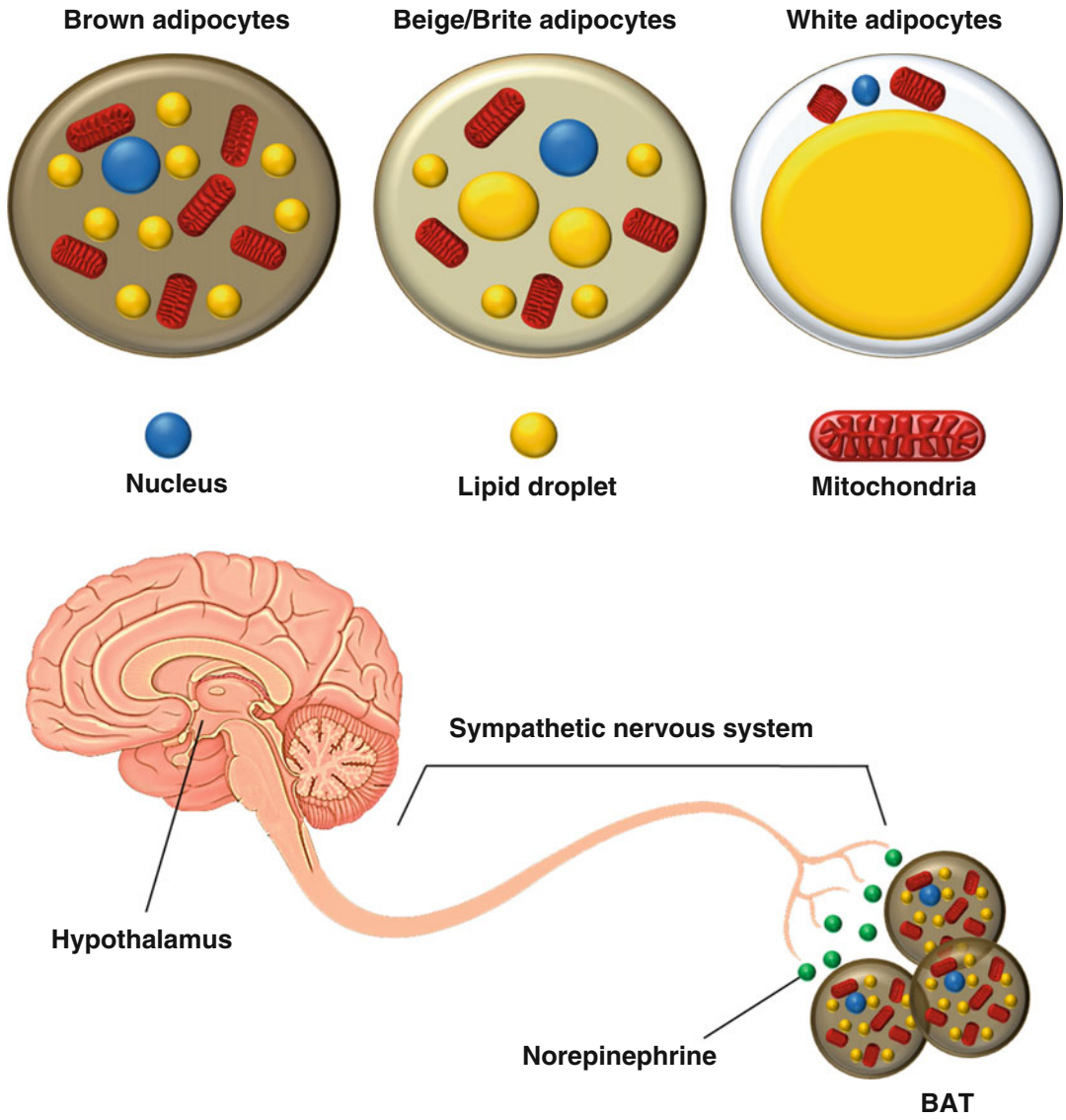

Fig. 2.1 (**a**) Types of adipocytes. Differences in cytoplasmatic composition and morphology of drops lipids, mitochondrias and nuclei. (**b**) BAT activation

During the neonatal period, BAT plays an important thermogenic function helping to counteract the cold stress of birth [7, 8]. In adult mammals, it has been observed that BAT not only maintains the temperature homeostasis of the body to acute or chronic cold exposure, but also in the heat production to maintain an equilibrium between the food intake and energy expenditure [1, 9]. This provides a protective mechanism against energy overload [10–12].

BAT characteristics are related with the functions performed: (i) it is highly vascularised and innervated in comparison with WAT, and (ii) it is composed of brown adipocytes which differ from white adipocytes in several features. White adipocytes present a compressed nucleus by lipids organized in a single large lipid droplet while brown adipocytes lipids have a roughly round nucleus organized as multiple small droplets. Moreover, mitochondria are large, numerous and are endowed with laminar cristae in brown adipocytes, whereas in white adipocytes mitochondrias are small and elongated, with randomly oriented cristae [3, 13, 14] (Fig. 2.1a).

Brown adipocytes express a specific mitochondrial protein, the uncoupling protein 1 (UCP1). This mitochondrial uncoupling protein transforms chemical energy into heat through uncoupling oxidative phosphorylation from ATP synthesis and it is considered as the molecular marker of BAT [1, 15]. The activation of brown adipocytes and subsequent activation of the UCP1 is through the control of the hypothalamus, which drives the release of norepinephrine (NE) by the sympathetic nervous system (SNS) that innervates BAT (Fig. 2.1b). This process leads to the hydrolysis of the triglycerides (TG) stored in the lipid droplets, and the released fatty acids activate UCP1 [9, 13].

Recently, it was discovered that white adipocytes can transdifferentiate into brown adipocytes, also known as brite (brown in white) or beige adipocytes. This process occurs in response to exposure of cold and β3-adrenergic receptors (AR) agonist stimulation and/or from the differentiation and maturation of white preadipocyte precursors [16]. When brite adipocytes are activated present many biochemical and morphological characteristics of BAT such as multilocular morphology and most notably the presence of UCP1 [2, 9]. Brite adipocytes could have a dual function, can acts as white adipocytes and store lipids, or can behave as brown adipocytes and dissipate energy when initiated by either cold exposure, stimulatory metabolic hormones, pharmacologic activator or sympathetic stimuli [17]. In fact, it has been reported that UCP1+ adipocytes could appear in WAT of mice in response to cold exposure, or different stimuli such as administration of PPARγ agonist, exposure to cardiac natriuretic peptides, FGF21, irisin or treatment with β-AR agonist [18–23].

BAT activity has an effect on metabolic disorders, reducing obesity and the associated risk of developing diabetes [13]. Anti-obesity effects of BAT have been demonstrated in experiments of genetic inactivation or upregulating UCP1 expression in murine models, and consequently these therapeutic effects were also evident in obesity related disorders, such as Type 2 diabetes [14]. Likewise, brite adipocytes have been shown to have anti-obesity and anti-diabetic activities in rodent models [17].

In this chapter, we present the main characteristics of BAT, by highlighting that makes it unique and different from WAT, including its localization in humans, origin and differentiation, physiology and molecular regulation. Moreover, we show its role in obesity and associated pathologies and how we can harness the anti-obesity potential for future therapeutic strategies.

Anatomical Locations of BAT in Humans

Human newborns and children have large deposits of BAT, whereas adults suffer an involution of this tissue, and its presence and activity are more restricted [4]. The major locations of subcutaneous BAT include depots in interscapular, paraspinal, supraclavicular and axillary sites [5, 13]. Also, we can find depots in the anterior abdominal wall and in the inguinal area [5]. In children, the interscapular, paraspinal and supraclavicular BAT accumulations are higher than in adults [15]. Furthermore, BAT has visceral localizations that include perivascular (aorta, common carotid artery, brachiocephalic artery, paracardial mediastinal fat, epicardial coronary artery and cardiac veins, internal mammary artery, and intercostal artery and vein), periviscus (heart, trachea, major bronchi at lung hilum, oesophagus, greater omentum and transverse mesocolon) and around solid organs (pancreas, kidney, adrenal, liver and hilum of spleen) [5].

The distribution of BAT depots is similar in men and women, but its mass and activity are higher in women. In fact, BAT was more prominent in cervical and supraclavicular zone in woman than in men at ratio 2:1 as detected by FDG-PET/CT [4]. Moreover, the reduction of BAT mass with age is more rapidly in males, while moderately declines in women [24]. Rodriguez-Cuenca et al. correlated the sexual dimorphism in rats with differences in lipolytic and thermogenic adrenergic pathway activation and suggest that these differences in adrenergic control could be responsible for the higher mitochondrial recruitment with a higher cristae density in female rats [25].

One external factor, the cold, appears to be associated with a higher mass of BAT. Studies of biopsy specimens in northern Finland revealed more BAT around the neck arteries in outdoor workers than in indoor workers [26]. This result is in concordance with the correlation observed between the prevalence of detectable BAT and outdoor temperature [4].

Regarding to relationship of age and BAT, BAT develops from the fifth gestational week, reaches maximum expression around birth, and in the past it has been thought that declines over the next 9 months of the birth [27]. However, recently it has been described the presence of brown adipocytes in classical subcutaneous localization and in WAT depots in non-obese children up to 10 years of age [28]. The involution of BAT with age could be related to heat production for the maintenance of body temperature, since the increase of body involves a decrease in surface/volume ratio and a decreased requirement of BAT for heat production [1, 9].

Origin and Differentiation

Despite the fact it was previously considered that brown adipocytes come from the same progenitor cell that white adipose cells, the lineage analysis revealed that their embryological origin is different. It has been determined that BAT precursor cells express myogenic factor 5, (Myf5+), which is also found in myoblasts, suggesting that BAT precursors develop from a progenitor close to skeletal muscle cells [29–31] (Fig. 2.2).

It is known that brown adipocytes initially arise in the fetus and form discrete depots in the interscapular and perirenal BAT and it is thought that they come from dermatomal precursors (Fig. 2.2) [8, 32]. In contrast, little is known about the developmental origin of "beige" adipocytes. The mRNA levels of general adipocyte markers as well as typical brown markers were very similar in classical brown and brite adipocytes populations [33]. However, it has been reported that there are different gene expression signatures to distinguish classical brown from brite adipocytes suggesting a different cell lineage from classical brown cells [17, 20]. Genes related with the presence of brown adipocytes include Myf5, PRDM16, BMP7, BMP4, and Zic1, while transmembrane protein 26 (Tmem26), CD137, and T-box 1 (Tbx1) are considered unique markers expressed by beige cells [17].

During the fetal life, brown adipocyte differentiation involves a cascade of transcriptional factor interactions similar to white adipocytes. The transcription factors peroxisome proliferator-activated receptor gamma (PPARγ) and the CCAAT/enhancer-binding proteins (C/EBP) family members (i.e. C/EBPα, C/EBPβ, and C/EBPδ) are the main key players which form part of the transcriptional cascade and direct differentiation of both brown and white adipocytes. However, during the development of brown adipose tissue an increase in expression of C/EBPβ and C/EBPδ comes before C/EBPα activation, then, PPARγ and C/EBPα coordinate the expression of many adipocyte genes to induce adipocyte differentiation [34].

It has been described that depending on the expression of the transcriptional positive regulatory domain containing 16 (PRDM16) cell fate switch between skeletal myoblasts and brown adipocytes. In fact, in the myogenic precursors the expression of PPARγ is induced by the PRDM16-C/EBP-β complex resulting in the activation of the brown adipogenic gene program [8]. Other transcriptional regulator of brown adipocytes is the master regulator of mitochondrial biogenesis, PPARγ coactivator-1α (PGC-1α) which is essential in brown adipogenesis since it stimulates UCP1 expression. In fact, UCP1 is responsible for the rapid generation of large amounts of heat at birth [35]. In addition, concentration gradients of certain morphogens and other secreted signals are implicated in the formation of brown adipocytes and may regulate their developmental patterning during embryogenesis. The morphogenic signals implicated includes Wnt- (named after the Wingless and INT proteins in *Drosophila*), the bone morphogenetic protein- (BMP), the fibroblast growth factor (FGF), and the Hedgehog-signaling pathways [36]. For instance, recently it has been shown that BMP7 and BMP4 induce the formation of brown

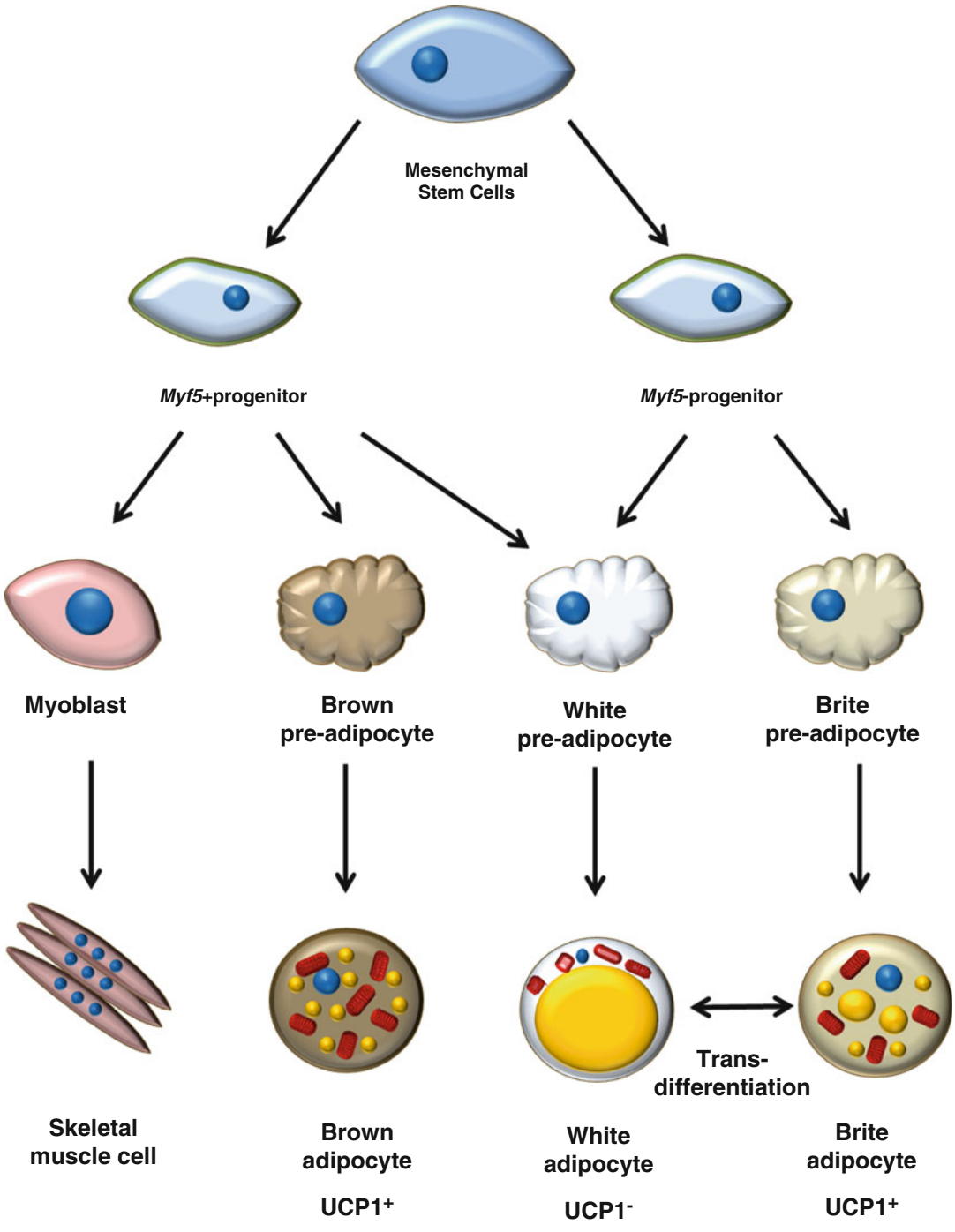

Fig. 2.2 Origen of adipocytes: from mesenchymal stem cells up to adipocyte progenitors. *Myf5* progenitor cells give rise to brown adipocytes and to skeletal muscle. Despite *Myf5* negative progenitors are common precursors for both beige and white adipocytes, recent studies suggest that white adipocytes can also derive from *Myf5*$^{+}$. Beige adipocytes can derive from the transdifferentiation of white adipocyte or from beige preadipocyte. Like brown adipocytes, beige adipocytes can express UCP1

adipocytes [37]. Similarly to BMPs, β-AR signaling is considered important for the development of brown and beige cells. Thus, adrenergic stimulation of β1-AR induces preadipocyte proliferation [38].

Concerning the developmental origin of beige cells several hypotheses have emerged: (i) One of them postulates that beige adipocytes came from the direct transformation or transdifferentiation of existing white adipocytes (Fig. 2.2). This approach is based on the observation of an increase in brown adipocytes but not in preadipocytes upon cold acclimatization [33, 39]. In addition, these cells also had a mixed mitochondrioma with classic brown and white mitochondria, suggesting an intermediate state between mature white adipocytes and brown adipocytes [39]. However, as only a subset of apparently white adipocytes is capable of turning into brite adipocytes upon cold adaptation, it is not well understood whether it is due to different white adipocyte populations or due to different microenvironments [40]. (ii) Others studies found that Myf5 precursors are not the exclusive source of brown adipocytes and contribute more to the mature white and brite adipocyte populations than previously thought [41, 42]. Recently, Sanchez-Gurmaches and Guertin quantified the Myf5 lineage contribution to the mature brown and white adipocyte population, proposing that brown, white, and brite adipocytes originate from multiple developmental lineages that are distributed heterogeneously in depot-specific patterns. They found that Myf5 lineage distribution in adipose tissue changes in response to modifiable and non-modifiable factors suggesting that adipocyte lineages may selectively expand in response to certain factors. They also observed that adipocyte lineages can compensate for each other indicating that lineage plasticity exists and that the degree of plasticity varies depending upon the depot [42]. For example, it has been described that the epididymal depot remains purely white fat in comparison to inguinal adipose tissue capable of transdifferentiation [40]. These results show a high degree of heterogeneity of adipogenic cells suggesting the relevance of physiological local signals that regulate their fate and that need to be determined.

Regulation of BAT Thermogenesis

BAT possesses a number of specialized features enabling it to function as a thermoregulatory organ. Apart from lipids stores in multilocular lipid droplets, brown adipocytes display more abundant mitochondria enriched in UCP1, which is located in the inner mitochondrial membrane. This UCP1 uncouples substrate oxidation from ATP production and as result heat is produced [1]. High vascularisation of BAT allows sufficient substrate and oxygen supply as well as the efficient distribution of heat within the body.

The thermogenic activity is primarily regulated by the SNS, reflected by the strong innervation of BAT by sympathetic nerve fibers and the high density of β-AR that are responsible for its activation. In the case of cold stimulus, input from the skin sensitive nerves are received and transmitted to a center for the integration of the thermal information. Likewise, the energy status is provided by inputs from the arterial chemoreceptor in sensory neurons about a variety of metabolic signals such as fuel substrate and oxygen [10–12, 43, 44]. Both cold stimulus and energy status regulate BAT activation through sympathetic neurons. Although this is the main way to control BAT activity, hormones (thyroid hormone triiodothyronine), cytokines, and other circulating factors also are involved.

Cold sensation triggers to stimulation of the hypothalamus which activates sympathetic nerve that highly innervates BAT. This activation causes the release of NE neurotransmissor that binds to β-ARs, which couple to Gα G-proteins activating downstream cAMP-PKA signalling that ends by increasing thermoregulatory gene expression, like UCP, and his activation, mitochondrial biogenesis and lipolysis (Fig. 2.3). This metabolic process is accomplished by adipose triglyceride lipase (ATGL) activation that hydrolyzes TG stored in the lipid droplet to free fatty acids (FFAs), which undergo β-oxidation [1, 45]. Thereby, respiratory chain proteins from the mitochondrial internal membrane generate a proton electrochemical gradient between the mitochondrial matrix and the intermembrane space, but the presence of UCP1 mediates the re-entry

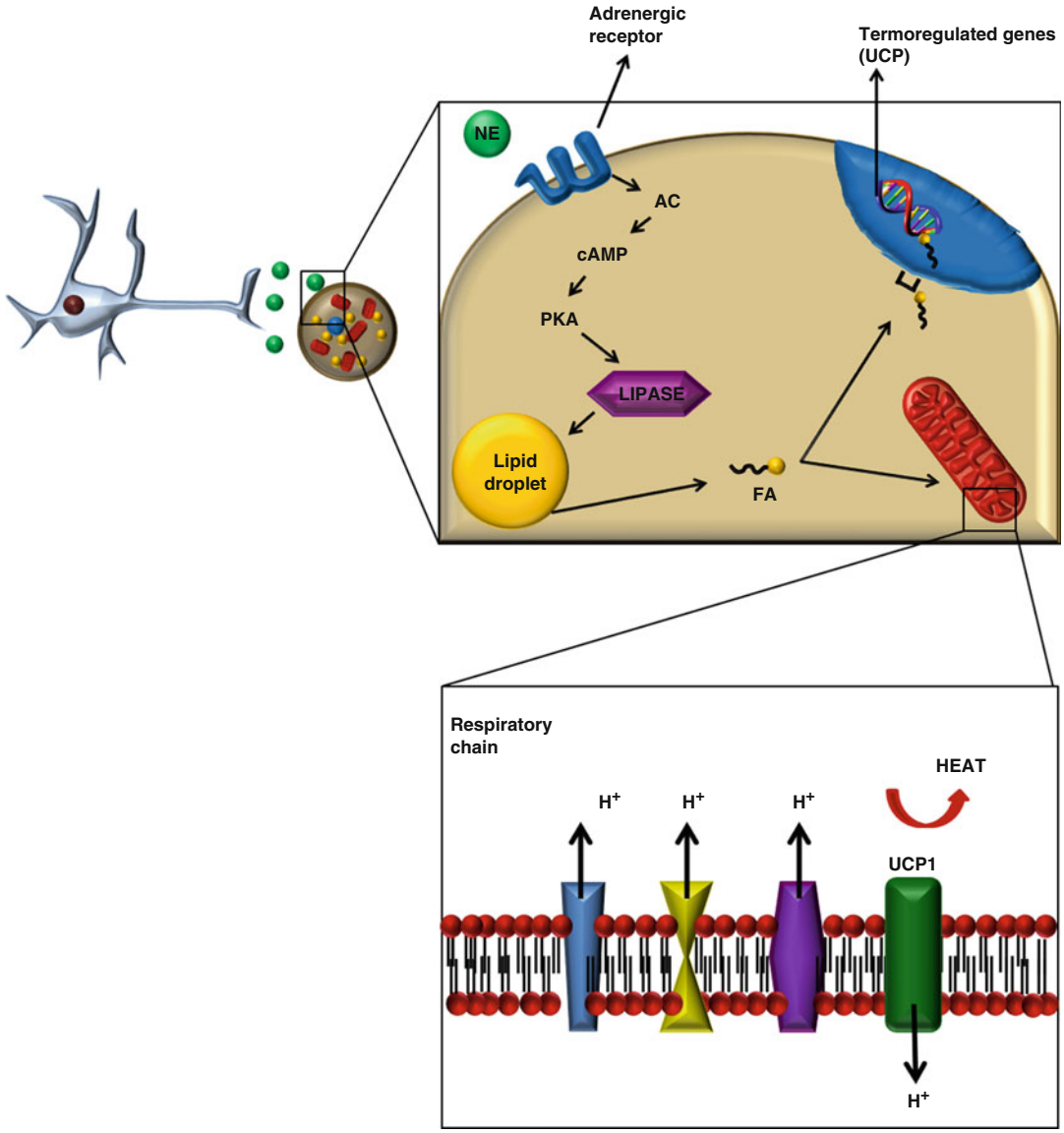

Fig. 2.3 Molecular machinery of brown adipocytes activation. The sympathetic nervous system triggers intracellular signalling events that lead to increased expression of UCP1 and other thermogenic genes, mitochondrial biogenesis and lipolysis. FFAs released by this process is followed by his oxidation that finally produces heat

of protons into the mitochondria and dissipates energy as heat instead of producing adenosine triphosphate (ADP) (Fig. 2.3) [46, 47]. In addition, apart from cAMP-PKA signalling, cGMP–PKG pathway shares the same final target. This pathway is activated by released cardiac natriuretic peptides in response to physical exercise or cold exporure, which can induce lipolysis and the expression of thermogenic genes [48, 49].

BAT thermogenesis requires the consumption of energy stores, initially those present in the BAT lipid droplets and, with extended BAT activation, those derived from catabolism of WAT, which provide FFAs to locally activate UCP-1 and to serve as substrates for oxidation [1, 50]. The substrate uptake machinery is also upregulated allowing to lipids released by WAT to be taken up by BAT [1]. Whether there is enough

activation that allows high TG metabolization, it would have an effect on body weight [51]. Apart from this cascade of intracellular signalling activation by central nervous system, chronic cold exposure will also induces proliferation and differentiation of brown adipocyte precursors, thus increasing thermogenic capacity [1].

BAT, Obesity and Obesity-Related Diseases

Obesity no longer refers only to being overweight. The World Health Organization (WHO) has officially recognized obesity as a chronic disease and it is defined as an accumulation of adipose tissue that is of sufficient magnitude to impair health (WHO, 2014).

Obesity is linked to health risks and can lead to various metabolic disorders, such as Type II diabetes, cardiovascular disease, hypertension and certain cancers. The fundamental cause of obesity is an energy imbalance between energy input and output. Generally, this may be due to the increased intake of energy-dense foods and decreased physical activity [52].

Obesity, well known to be associated with a number of co-morbidities, including insulin resistance and Type 2 diabetes, has become a major public health problem in recent decades reaching epidemic proportions, not only in high-income countries, but also in most middle-income societies. Excess weight is usually defined by the body mass index or BMI. The normal BMI range is 18.5–25 kg/m^2, although the range may vary for different countries. Individuals with a BMI above 30 kg/m^2 are classified as obese; those with a BMI between 25 and 30 kg/m^2 are considered to be overweight. In general, the term obesity applies to both the obese and the overweight subjects.

WAT is the dominant type of adipose tissue distributed throughout the human body. It functions primarily to store excess energy in the form of TGs. As a person's weight increases, WAT is expanded by both increased adipocyte size (hypertrophy) and increased adipocyte numbers (hyperplasia) [52]. More than the total body weight, the distribution of the stored fat is of importance for the development of obesity and its co-morbidities. Thus, central or visceral obesity, in which fat accumulates in the trunk and in the abdominal cavity (in the mesentery and around the viscera), is associated with a much higher risk for several diseases than excess subcutaneous fat accumulation. Obesity has profound effects on tissue insulin sensitivity, and therefore on systemic glucose homeostasis [53].

Distribution areas of fat depots in the body play contrasting healthy and pathological metabolic roles. Thus, BAT has beneficial effects, subcutaneous WAT (SAT) especially gluteofemoral, appears metabolically protective, and visceral WAT, together with intra-abdominal tissue lipid, are considered potentially harmful. Variation in these different lipid depots may therefore impact significantly on metabolic health. In fact, it has been demonstrated that humans who remain insulin-sensitive despite being obese have lower amounts of intra-abdominal fat compared to insulin-resistant obese humans. There are several suggestions as to the means by which intra-abdominal fat creates its adverse effects: (i) lability of lipolysis with direct drainage of fatty acids to the liver via the portal vein; (ii) the excessive production of inflammatory molecules from immune cells whose numbers may be higher in visceral fat than other fat depots in lean and obese humans; (iii) as possible mediator of inflammation in liver and kidney [54, 55]. Also, it is possible that visceral fat is the source of an as-yet-undiscovered adipokine(s) with adverse systemic effects, including inhibition of adiponectin secretion, which is strongly linked to visceral fat volume [56].

Because BAT was recently discovered in adult humans and is correlated inversely with obesity, it has gained a considerable amount of attention with regard to efforts to overcome obesity by burning excess energy. Recent studies suggest an inverse correlation between BAT activity and BMI as well as between BAT activity and percentage of body fat [4]. Moreover, increased BAT metabolism may significantly contribute to energy expenditure during acute cold exposure in humans [57]. Therefore, adults also have

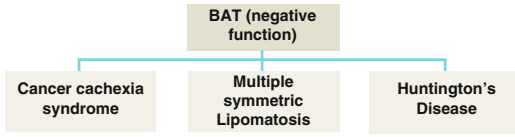

Fig. 2.4 Pathologies related whit a negative role of BAT in human

metabolically active BAT that may play an important role in energy homeostasis, and it can be induced to increase glucose uptake [58]. In fact, characteristic genes of human BAT have been shown to negatively correlate with obesity and insulin sensitivity [59].

Metabolic syndrome is a disorder that includes numerous diseases or risk factors such as impaired glucose (diabetes), low HDL-cholesterol, increased production of TGs, high blood pressure and abdominal obesity, factors that all are associated with obesity. Thereby, dysfunctional adipose tissue with low-grade, chronic and systemic inflammation links the metabolic and vascular pathogenesis including dyslipidemia, low-grade inflammation and insulin resistance. This dysfunctional adipose tissue is a hallmark of disorders such as Type 2 diabetes and cardiovascular disease. In addition, factors such as lifestyle and genetic predisposition are also implicated [59].

Often BAT is associated with improving benefits in obesity in adult humans, but there are some diseases or conditions where BAT plays an antagonist role and might not be beneficial to health (Fig. 2.4). Some of these cases are:

Cancer Cachexia Syndrome (CCS)

It is a progressive metabolic syndrome clinically characterized by profound weight loss, fat depletion, skeletal muscle wasting, and asthenia that are not solely attributable to inadequate nutritional intake. Until the present, there is not evidences about the molecular mechanisms implicated in the clinical manifestations of the disease. Inasmuch as regions of BAT are not only lipid depots but has a significant role in regulating energy balance and fat accumulation in rodents and humans, its involvement in hypermetabolic diseases such as cancer cachexia has been suggested [60]. The activation of BAT results in a hypermetabolic state that is partially responsible for weight loss in cancer patients.

Animal studies of cancer cachexia models show some degree of BAT activation, but they do not establish the quantitative impact on the amount of hypermetabolism that is relevant to the development of cachexia [61]. Energy homeostasis in metabolic organs is controlled by central and peripheral circadian clocks through tight regulation of expression and activity of enzymes involved in metabolic pathways. In fact, aberrant circadian rhythms provoke hyperphagia, obesity and metabolic syndrome [62]. Recently, Tsoli et al. showed BAT activation in cachectic mice bearing tumours that cannot be attributed to the effects of reduced food intake or inability to maintain core body temperature. Moreover, they demonstrated a disruption of diurnal regulation of the transcription factor that control lipid homeostasis and thermogenesis in BAT. Finally, they described the role of cytokine signalling in BAT for tumour-induced systemic inflammation [60].

In human, autopsy samples have shown increased BAT in periadrenal tissues of cachectic cancer patients. BAT was observed in 80 % of the cancer patients compared with 13 % of the age-matched patients who died from other illnesses without cancer or cachexia [63]). Moreover, in some type of tumors it has been shown a potential correlation between BAT hyperactivity and body weight loss in cachexia in humans. For example, in hibernoma, a rare soft tissue benign tumor composed of brown fat cells, has been described a massive weight loss as a primary symptom [64]. Also, in pheochromocytoma an abundant BAT hyperactivity can also be seen on F-FDG PET scanning as a result of chronic stimulation of the SNS by high levels of circulating catecholamines [18]. In one case, after removing the pheochromocytoma, and thus the excess of NE, the intense uptake of FFDG in BAT was no longer seen, presumably reflecting an involution of BAT [65, 66]. Other studies addressed a possible relationship of BAT F-FDG activity with cancer; however, none of these observed a higher

incidence of BAT activity in active and/or PET-positive cancer patients [18]. BAT activity was generally found in about 50 % of cases, either with or without active malignancy [63].

Thus, animal and human data in cancer cachexia indicate that BAT activation occurs, but its quantitative contribution to any alteration in energy expenditure and, thus, on the degree of cachexia remains controversial. Careful consideration of factors co-acting on BAT recruitment and activity, such as diet, cold exposure, physical activity, insulin levels and BMI are necessaries to understand the real role of BAT in cachectic cancer patients. Therefore, further studies using PET should focus in the quantitative significance of BAT activity for increased energy expenditure and body weight loss in humans.

Multiple Symmetric Lipomatosis (Madelung's Disease/Syndrome or Launois Bensaude Syndrome) (MSL)

It is a rare syndrome originally described in 1846, characterized by the painless and symmetrical accumulation of abnormal tumour-like SAT, mostly affecting heavy drinking men. Individuals with MSL have increased SAT, either as discrete non-encapsulated lipomas or as a confluent increase in SAT in a symmetrical distribution on the neck, the back, mediastinum, upper arms or on the thighs. MSL usually spares the distal limbs but not in many women with MSL where the altered fat may be global. Moreover, this syndrome is accompanied by the presence of a somatic and autonomic neuropathies and alcohol-induced liver disease [67]. There is not inherited demonstrated about MSL but is thought that mitochondrial mutations would be related. In addition, the phenotype of MSL may require a combined effect of alcohol and a currently unknown genetic mutation.

The localization of lipomatous masses suggests that MSL lipomas could originate from BAT. It is believed that MSL SAT is derived from BAT or WAT that transdifferentiates into BAT. Adipocytes in MSL SAT are monovacuolar or multivacuolar. Moreover, stem and immune polymorphic cells, present in the stroma vascular fraction, contain thin microfilaments suggestive of elevated metabolic activity, are multivacuolar, and with large mitochondria packed with cristae suggesting a more BAT phenotype. The ultrastructure of these cells can be described as similar to that recently reported for the pauci-locular adipocytes, considered intermediate stage of transdifferentiating adipocytes, i.e. cells with intermediated morphology between white and brown adipose fat cells. The bidirectional switch between brown fat cells (and not white fat cells) and skeletal myoblasts controlled by PRMD16-C/EBP-β transcriptional complex suggest a transdifferentiation process rather than a lipomatous adipocytes infiltration.

The hypothesis that brown fat cells of MSL could arise from a common skeletal muscle and brown adipose cell precursors has been proposed. An alternative explanation is that adipocyte precursors residing within the muscle or de novo differentiation could be the sources of the adipocyte infiltration [39]. In addition, SAT cells from subjects with MSL express UCP-1 suggesting its origin as BAT [67].

The increase in MSL fat is extensive and deforming, compressing tissue structures and vessels. Early, MSL SAT is watery but later becomes fibrotic and scars easily. Similarly to obesity, fat excess physically impedes collection and flow lymph. Therefore, protein-rich lymphatic fluid collects in SAT, resulting in lymphedema and tissue hypoxia. Further accumulation of fluid in the setting of decreased oxygen tension leads to fibrosis. Congestion of lymph nodes by other means, such as lymphoma in the neck, induces fat growth similar to MSL [67]. All data indicate that the pathogenesis of MSL lipomatous fat deposits may originate from functionally defective BAT, accumulating an excess of lip. In fact, these findings are consistent with the hypothesis that MSL is a neoplastic disease originating from brown adipose cells as the result of a disorder in the proliferation and differentiation of human BAT cells.

Huntington's Disease (HD)

It is an adult-onset dominantly heritable neurodegenerative disorder with a prominent energy

deficit phenotype. It is caused by the expansion of a CAG repeat in the gene encoding the protein huntingtin, leading to expression of mutant huntingtin with expanded polyglutamine repeats. The huntingtin protein was recently shown to play a role linking the glycolytic enzyme GAPDH to vesicles, to supply energy from glycolysis for fast axonal transport. Both, a gain-of-function (for mutant huntingtin) and a loss-of-function (for normal huntingtin) hypothesis have been put forward to explain HD pathogenesis. HD is characterized by progressive motor impairment, personality changes, psychiatric illness and gradual intellectual decline [68].

Transcriptional deregulation, protein aggregation, mitochondrial dysfunction and enhanced oxidative stress have been implicated in the disease pathogenesis. A key feature of HD patients is pronounced weight loss, despite sustained caloric intake. Deficits in energy expenditure have been linked with mitochondrial dysfunction in HD [69]. PGC-1 family of co-activators is an extensively regulated group of proteins that are highly responsive to a variety of environmental cues, from temperature to nutritional status, to physical activity. Impaired PGC-1α expression and/or function has emerged as a common underlying cause of mitochondrial dysfunction in HD [70]. Involvement of PGC-1α in HD was first suggested by the findings that PGC-1α knockout mice exhibit mitochondrial dysfunction, defective bioenergetics, a hyperkinetic movement disorder and striatal degeneration, which are features also observed in HD. PGC-1α, which was initially identified as a PPARγ-interacting protein from brown fat, plays an important role in induction of UCP1 [69]. Two studies using transgenic mouse models of HD demonstrated that mice had hypothermia and significant reductions in body temperature during cold challenge and found that UCP-1 mRNA up-regulation was severely blunted. Moreover, BAT from these transgenic mice showed abnormal lipid-containing vacuoles [9, 71].

Role of Bat in Obesity Treatment

The epidemic of obesity is widely recognized as a major public health problem, given the worldwide increasing prevalence over the last decades. Generally, obesity develops upon chronic imbalance between energy intake and energy expenditure. Changes in lifestyle, basically the reduction of food intake and increased physical activity, are considered to be key elements of obesity treatment. However, most people fail to substantially and sustainably reduce body weight by basic behavioral changes, in particular due to potent compensatory mechanisms promoting re-gain of body weight [1].

One exciting prospect in this area is to increase the amount and/or activity of brown or beige fat. Animals with high BAT and/or beige/brite abundance are protected against obesity, diabetes, hepatic steatosis, and hyperlipidemia. Therefore, BAT and/or beige/brite fat expanding strategies would have good therapeutic results in the fight against obesity and related disorders in humans [55].

Pharmacological Strategies

There are some obesity therapies ranging from weight loss-promoting drugs to surgical interventions, in cases of extreme obesity after failure of conventional treatments, but only have limited success. Since it has been determined that, in addition to thermogenic function, BAT acts as a crucial regulator in energy metabolism due to its high oxidative capacity, the idea of inducing weight loss by pharmacological targeting of thermogenic adipose tissues has been revived. In rodent models, pharmacological induction of BAT function has been shown to be beneficial in counteracting obesity using indirect sympathomimetics such as β3-AR agonists (for example, ephedrine and sibutramine). However, in humans are ineffective not only because β3-AR are expressed at low levels in adipocytes but also they produces adverse effects due to the broad and nonspecific action of adrenergic stimulation, particularly the heart increasing cardiovascular complications and stroke events. In this regard, non-canonical thermogenic stimulators, which work independently of adrenergic receptors, could help increasing BAT activity without causing adverse outcomes or patient discomfort [72].

Irisin and BMP7

Non-SNS therapeutics based on newly discovered fat browning and/or BAT-activating cytokines have strong potential. FGF21 and irisin are particularly relevant as they are potent endocrine human BAT activators that are stimulated by cold exposure in adults. It is important to point out that in all of these studies it is not possible to exclude non-cell autonomous effects for all of these perturbations including a central effect to repress food intake [55].

The hormone-like myokine termed irisin has recently been described that induces the browning of adipose tissue and BAT activation. As this molecule was originally reported to be released after physical activity, it gained huge interest as a potential mediator of the health-promoting effects of physical exercise. Irisin is a 112 amino acid peptide cleaved from fibronectin type III domain containing protein 5 (FNDC5), a type I membrane protein which was claimed to be upregulated by exercise training in both mice and humans [73]. In addition, a moderate increase in circulating irisin levels by three folds augmented energy expenditure, reduced the body weight gain under high-fat diet, and improved diet-induced insulin resistance. These results suggested a potential protective role of irisin in the development of Type 2 diabetes, one of the major obesity- associated metabolic diseases [74].

As irisin has initially been described to protect against diet-induced weight gain, mediated by browning of WAT and thus increased energy expenditure, many studies have investigated the correlation of circulating irisin with obesity in humans. In line with the suggested protective role of the myokine irisin against obesity, negative correlations of circulating irisin levels with the BMI have been reported in humans [75]. However, controversy exists regarding the relation between irisin levels and the BMI. Several studies reported a positive correlation of serum irisin levels with BMI while others could not detect a change in circulating irisin in obesity [76, 77]. This could be related to different populations analyzed in the different studies, as some include obese subjects without metabolic disorders whereas others enclose obese patients with metabolic diseases such as type 2 diabetes [74].

Since current data obtained from human reveal that FNDC5/irisin has no a real effect on browning of WAT depots, other alternative therapeutic strategies could be the use of inducers of BAT differentiation such as BMP7. A recent study demonstrated that in high-fat diet fed lean mice BMP7 mediated recruitment and sympathetic activation of BAT at subthermoneutral temperature. BMP7-treated mice diminished WAT mass, increased genes related to intracellular lipolysis and browning of WAT [16].

Cold-Induced Energy Expenditure

On the other hand, an increase in BAT activity and cold-induced energy expenditure was also observed in response to acute cold exposure in subjects with low BAT activity, demonstrating the possible occurrence of BAT recruitment in humans. Very recently, chronic cold acclimation in human subjects was reported to increase the volume of metabolically active BAT, increasing its oxidative capacity and therefore, promoting cold-induced thermogenesis. Last studies are in keeping with data showing a physiological role of BAT in whole-body energy expenditure, glucose homeostasis and insulin sensitivity in humans during prolonged cold exposure [53].

Melatonin

The manipulation of photoperiods could be used to induce BAT formation. Melatonin (MEL) is naturally produced in the body in response to the perception of light and may play a valuable therapeutic role in the differentiation of adult stem cells (ASCs) into brown adipocytes. MEL is mostly secreted by the pineal gland, reaching the highest physiological levels at night, and its secretion is substantially greater in winter than in summer. MEL biosynthesis in the pineal gland declines with age and this decline has been correlated with increased visceral adipose tissue in small mammals [13]. The effects of MEL on

obesity and metabolic disorders are encouraging given that it has been demonstrated that MEL restrains body weight gain without changing food intake [78]. We recently have shown the beneficial effects of melatonin on metabolic disorders using the Zücker diabetic fatty (ZDF) rat model. This active component has shown amelioration of inflammation and oxidative stress related to an excess of WAT, an improvement of glucose homeostasis and beneficial effects on the lipid profile [79–81]. Finally, the potential of melatonin to promote BAT development in WAT has been demonstrated. Chronic oral administration induced browning of inguinal WAT and induced measurable amounts of UCP1 and stimulated ~2-folds the levels of PGC-1α in ZDF animals [82].

Cell-Based Therapies

BAT transplantation or cell-based therapies could be used to expand BAT. Human adipose-derived stem cells (hASCs) and inducible pluripotent stem (iPS) cells have been used to investigate and understand the signaling that determines progenitor fate and activity during BAT expansion and WAT browning. Extracellular environment parameters such as tissue vascularization, angiogenesis and innervation levels must be considered when decoding the integration of the signals that direct the behavior of progenitor [72].

Cell-therapy strategies to improve metabolic disorders are based on the implantation of brown adipocyte cells in the interscapular areas to regenerate BAT in humans. Injection of ASCs and preadipocytes from WAT formed BAT pads when implanted into the interscapular regions of mice [83, 84]. Moreover, adult progenitor cells can be induced to differentiate into BAT and are easily expanded in the laboratory for transplantation. Thereby, the transplantation of genetically manipulated hASCs with specific BAT transcription factors has been proposed to promote adipogenesis by inhibiting differentiation into unwanted cell lineages. The use of adenoviral vectors has been tested in animals for this purpose, although liposomes would be more suitable in humans because they may trigger a lower inflammatory response when releasing the RNA into the cell [13].

In humans, ASCs isolated from skeletal muscle have also been differentiated into brown adipocytes expressing UCP1 [85]. A recent study showed that local administration of BMP2 leads to the expansion, migration, and differentiation of progenitor cells from the peripheral nerve perineurium to brown adipose-like cells [86]. Furthermore, as already described in this review, MEL, a physiological molecule, can stimulate ASCs differentiation into BAT precursor cells, and it may also have the potential to recruit BAT and activate nonshivering thermogenesis. Taking together, these properties make ASCs an attractive cell candidate to be investigated for the regeneration of BAT.

Conclusion

Until recently, it was thought that the presence of BAT was restricted to newborns and child. Considerable amounts of BAT are present in adult humans and each time it becomes clearer its morphology, physiology, molecular regulation and origin. The involution of BAT with age could be related to heat production to maintenance body temperature, and the distribution in adults along the vasculature and around critical organs are related with the maintenance of vital functions in cold environments. This fact is supported by the BAT increase in people exposed to cold environments, as well as BAT deposits in WAT, and the process which permits transform white adipocytes in brown adipocytes.

BAT and obesity are closely related based in the anti-obesity effect of this tissue. In fact, the increased presence and activity of BAT is limited to thin people. However, there are some diseases or conditions where BAT plays an antagonist role causing certain pathologies. Novel therapeutic strategies based in BAT regeneration, activation or white-to-brown adipocyte trandifferentiation are being studied to treat obesity and related disorders. Potential therapies are based on pharmacological strategies, hormones and transcription factors,

cold-induced energy expenditure, the manipulation of photoperiods and cell-based therapies. The development of new treatments focused in BAT properties aimed at increasing energy expenditure and, therefore, to reduce WAT mass and restore body energy balance, suppose a challenge for researchers since a huge number of patients affected by obesity and associated metabolic disorders will be benefitted.

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3 Long-Chain Omega-3 Polyunsaturated Fatty Acids and Obesity

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and Damien P. Belobrajdic

Introduction

In recent years overweight and obesity has steadily increased in many countries across the globe and in 2014 more than 1.9 billion adults were found to be overweight and over 600 million were obese [1]. Similarly, nearly 42 million children under the age of 5 years were overweight or obese. The global rate of obesity is on the rise with estimates showing 13 % of world's adult population as obese [1]. Countries with higher rates of obesity include the United Arab Emirates, United States, Mexico and New Zealand where more than one in three adults are obese, whilst Australia, Canada, Chile and Hungary have adult obesity rates >25 % [2].

In most instances obesity is preventable because the fundamental cause is an energy imbalance between the overall calorific intake and expenditure. Fittingly, obesity falls into the category of preventable diet and life style disorders which is closely linked, and a major risk factor for several chronic degenerative diseases including cardiovascular disease, diabetes, musculoskeletal pathologies including osteoarthritis and certain cancers [3].

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The aetiology of most of these health problems also points to a strong dietary component suggesting that diet-based approaches may be of benefit. Common underlying mechanisms in these conditions include not only an altered plasma lipid profile but more importantly an enhanced endogenous reactive oxygen species (ROS) burden as well as a shift towards a more pro-inflammatory metabolic milieu. It is also well recognised that both omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFA) are strong modulators of these metabolic syndromes.

Essential Fatty Acids

The current Western diet mostly contains high levels of n-6 PUFA, the bulk of which is derived from vegetable oils. In contrast, the intake of n-3 PUFA is low thus resulting in a considerable imbalance in the dietary n-3/n-6 PUFA ratio (Fig. 3.1); with some estimates claiming it to be at 15/1 or higher [4]. Considering the general consensus that human beings evolved on a diet containing both equal amounts of n-3 and n-6 PUFA, there appears to be insufficient presence of n-3 PUFA in the Western dietary practises.

Furthermore, these two fatty acid families (n-3 and n-6) are *'essential'*, as humans are unable to synthesise the precursor fatty acids - linoleic acid (18:2n-6) and α-linoleic acid (α18:3n-3) nor any of their respective elongated

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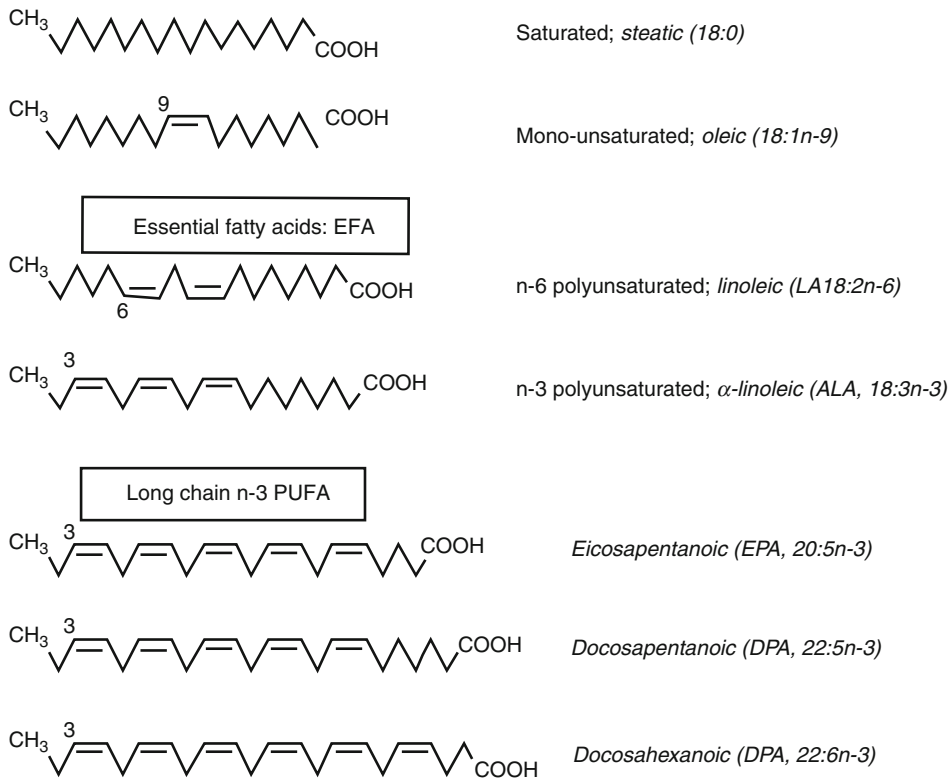

Fig. 3.1 Nomenclature of fatty acids. The (c:d *n-x*) nomenclature of fatty acids refers to the fatty acid chain length (*c*), the number of double bonds (*d*), and *n-x* defines the appearance of the first unsaturation (i.e. double bond) counting from the terminal methyl end of the fatty acid chain; either the letter *n* or *ω* is used to identify the first carbon atom (Reprinted from: Abeywardena [116]. With permission from Nova Science Publishers, Inc.)

products within a given fatty acid series (Fig. 3.2). Humans are only able to synthesise up to 18:1 (n-9; oleic acid), unless in conditions of essential fatty acid deficiency, where further elongation and desaturation of 18:1 takes place to produce 20:3n-9 (mead acid). Elevated presence of mead acid in blood is regarded as a diagnostic marker of essential fatty acid deficiency.

These specific fatty acid series (n-3, n-6 and n-9) are mutually exclusive. Moreover, the conversion of precursor fatty acids in n-3 and n-6 series to longer ($\geq C_{20}$) PUFA, is a rather inefficient process in humans due to a rate limiting step involving the delta-6 fatty acid desaturase/elongase complex. Whilst this limitation is not so evident for the n-6 series because of an abundance of linoleic acid (18:2n-6). In present day food supply, however, most Western dietary practises do lack sufficient α-linoleic acid (α18:3n-3) to permit sufficient conversion to longer ($\geq C_{20}$) metabolites. In deed recent evidence shows that LC n-3 PUFA levels are primarily regulated by the substrate levels for the existing enzyme complexes, rather than up-regulation by biosynthesising enzymes and/or transcription factors [5]. Therefore, particularly for LC n-3 PUFA, pre-formed versions (i.e. dietary sources rich in EPA and DHA) of these important fatty acids are the most appropriate strategy to ensure sufficient intakes.

Arachidonic acid (20:4n-6) is the main biologically active LC PUFA in the n-6 pathway and serves as the primary substrate for the production of 2-series prostaglandins and thromboxane and 4-series leukotrienes [6]. These are important mediators in maintaining cardiovascular

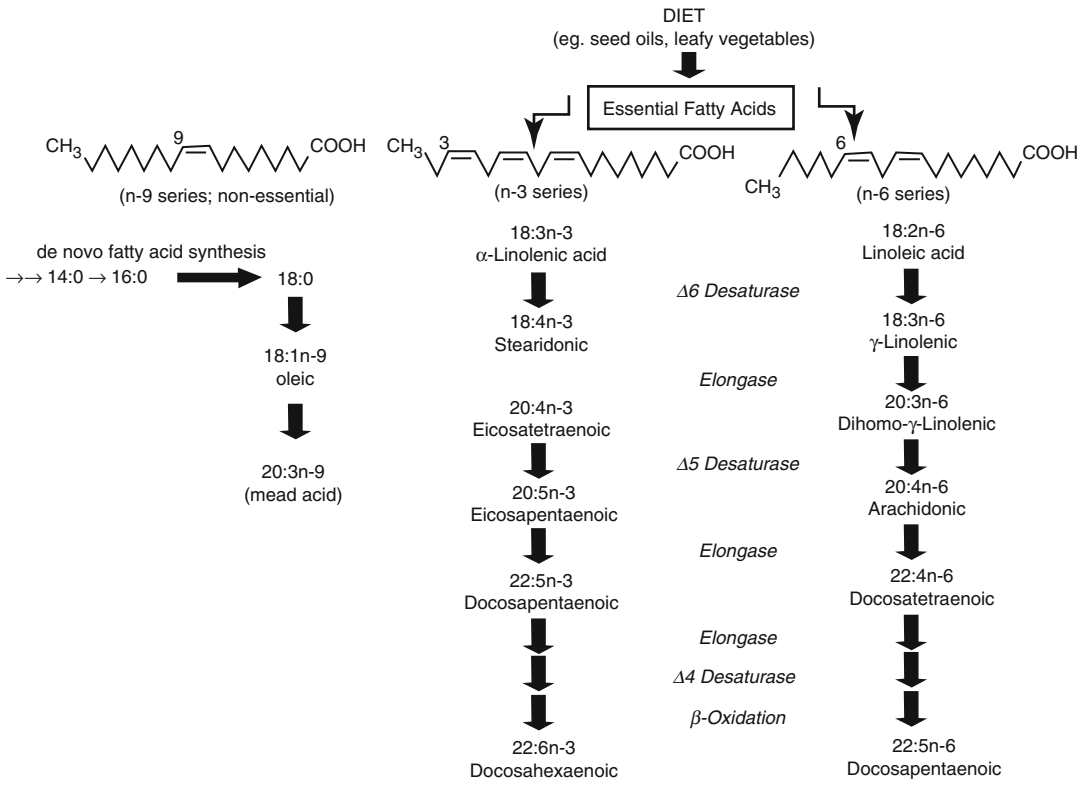

Fig. 3.2 Metabolism of n-3, n-6 and n-9 fatty acids. The shorter chain n-3 and n-6 PUFA; α-linolenic (18:3n-3, ALA) and linoleic (18:2n-6, LA) are essential fatty acids as they must be obtained through the diet and cannot be produced endogenously. Saturated (e.g., myristic, 14:0; palmitic, 16:0: stearic, 18:0) and mono-unsaturated (e.g., oleic, 18:1n-9) fatty acids can be synthesized de novo from other dietary precursors. The conversion of precursor fatty acids in n-3 and n-6 series to longer ($\geq C_{20}$) PUFA, is a rather inefficient process in humans due to a rate limiting step involving the delta-6 fatty acid desaturase/elongase complex. Therefore, humans are dependent on dietary sources of LC n-3 PUFA to increase the levels of these fatty acids. The fatty acids highlighted in bold are considered 'biologically active'

homeostasis. Conversely, in the case of the n-3 pathway, both C_{20} and C_{22} LC PUFA are known to produce 3-series eicosanoids and 5-series leukotrienes which have different biological efficacies compared to those derived from arachidonic acid.

In addition to the enzyme-mediated induced synthesis (involving cyclo-oxygenase and lipoxygenase), a range of other cyclic oxygenated metabolites of n-3 and n-6 PUFA are formed *in vivo* via non-enzymatic ROS induced peroxidation (isoprostanes, phytoprostanes, neuroprostanes, isofurans etc. [7]. Emerging evidence also suggests that these metabolites are associated with a myriad of biological activities [8, 9].

Omega-3 Long Chain-Polyunsaturated Fats and Obesity

Human Evidence

Randomized Controlled Trials (RCT)

Randomized controlled trials show that LC n-3 PUFA may have modest, yet significant effects on reducing body weight and waist circumference. A recently completed meta-analysis of 15 RCT showed that participants taking fish or fish oil lost 0.59 kg more body weight in conjunction with reductions in BMI (0.24 kg/m^2), body fat (0.49 %) and waist circumference (0.81 cm) compared with control [10]. This is consistent

with a narrative review conducted by Buckley and Howe who concluded that increasing the intake of LC n-3 PUFA by 0.3–3 g/day is effective for reducing body weight and improving body composition in humans [11]. However, both publications highlighted the need to examine the longer term effects of LC n-3 PUFA intake on body weight and adiposity as a majority of studies are less than 12 weeks in duration and only one study was conducted for more than a year [12].

Observational Studies

Large long-term prospective cohort studies show inconsistent effects of LC n-3 PUFA supplementation on body weight and body fat. The Health Professional Follow-Up Study showed that men with high fish consumption (consuming fish ≥5 times per week) were less likely to be overweight than those with low fish consumption (consuming fish less than once per month), and the percentage of overweight volunteers was inversely related to the LC n-3 PUFA intake [13]. Conversely, the Nurses' Health Study showed that higher intakes of fish and LC n-3 PUFA were associated with a higher prevalence of obesity, with the proportion of participants with a body mass index (BMI) ≥ 29 kg/m^2 increasing progressively as fish intake increased from less than once per month to ≥5 times per week [14]. While the higher prevalence of obesity associated with fish intake could be accounted for by a higher energy intake, this was not the case for LC n-3 PUFA intake. It is not clear whether the difference in findings of the two studies is due to confounding or gender differences. In addition, both studies estimated dietary fatty acid intakes from semi-quantitative food frequency questionnaires which might not be particularly sensitive in their ability to accurately quantify intakes of different types of fat, particularly LC n-3 PUFA. To address this, alternative approaches have been used to quantify LC n-3 PUFA intakes by measuring tissue and plasma fatty acid levels.

Measurement of fatty acid composition of adipose tissue samples may be a good surrogate biomarker to determine LC n-3 PUFA intake. Garaulet et al. showed that in obese patients (BMI 27–35 kg/m^2), LC n-3 PUFA content (in particular the DHA content) of peri-visceral and omental adipose tissue samples was inversely related to abdominal obesity as assessed by waist-hip ratio and visceral abdominal fat area [15]. This group also showed that the LC n-3 PUFA content of the subcutaneous adipose tissue (but not other adipose tissue depots) was inversely related to adipocyte size, which suggests that reduced abdominal obesity is the result of a reduced adipocyte size [16]. However, a major limitation of this method is the considerable level of invasiveness required to collected adipose tissue samples; consequently this marker has not been used in a large epidemiological trial.

An alternative approach is to use blood based measures to assess relationships between LC n-3 PUFA consumption and obesity. Studies that have measured fatty acid levels in plasma phospholipids have shown either positive correlations for plasma LC n-3 PUFA with waist circumference or inverse correlations with measures of adiposity [17–22]. This lack of consistency may be due to the highly variable nature of measuring plasma phospholipid fatty acid levels which can change in relatively short period of time (weeks). Alternatively, erythrocyte levels may provide a more stable marker of fatty acid intake as their levels are less influenced by daily variations reflecting intake over several months [23, 24]. DHA in particular is incorporated and retained predominantly inside the plasma membrane for the life of the erythrocyte which is ~4 months [23]. A recent analysis of a cohort of almost 3000 subjects from the Framingham Heart Study indicated a modest inverse relationship between erythrocyte LC n-3 PUFA and waist circumference [25]. In a somewhat smaller study (291 women, 185 men) Howe and colleagues showed a strong gender difference, whereby the association of DHA with lower adiposity was evident in women only whereas men tended to show an inverse association between erythrocyte DPA and adiposity [26]. It was also apparent that erythrocyte EPA had little association with adiposity. Taken together these studies highlight the potential usefulness of measuring erythrocyte LC n-3 PUFA in larger trials that evaluate the

gender-specific relationship between LC n-3 PUFA intake and measures of adiposity.

Animal Evidence

Animal studies have provided important insights into how dietary factors such as amount of fat, the type and amount of carbohydrate and other contaminants affects whether LC n-3 PUFA inclusion in diets modulate adiposity and body weight.

A growing body of evidence show that diets containing LC n-3 PUFA reduce adiposity and may also reduce body weight gain in rodents [27, 28]. A majority of the studies that have reported on the effects of LC n-3 PUFA in lowering adiposity have been conducted using diets with a high fat content (20–30 % total fat by weight). Together they have shown that the addition of fish oil reduced the mass of at least one type of visceral or subcutaneous fat pad and/or increased brown fat mass [27, 29–35]. Whereas one LC n-3 PUFA intervention study with a high fat background diet and two studies with low fat background diets (<10 % fat by weight) did not report a change or showed no change in fat pad weights [36–38].

To examine whether the effect of LC n-3 PUFA on adiposity was influenced by the amount of fat in the diet, Poudyal et al. investigated this in rats fed a low or high fat diet [39]. They showed that low fat diets containing n-3 PUFA had a greater effect on reducing visceral and subcutaneous fat mass than n-3 PUFA addition to high-fat diets. It was suggested that the proportion of fatty acids in the dietary lipid pool and not the total amount in the diet that plays a significant role in modulating the metabolic effects of LC n-3 PUFA. However, there were some differences between the composition of the low and high fat diets that may have also contributed to this difference. For instance, the low fat diet was particularly deficient in dietary protein, containing 3.2 g protein/100 g (high fat diet contained 5.8 % protein) which may have exacerbated these effects. In addition, differences in carbohydrate types between the low fat (carbohydrate source primarily cornstarch) and high fat (carbohydrate source fructose and condensed milk) diets may have also modulated the effects of LC n-3 PUFA on adiposity. This is an important difference as a study by Hao et al. showed that mice receiving a high fish oil diet supplemented with fructose had ~50 % less white adipose tissue mass than mice fed a high fish oil diet supplemented with either glucose or sucrose, indicating that the glucose moiety of sucrose was responsible for the obesity-promotion [40]. In subsequent studies they also concluded that the amount of available carbohydrate overrides the anti-obesity effects of fish oil, but the concomitant reduction in extremely high dietary protein may be a major contributing factor. A limitation of these studies was that equivalent dietary treatments without n-3 PUFA were not included; therefore it was not possible to determine the magnitude of effect attributable to n-3 PUFA [40]. Thus, further investigation is necessary to clearly determine the role that macronutrient type and amount have on modulating the effects of LC n-3 PUFA on adiposity.

In an animal model of established adiposity, incorporation of LC n-3 PUFA into a high fat diet may reduce energy utilisation. Using mice that had been initially classified as diet-induced obese or diet-resistant in response to high fat feeding, Huang et al. demonstrated that LC n-3 PUFA was effective in reducing the body weight and fat mass of diet-induced obese animals to the same extent as the obesity resistant mice and controls that were fed a low fat diet [41]. Although this reduction in body weight and adiposity could not be attributed to reduced food intake, mice fed the LC n-3 PUFA diet showed the lowest food efficiency (e.g. lowest weight gain per unit energy intake) which suggests a reduction in metabolic efficiency.

Persistent organic pollutants (POP) have been identified as dietary factors that may mediate any beneficial effects of LC n-3 PUFA on adiposity. Ibrahim et al. showed that consumption of Atlantic salmon with a high level of POP for 8 weeks caused obesity in mice and when the levels of POP in the salmon were reduced, obesity development in the mice decreased concomitantly [42]. This finding is supported by a study in rats where inclusion of purified salmon oil

attenuated obesity, whereas crude salmon oil exaggerated obesity development [43]. Although a direct causal link between human obesity and POP exposure remains to be established, human intervention trials that investigate fish or seafood as a source of n-3 PUFAs need to consider possible exposure to POP [44].

Potential Mechanisms of Action

There are a number of mechanisms proposed for how LC n-3 PUFA may assist with body weight and body fat reduction (Fig. 3.3). The strongest evidence comes from changes in expression of genes involved in the regulation of fat oxidation in adipose, liver, cardiac, intestinal and skeletal muscle tissue, and in the impairment of adipogenesis in adipose tissue. Improvements in pathways involving reduced inflammation and increased energy utilisation have also been demonstrated that include improved insulin sensitivity and increases in skeletal muscle blood flow and increased vasodilator function. Increased post-prandial satiety has also been proposed but there is little evidence supporting this effect.

Increased Fat Oxidation

Animal studies show that LC n-3 PUFA stimulate mitochondrial carnitine palmitoyl transferase 1 (CPT1), a major enzyme that controls fat oxidation in the mitochondria of liver, cardiac and skeletal muscle cells. In particular, a study by Flachs et al., showed that at least 15 % fish oil in the rat

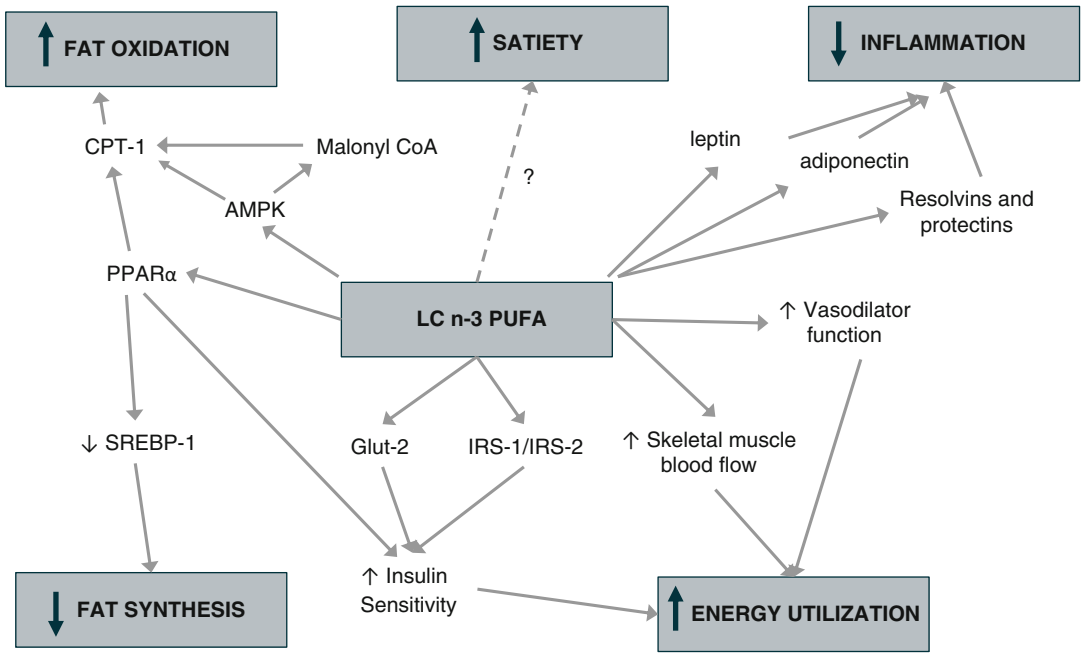

Fig. 3.3 Adiposity reduction: possible mechanisms of action of long chain n-3 polyunsaturated fatty acids (LC n-3 PUFA). LC n-3 PUFA modulate the expression of genes involved in the regulation of fat oxidation in rodent adipose, liver, cardiac, intestinal and skeletal muscle tissue, and in the impairment of adipogenesis in adipose tissue. Improvements in pathways involving reduced inflammation and increased energy utilisation have also been demonstrated and include improved insulin sensitivity and increases in skeletal muscle blood flow and increased vasodilator function. Increased post-prandial satiety has also been proposed but the mechanisms responsible have not been identified. *AMPK* 5′ AMP-activated protein kinase, *CPT-1* carnitine palmitoyl transferase 1, *IRS* insulin substrate receptor, *Glut2* glucose transporter-2, *PPAR-α* peroxisome proliferator-activated receptor-α, *SREBP-1* sterol regulatory element binding protein-1

diet increased CPT1 specific activity and tissue capacity in heart, skeletal muscle, and adipocytes. Animal studies suggest that this stimulation of CPT1 gene expression may be through peroxisome proliferator-activated receptors (PPAR) and/or inhibition of malonyl-CoA decarboxylase that occurs through AMPK activation [27, 45].

LC n-3 PUFA may also stimulate enzymes that play a central role in lipolysis, an essential process for the mobilisation of stored fat and subsequent utilisation by CPT1 and peroxisomal acyl-CoA oxidase. These enzymes include lipoprotein lipase and adipose triacylglycerol lipase that hydrolyse triglyceride into fatty acids in skeletal muscle and monoacylglycerol into lipoproteins in adipose tissue [46, 47]. A number of studies suggest that n-3 fatty acids and their metabolites are highly potent ligands for PPAR-α and PPAR-c which seem to regulate the expression of both lipoprotein lipase and adipose triacylglycerol lipase [47–53].

LC n-3 PUFA may also be contributing to increase fat oxidation by directing fatty acid oxidation to a less efficient pathway that yields less energy and more heat. A study in Fisher 344 rats showed that a diet containing fish oil (40 % energy) increased peroxisomal acyl-CoA oxidase gene expression by 2–3 fold in liver, skeletal muscle, and heart in comparison to a diet containing corn oil [32]. This shift in fat oxidation from mitochondrial beta-oxidation to peroxisomal fatty oxidation yields more than 30 % heat and therefore less ATP than mitochondrial beta-oxidation and may significantly contribute to the reduction in adipose tissue mass [54, 55].

Suppression of Fat Synthesis

LC n-3 PUFA can suppress fat synthesis and increase metabolism in adipose tissue via suppression of the sterol regulatory element-binding protein-1 (SREBP-1); a transcription factor responsible for activating genes involved in fatty acid synthesis, in a PPAR-α dependent process [41, 56]. In-vitro studies with lipid droplets specifically implicate DHA in these mechanisms [13].

Improved insulin sensitivity

In a genetic mouse model Gonzalez-Perix et al. [57] examined the effects of LC n-3 PUFA on the development of hepatic steatosis and showed upregulation of genes involved in insulin sensitivity, glucose transport and insulin receptor signalling. In addition, adiponectin (an anti-inflammatory and insulin-sensitizing adipokine) expression was increased, and AMPK phosphorylation (a fuel-sensing enzyme and a gatekeeper of the energy balance) was induced. These authors postulated that the formation of n-3 PUFA-derived resolvins and protectins may play a role in the insulin-sensitizing and anti-steatotic effects observed. However, other animal models have not shown LC n-3 PUFA to improve insulin sensitivity as measured by glucose tolerance tests [36, 39]

Satiety

There is little evidence from clinical studies that supports the concept that LC n-3 PUFA have specific satiating effects when compared to the consumption of meals or capsules that contain other types of fatty acids. Fish oil supplementation compared to oleic acid rich oil had no effect on 24 h energy intake and increased hunger in a 3 week intervention [58, 59]. Alternatively, in an energy restricted dietary setting Parra and colleagues demonstrated that a LC n-3 PUFA meal increased satiety 2 h after the meal [60]. However, it is not known whether this increased satiation can reduce energy intake at subsequent meals.

Increased Muscle Blood Flow

Increased muscle blood flow is proposed as a physiological mechanism whereby the vasodilatory effects of LC n-3 PUFA improve nutrient utilization for energy production with reduced conversion to fat storage. These effects are potentially important in obesity as reductions in nutrient disposal are associated with arterial vasodilator function and skeletal blood flow [61–64]. Interventional studies show that LC n-3 PUFA

improve vasodilator function and increase skeletal muscle blood flow during exercise [65, 66].

Reduced Adipose Tissue Inflammation

Chronic low-grade inflammation in adipose tissue is a long-term inflammatory response triggered by nutrients and metabolic surplus that is recognized as a key step in the development of obesity-associated complications [67]. It involves a similar set of molecules/signalling pathways to those involved in classical inflammation, but in obesity-induced inflammation these molecular and signalling pathways act as inflammatory mediators as well as regulators of energy storage and metabolism. These pathways include a rise in pro-inflammatory cytokines and adipokines such as TNF-α, interleukin-6 (IL-6), IL-1β, monocyte chemoattractant protein-1 (MCP-1), leptin and resistin accompanied by a reduction in adiponectin, an anti-inflammatory and insulin-sensitizing adipokine [68].

The link between LC n-3 PUFA and reduced adipose tissue inflammation is supported by feeding trials in rodents and several lipid mediators derived from the metabolism of n-3 PUFAs, resolvins and protectins have been postulated as molecules facilitating the resolution of inflammation [69]. A study in C57BL/6 J mice showed that EPA supplementation reversed high-saturated fat diet-induced insulin resistance and hepatic steatosis and increased adipose tissue MCP-1 and plasminogen activator inhibitor (PAI)-1 concentration [70]. In diabetic mice, the LC n-3 PUFA diet completely prevented macrophage infiltration induced by high-fat diet and induced changes in inflammatory gene expression which suggests that the beneficial effects of LC n − 3 PUFA on diabetes development could be mediated by their effect on adipose tissue inflammation [38].

Although some clinical trials show changes in inflammatory makers following LC n-3 PUFA additional research is required for its confirmation. A recent systematic review on the effect of n-3 fatty acids on biomarkers of inflammation concluded that the evidence was weak for modulation of inflammation in hypertriglyceridemia/diabetes and obesity cohorts. Hence a need for clinical studies with larger sample sizes is required. This is particularly important given the low levels of circulating inflammatory markers and the limited sensitivity of cytokine assays. Furthermore, differences between genders may also contribute to the effectiveness of LC n-3 PUFA. For instance, two studies have shown that serum adiponectin levels increased in healthy subjects when fed diets containing a lower n-6/n-3 ratio or a salmon rich diet [71, 72]. Conversely, there was no change in serum adiponectin following n-3 PUFA supplementation in overweight and moderately obese women [73]. A more recent study by Kondo et al. reported a gender difference in that LC n-3 PUFA supplementation (3 g/d derived from fish) led to an increase in serum adiponectin in women (from 13.5 ± 4.6 to 15.8 ± 5.2 μg/ml. $p < 0.01$), but not in men [74]. Differences in the serum uptake and accumulation of LC n-3 PUFA between the two sexes suggest that endogenous n-3 content may be an important factor in regulating serum adiponectin concentration. Although the accumulation of LC n-3 PUFA in adipose tissue is rather limited, fish oil fatty acids have been linked to several processes in adipose tissue including prevention of hyperplasia and hypertrophy, induction of mitochondrial biogenesis, induction of adiponectin and reduction in adipocyte inflammation [75, 76].

A recent study investigating the association between dietary and plasma fatty acids with several inflammatory and coagulation markers in 374 healthy men and women showed that plasma n-3 fatty acids were inversely associated with C-reactive protein (CRP), IL-6 and TNF-α, and plasma n-6 PUFA with CRP, IL-6 and fibrinogen [77]. It was also interesting to note that the most positive association for all the markers was observed with the n-6/n-3 ratio of plasma fatty acids, but not with the intake of different dietary fatty acids. Feeding of 2 g/d (3 mo) of LC n-3 PUFA to elderly patients ($N = 74$) with chronic heart failure led to a significant reduction in IL-6, TNF-α and intercellular adhesion molecule-1 with a positive effect on CRP being found only in smokers [78]. In contrast, a 3 year study of 563

men (64–76 yr) with high cardiovascular risk found that only serum levels of IL-18 were reduced (−10.5 % vs. baseline) by increased consumption of n-3 PUFA, achieved by dietary counselling (towards a Mediterranean diet) or via supplementation (2 g/d). Other inflammatory markers – CRP, TNF-α, IL-6 – were also reduced compared to baseline values, but no differences between groups were apparent. Adiponectin on the other hand remained unchanged [12]. However as recognised by the authors, there were several limitations in this study including the heterogeneity of the elderly population which carried a broad spectrum of morbidity, use of multiple medications as well as the possibility of survivor bias as the subjects were long-term survivors from a high risk population.

Which LC N-3 PUFA – EPA, DPA OR DHA?

Marine oil preparations contain both C_{20} and C_{22} long fatty acids. Most commercial preparations usually contain more EPA (20:5 n-3) than DHA (22:6 n-3) but there are a number that contain a higher content of DHA as a result of further processing. Both EPA and DHA are considered beneficial for several aspects of cardiovascular health. Indeed, several pharmaceutical grade LC n-3 PUFA are now available for the treatment of specific disease conditions. Whilst the majority of findings suggest both EPA and DHA are effective, there is a growing body of evidence that shows more specific or differential protective actions of a given fatty acid [79, 80]. For example, DHA has been reported to be more effective than EPA for lowering blood pressure, heart rate variability and promoting vascular health. Although, a strong body of evidence exists to support the view that EPA may be the active fatty acid for lowering triglyceride, a more recent systematic review and meta-analysis on EPA or DHA monotherapy on plasma lipid effects concluded that DHA is more effective in lowering triacylglycerols (TAG) and raising HDL-cholesterol (HDL-c) than EPA [81]. Alternatively, EPA may have greater anti-platelet and anti-inflammatory properties [82, 83]. More recent studies have uncovered further differences between EPA and DHA on cell function including phagocytosis, gene expression and intracellular signalling pathways as well as biophysical changes in plasma membrane [reviewed in [84]]. However, in a rat feeding trial Poudyal et al. showed that diets containing purified sources of either EPA or DHA had similar effects on lowering adiposity, but tended to be lowest with DHA [39].

Whilst EPA and DHA are the most studied n-3 PUFA, emerging data suggests that DPA docosapentaenoic acid (22:5n-3), an intermediate between EPA (20:5n-3) and DHA (22:6n-3) in the omega-3 synthesis pathway may also play specific physiological roles [85, 86]. However, detailed studies involving DPA are rare because of its limited availability in an enriched or pure form. Also natural sources of DPA are limited; with the two major sources (both of which contain DPA at low levels) being seal oil (up to ~8–10 % DPA) and menhaden oil (2 % DPA). Both oils also contain EPA and DHA at relatively higher concentrations than DPA, which complicate studies designed to determine any distinct physiological role of DPA.

In population studies, higher circulating levels of DPA are associated with lower coronary heart disease risk and DPA is more effective than EPA and DHA in inhibiting platelet aggregation [87, 88]. DPA has also been shown to have a 10-fold greater ability to promote endothelial cell migration than EPA [89, 90]. Endothelial cell migration and proliferation are important processes in wound healing of blood vessels. Recent research using pure forms of fatty acids has shown that C_{22} n-3 fatty acids (DPA, DHA) are more selectively incorporated in to heart and skeletal muscles than EPA (C_{20} n-3) [91]. Similarly, DPA is incorporated into human plasma and red blood cells faster than EPA, which has led to the suggestion that DPA may act as a reservoir of the major LC n-3 PUFA in humans [85, 92]. Furthermore, there is evidence to show that DPA and EPA are metabolised differently *in vivo* and follow different incorporation patterns [93].

A recent study which investigated the postprandial metabolism of DPA and EPA in humans showed that these two fatty acids undergo different metabolic fates [93]. Of particular importance, the

inclusion of DPA (2 g) in a meal containing olive oil (18 g) almost entirely prevented the incorporation of fatty acids in chylomicrons (decreased chylomicronemia); an effect not observed with EPA [93]. One explanation proposed for this action was that DPA inhibited pancreatic lipase, an important enzyme for the digestion of dietary fat [94]. Inhibitory action on this enzyme can result in impaired digestion of ingested fat, leading to lower absorption and increased excretion. Further studies are warranted to confirm this finding, which may have considerable implications for it as a potential anti-obesity agent.

It is noteworthy to mention that the current drug of choice for long-term treatment of obesity, Orlistat (Xenical®), exerts its actions based on the inhibition of gastrointestinal lipases. Therefore, the potential scope of application for a natural DPA-based approach can be regarded as considerable. Furthermore, a number of obesity-related disorders (e.g. cardio-vascular, plasma lipids) can also be expected to benefit from an LC n-3 PUFA based approach to obesity.

Bioavailability of different forms of LC n-3 PUFA (free fatty acids, ethyl esters, triacylglycerols and phospholipids) has been gaining importance in recent discussion that these fatty acids may be used in enriching food products. More recently, omega 3-monoglycerides (MAG) has been identified as an alternative (perhaps more effective) form of fatty acid delivery/absorption because it does not require the action of pancreatic lipases (unlike TAGs) to be absorbed. Whilst the biological efficacies of MAG- LC n-3 PUFAs are not fully characterised, emerging evidence show a superior anti-proliferative and pro-apoptotic actions of MAG-DPA when compared to MAG-DHA and MAG-EPA [95]. Another recent study reported MAG-DPA as being effective in reducing inflammation and vascular remodelling in experimental hypertension [96].

LC N-3 PUFA – Supply and Demand

Due to the pleiotropic nature of EPA and DHA global agencies such as the WHO, FAO and the 2010 dietary guidelines of the United States recommend a daily intake of at least 250 mg EPA + DHA to maintain good health [79], whereas for the secondary prevention of coronary artery disease, the American Heart Association guidelines stipulate an intake of 1 g/d of EPA + DHA via daily consumption of fish, or alternatively by taking fish oil supplements [97]. However, these recommended intake levels fall far short from the current consumption levels in the US, which is estimated to be about 110 mg/day [97, 98]. Against this backdrop of advice it is important to consider major limitations in the supply, cost and safety of these products at the consumer level.

For instance, the global production of fish oil is about 1 million tonnes per annum and has remained fairly steady for the last decade. Although commercial sources of LC n-3 PUFA such as micro algal-based oils from krill harvested from Antarctic waters have increased in recent years, continued expansion of harvest has the potential to adversely affect global fish stocks, as these tiny crustaceans are themselves an integral part of the aquatic food chain.

It has been recognised for some time that the world fish stocks, both wild and farmed, are insufficient to meet the rising global demand for LC n-3 PUFA prompting scientists to explore alternative means of producing these bioactive fatty acids [99]. These genetically modified yeast and transgenic land-based plants have been proposed as potential future sources of LC n-3 PUFA [79, 100–105]. The transgenic approach to increase the availability of LC n-3 PUFA in the food chain, a genetically modified soybean containing the shorter (C_{18}) n-3 PUFA SDA (18:4 ω3; 16–28 %) has recently been made available. Initial clinical trials have shown an elevation of plasma and red blood cell levels of EPA [106, 107]. The amount of EPA accumulation was relatively small, compare to the relatively high intakes of SDA used in these studies (3.66–4.2 g/d) and no change in plasma lipids was observed following by the SDA treatment.

The Omega-3 index, a surrogate emerging biomarker of CVD was increased as a result of the small increase in EPA but a key limitation of this strategy of using SDA-rich oils was its

inability to increase plasma or tissue DHA levels. Both human and animal feeding trials using different oils rich in SDA have all reported the lack of conversion of SDA to DHA (Fig. 3.1) [106–109]. A recent review has concluded that there is no convincing evidence of any health benefit of SDA supplementation in food [109]. The review also indicated that supplying pre-formed ≥ C_{20} LC n-3 PUFA would have a greater impact in increasing the endogenous levels of these bioactive fatty acids. Using a similar approach to the genetically modified SDA-soybean preparation, several laboratories have reported the successful synthesis of both EPA and DHA in several crop plants [79, 100, 102, 110–113]. DHA levels comparable to those found in fish (up to 15%w/w) have been achieved in the seeds of the genetically modified plant *Arabidopsis thaliana* [114, 115] as compared to 12 % of DHA generally found in bulk fish oil. Such fast emerging advances in genetic engineering of oilseeds equivalent to the fish-oil levels of ≥ C_{20} LC n-3 PUFA are highly exciting developments and should pave the way in achieving sustainable and cost-effective means of meeting the predicted future global demand for the above mentioned fatty acids.

Conclusion

The global rate of obesity is on the rise with recent estimates showing 13 % of world's adult population as obese. This epidemic is also accountable for parallel increases in several chronic diseases and have serious consequences not only on people's lives but also imparts a considerable burden on the national as well global health budget. Obesity is primarily a diet and lifestyle disease and therefore normally preventable. Both the type and the amount of dietary fatty acids have been shown to influence adiposity resulting in weight gain and obesity.

Whilst the obesogenic actions of saturated fats are well documented, the research data in relation to polyunsaturated fatty acids remain inconclusive. With regard to LC n-3 PUFA, randomised controlled trials have shown modest reductions in body weight and waist circumference following consumption of oil rich fish or fish oil. Although it is difficult to draw a consistent conclusion from the epidemiological data, there exist a large body of evidence suggesting that the beneficial effects of EPA and DHA are at the cellular level, for example, impairment of adipogenesis, increased fat oxidation and energy utilisation and also via favourable changes in the metabolic milieu by modulating the inflammatory mediator profiles. Collectively, these mechanisms would favour a reduction in the overall metabolic risk associated with obesity and obesity related disorders.

In addition, emerging evidence suggests DPA (22:5n-3) may influence absorption of fat potentially acting as an inhibitor of pancreatic lipase. This finding is worthy of further investigation as DPA shows considerable potential as an anti-obesity agent. The unprecedented consumer demand for LC n-3 PUFA by way of fish and fish oil supplements in recent years has also exposed the relatively fragile landscape of the global fish stocks, surrounding sustainability, environmental pollution and supply shortages as well as concerns on affordability. In response to such concerns recent efforts have reported the successful synthesis of LC n-3 PUFA by transgenic crop plants, an achievement that has the potential to supply adequate quantities to meet the growing demand for this family of bioactive fatty acids.

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Leptin and Obesity

4

Yuanyuan Zhang and Jun Ren

Introduction

Obesity has been officially recognized as an independent disease entity by the American Medical Association. The World Health Organization (WHO) has classified obesity as one of the leading risk factors for global deaths due to its tight association with multiple chronic diseases, such as cardiovascular disease, type II diabetes, and certain forms of cancers [1]. The development of obesity may be originated from an imbalanced energy intake and expenditure, which involves genetic and environmental interactions. Adipose tissues have long been recognized as a lipid storage organ although adipocytes also secret an array of biologically active factors in an endocrine fashion. These adipose tissue-derived cytokines (also known as adipokines) are widely involved in physiological functions such as food intake, nutrient metabolism, energy homeostasis, inflammation, coagulation, cardiac function and blood pressure regulation [2]. Leptin is the first-ever identified adipokine with an important role in the regulation of food intake, energy expenditure, cardiovascular homeostasis, neuroendocrine axis, glucose and lipid metabolism, hematopoiesis, as well as immune responses. This chapter aims to summarize the general biology and various cell signaling mechanisms of leptin, and discuss the major function of leptin in adiposity, weight control and obesity. Last but not the least, progresses and concerns in the therapeutic application of leptin in obesity will be discussed.

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Leptin Biology

Gene and Structure

Leptin was first discovered in 1994, named after the Greek word “leptos”, meaning thin [3]. It is a 167-amino acid peptide hormone encoded by the obesity gene (*ob* or *lep*) localized on human chromosome 7 [4, 5]. The crystal structure of leptin displays a four-helical bundle shape which is similar to that of the long-chain helical cytokine family [6]. Although leptin contains only 67 % sequence homology among diverse vertebrate species, the tertiary structures are conservative, indicating the evolutionarily conserved nature for the binding of leptin to its receptor [6, 7].

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Table 4.1 Factors that regulate leptin secretion

Factor promoting leptin secretion	Factor inhibiting leptin secretion
Overfeeding	Fasting
Insulin	Thyroid hormones
Glucocorticoids	Catecholamines
Estrogen	Testosterone
Acute infection	Cold exposure
Pro-inflammatory cytokines	

Production and Regulation

Leptin is primarily synthesized and secreted by the white adipose tissue (WAT). Circulating leptin levels are pulsatile, displaying a circadian rhythm with peaks between midnight and early morning and the lowest level around noon to mid-afternoon in both lean and obese subjects [8, 9]. Serum leptin levels are positively correlated with the amount of body fat, as obese subjects display higher leptin levels compared with the lean subjects [10]. Women possess higher leptin levels than their male counterparts, even after adjusting for body mass index. This gender disparity is likely due to the differences in the body fat distribution since women have more subcutaneous fat which produces more leptin than the visceral fat [11, 12]. Sex hormones are reported to regulate leptin synthesis although it remains controversial with regards to the role of sex hormones in the discrepant leptin levels between genders [13–16]. Besides sex hormones, leptin levels may be regulated by several factors, including caloric intake [17–19], insulin [17, 20], glucocorticoids [21–23], pro-inflammatory cytokines [24, 25], melatonin [26], catechol amines and β-adrenergic receptor activation [27, 28]. Factors that regulate circulating leptin levels are summarized in Table 4.1.

Leptin Receptor

Leptin functions by binding to its membrane receptors (LepRs) expressed in the central nervous system and peripheral tissues such as heart, liver, pancreas, adrenal gland and adipose tissue [29]. LepR belongs to the family of class 1 cytokine receptors, the same family as receptors for interleukin 6, leukemia inhibitory factor and granulocyte-colony stimulating factor (GCSF) [30]. There are six different isoforms of LepR (LepRa-f), generated by alternative splicing of leptin receptor gene (*db* or *lepr*) [31, 32]. These isoforms share a common leptin binding domain although with different intracellular domains. All LepRs contain a single transmembrane domain with the exception of LepRe, the unique soluble isoform capable of binding with the circulating leptin molecules [32]. LepRb, the long leptin receptor isoform expressed in hypothalamus, is mainly responsible for the physiological responses of leptin on food intake, energy homeostasis and neuroendocrine functions [30, 32, 33]. Deletion of LepRb from peripheral tissues does not affect energy homeostasis [34].

Animal Models of Leptin Deficiency

Mice with a homozygous mutation of leptin (*ob/ob* mice) contain a stop codon at position 105 instead of arginine due to a single base mutation, resulting in the production of a truncated leptin protein that cannot be secreted [3]. *ob/ob* mice exhibit hyperphagia, obesity, diabetes, infertility, and neuroendocrine abnormalities along with hypoleptinemia [35, 36]. Mice with a homozygous mutation of leptin receptor (*db/db* mice) have a premature stop codon inserted in the 3′ end of *Leprb* mRNA transcript, leading to the synthesis of LepRa instead of LepRb [32, 33]. Similar to *ob/ob* mice, *db/db* mice develop hyperphagia, obesity, and cold intolerance although with hyperleptinemia [32, 33]. Peripheral and central administration of leptin is capable of reducing food intake and body weight in the hypoleptinemic *ob/ob* mice, but not in *db/db* mice [37].

LepR mutations are also present in rats [31, 38, 39]. Zuker fatty (*fa/fa*) rats display a decreased cell surface expression of LepR and reduced leptin binding due to the substitution of glutamine for proline at amino acid position 269 in the extracellular domain of LepRb [31, 39]. The *fa/fa* rats exhibit hyperphagia, obesity, hyperlipidemia and hyperglycemia although they respond well to

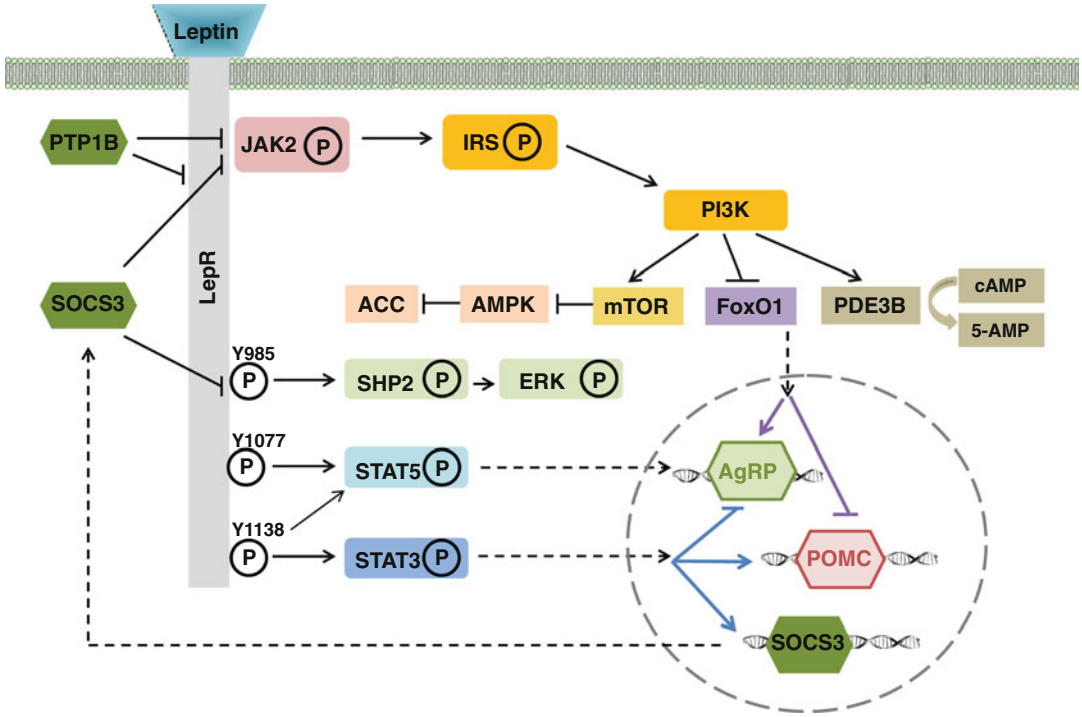

Fig. 4.1 Leptin signaling pathways. Leptin binds to LepR, which recruits and phosphorylates JAK2. Activated JAK2 induces phosphorylation of LepR at three tyrosine residues (Y985, Y1077, and Y1138) which initiate various downstream signaling. Especially, phosphorylated STAT3 translocates into nucleus to regulate AgRP and POMC gene expression, leading to decreased food intake and increased energy expenditure. JAK2 also induces signaling cascade through IRS-PI3K signaling. PTP1B and SOCS3 are two inhibitors which negatively regulate leptin signaling through interaction with JAK2 and LepR

high doses of leptin administered through intracerebroventricular injection, suggesting the partial function of LepR (selective leptin resistance) and decreased leptin sensitivity [40].

Leptin Signalling

The binding of leptin to the LepRb receptor allows the recruitment and activation of Janus kinase 2 (JAK2), leading to the phosphorylation of JAK2 and LepRb [41–43]. LepRb receptor can be phosphorylated at three conserved tyrosine residues (Y985, Y1077 and Y1138) to induce various downstream signaling pathways [41, 42, 44]. For example, phosphorylation at Y985 activates Src-homology-2 domain protein (SHP2) and mitogen-activated-protein-kinase (MAPK); phosphorylation at Y1077 activates signal transducer and activator of transcription 5 (STAT5); phosphorylation at Y1138 activates signal transducer and activator of transcription 3 (STAT3), as well as STAT5 to a weaker extent. Mutation in all three tyrosine residues located on LepRb results in the development of overt obesity [45]. However, phenotype of these mice, such as adiposity, hyperphagy, physical activity, adaptive thermogenesis, and glycemic control, are not as severe as the LepRb-deficient *db/db* mice, indicating that LepRb functions through not only tyrosine-dependent mechanism, but also tyrosine-independent mechanisms [45]. Indeed, leptin activates insulin receptor substrate (IRS) – phosphatidylinositol 3-kinase (PI3K) pathway which further induces several downstream signaling pathways [46]. The major leptin signaling pathways are summarized in Fig. 4.1 and are also introduced as follows.

JAK2/STAT3

The JAK2/STAT3 signaling mediates the major biological actions of leptin ranging from energy homeostasis to neuroendocrine regulation. Following the phosphorylation of Y1138 on LepRb, STAT3 is recruited to the JAK2/LepRb complex and phosphorylated. Phosphorylated STAT3 gets translocated to the nucleus and binds to the promoter regions of target genes to regulate gene expression [41, 42]. STAT3 stimulates pro-opiomelanocortin (POMC) expression and inhibits agouti-related peptide (AgRP) expression [47]. In addition, STAT3 mediates the transcription of suppressor of cytokine signaling 3 (SOCS3), which in turn inhibits LepRb/STAT3 signaling by coupling the Y985 tyrosine residues with LepRb [42, 48, 49].

The contribution of STAT3 signaling to the biological action of leptin has been elucidated with several mouse models [50–52]. For example, mice with a neural-specific disruption of *Stat3* exhibit hyperphagia, obesity, diabetes, infertility and thermal dysregulation [51]. Another murine model with tyrosine at 1138 in LepRb being replaced by serine exhibits hyperphagia, obesity, and suppressed hypothalamic melanocortin system. Nonetheless, these mice are fertile and less hyperglycemic compared with *db/db* mice [50]. The studies have depicted the critical role for STAT3 signaling in the regulation of energy homeostasis, although there are some discrepancies with regards to the role of Stat3 in fertility, growth, and glucose homeostasis. In order to address this discrepancy, another mouse model was generated with STAT3 specifically disrupted in the LepRb neurons [52]. These mice exhibit obesity and hyperglycemia with increased linear growth and normal fertility, suggesting an unlikely role for STAT3 from LepRb neurons in the regulation of linear growth or fertility [52].

JAK2/STAT5

STAT5 is expressed in distinct neuronal populations in the hypothalamic arcuate nucleus (ARC) [53]. The activation of STAT5 is mainly mediated by phosphorylation of Y1077 on LepRb, although Y1138 also contributes to STAT5 activation [44, 54]. Similar to STAT3, STAT5 also gets translocated to the nucleus for regulating target gene expression. Mice with deletion of *Stat5* locus in the central nervous system develop hyperphagia, obesity, insulin resistance, and impaired thermal regulation [55]. A recent study indicated that female mice with mutation at Y1077 tyrosine residences on LepRb display impaired estrous cycle, suggesting a possible role for STAT5 in leptin-induced reproductive responses [56].

SHP2/ERK

The residue of Y985 on LepRb exerts dual regulatory roles in leptin signaling [57]. On one hand, phosphorylation of Y985 binds Src homology-2 domain of tyrosine phosphatase 2 (SHP2) and activates extracellular signal-regulated kinase (ERK), which positively mediates leptin effects on food intake and body weight [58]. Pharmacological blockade of hypothalamic ERK1/2 reverses the anorectic and weight-loss effects of leptin, as well as abolishing leptin-mediated thermogenic sympathetic outflow to brown adipose tissue (BAT) in rats [58]. On the other hand, Y985 also serves as the binding site for SOCS3, a negative feedback inhibitor of leptin signaling [48, 49]. As mentioned earlier, the SOCS3 gene expression is upregulated by JAK2/STAT3 signaling. SOCS3 binds to JAK2 and LepRb at Y985 to terminate the leptin signaling cascade. Selective mutation of Y985 results in decreased feeding, increased leptin sensitivity, and protection from diet-induced obesity, especially in females, indicating a unique role for Y985 in the inhibition of leptin signaling [59]. Similarly, selective deletion of SOCS3 in POMC neurons enhances leptin sensitivity, increases energy expenditure, and improves glucose homeostasis in mice, while overexpression of SOCS3 in POMC neurons results in leptin resistance, obesity and glucose intolerance [60–62]. In addition to SOCS3, protein tyrosine phosphatase 1B (PTP1B) also negatively regulates leptin signaling partially by dephosphorylating LepR and JAK2 [63–65]. More evidence from our group suggests that

PTP1B is induced by ER stress via the activation of the ROS-NFκB axis, *en route* to mediate insulin resistance in obese condition [66]. Both leptin and leptin resistance are well known to elicit cell stress conditions including ER stress [67, 68]. Not surprisingly, mice lacking PTP1B are hypersensitive to leptin and resistant to diet-induced obesity [69].

IRS/PI3K

Ample evidence has revealed that leptin and insulin may share similar intracellular pathways in hypothalamic neurons [46, 70]. Intracerebroventricular administration of leptin increases hypothalamic PI3K activity and reduces cyclic AMP (cAMP) levels in hypothalamus [71]. The inhibition of PI3K negates several actions of leptin, including leptin-mediated inhibition of hypothalamic neuropeptide Y (NPY) and AgRP expression, acute suppression on food intake in POMC neurons, glucose regulation in ARC, neuronal activity in paraventricular nucleus (PVN) and ventral premammillary nucleus (PMV), as well as suppression of lipogenesis in WAT [72–75]. Enhanced leptin-stimulated PI3K activation may promote the transdifferentiation of white adipocytes to brown-like adipocytes in CNS [76].

Other Leptin Signaling Downstream of IRS-PI3K

The IRS/PI3K signaling cascade also triggers other leptin downstream signaling pathways to regulate energy homeostasis either directly or indirectly, such as forkhead box O1 (FoxO1), the mammalian target of rapamycin (mTOR), 5′ adenosine monophosphate-activated protein kinase (AMPK) – acetyl-CoA carboxylase (ACC), and phosphodiesterase 3B (PDE3B).

FoxO1 is a transcription factor inactivated by PI3K-Akt signaling. It may downregulate POMC expression and promote AgRP expression [77]. Constitutively activated FoxO1 in ARC blunts leptin-induced suppression of food intake in mice, while deletion of FoxO1 in POMC neurons or AgRP neurons decreases food intake in mice [78–80].

mTOR is a serine/threonine protein kinase recently discovered to be involved in leptin signaling pathway, as a downstream target of PI3K signaling [81]. Leptin stimulates phosphorylation of hypothalamic p70 S6 kinase (S6K) via mTOR; inhibition of either mTOR or S6K attenuates the anorexigenic effect of leptin [82, 83].

AMPK is stimulated by leptin in the peripheral tissues to promote catabolic pathways. However, AMPK activity is inhibited by leptin in the brain, leading to the activation of ACC and anorexigenic effect [84, 85]. Constitutive activation of AMPK or inhibition of ACC in hypothalamus blocks leptin-mediated decrease in food intake and body weight [85, 86]. It has been reported recently that leptin inhibits hypothalamic AMPK through mTOR/S6K [87].

PDE3B functions to convert cyclic adenosine monophosphate (cAMP) to AMP. Leptin-mediated activation of PDE3B results in a decrease of cAMP levels in hypothalamus [71, 88]. Inhibition of PDE3B activity blocks leptin-induced activation of STAT3 and suppression on food intake as well as body weight gain [71]. The PI3K-PDE3B-cAMP pathway is believed to be associated with the "selective" leptin resistance in the hypothalamus, therefore constituting another critical component of leptin signaling [88].

Leptin Function

Leptin targets both CNS and peripheral tissues to regulate biological actions such as food intake, energy expenditure, glucose metabolism, reproductive function, immune response, and bone metabolism (Fig. 4.2). The following paragraph mainly focuses on the major functions of leptin that are closely related to obesity.

Food Intake

ARC has been shown to be the primary site where leptin regulates energy homeostasis [89, 90].

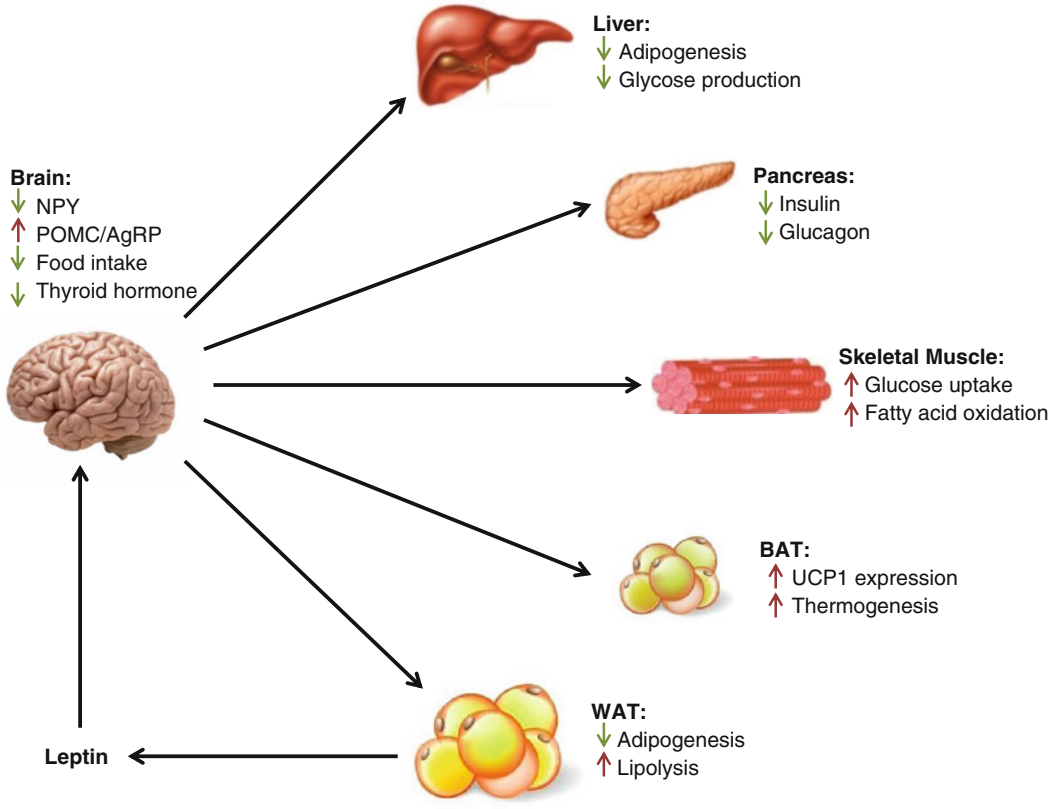

Fig. 4.2 The effect of leptin on energy and metabolic homeostasis. Leptin is secreted mainly from WAT and targets LepR-expressing cells in the brain and peripheral tissues. Leptin regulates energy homeostasis by suppressing food intake and increasing energy expenditure. It also ameliorates glucose and lipid metabolism by suppressing glucose production in liver, enhancing glucose uptake in peripheral tissues, inhibiting adipogenesis in liver and adipose tissue, and promoting fatty acid oxidation in skeletal muscle, etc. The neuroendocrine function of leptin is not shown in this figure

There are two main neural subsets in the ARC: one population expresses POMC and cocaine- and amphetamine-regulated transcript (CART), which may activate melanocortin-4-recepotors (MC4R) to suppress food intake and increase energy expenditure; the other population expresses NPY and AgRP, which inhibits MC4R to increase food intake and reduce energy expenditure [91]. Leptin is believed to regulate energy homeostasis by activating the anorexigenic POMC/CART neurons while inhibiting the orexigenic NPY and AgRP neurons [47, 92]. Nonetheless, it is noteworthy that ARC is not the solely area in the brain contributing to leptin effect, since the pathology of mice with LepR or STAT3 specifically deleted in POMC and/or AgRP/NPY neurons is less severe compared with that from *db/db* mice [93, 94]. Indeed, leptin also targets at other hypothalamic and extra-hypothalamic sites in brain for anorexic and weight-loss effects, as evidenced by the following seminal studies. First, leptin decreases the expression of melanin-concentrating hormone (MCH) and orexins in the lateral hypothalamic area (LHA) [95, 96]. Second, leptin stimulates the expression of transcription factor steroidogenic factor-1 (SF-1) and brain-derived neurotrophic factor (BDNF) in the ventromedial hypothalamus (VMH) to regulate energy balance [97, 98]. Third, leptin may interact with the mesolimbic dopamine system to modulate the hedonic control of feeding by targeting LepRb-

expressing neurons in the LHA and ventral tegmental area of midbrain (VTA) [99]. These notions received support from the observations that microinjection of leptin directly to ARC, VMH, and LHA of hypothalamus, as well as hindbrain, all suppresses food intake in mice [89, 99, 100].

Energy Expenditure

Leptin increases energy expenditure by up-regulating both energy expenditure and locomotor activities [90, 101]. Leptin supplement reverses sympathetic activity and body temperature in *ob/ob* mice [102]. In wild type rodents, leptin administration increases sympathetic nerve activity to BAT, kidney, hindlimb, and adrenal gland, and stimulates BAT thermogenesis as well [103, 104]. These pro-energy actions are essential in the weight loss property of leptin. Up-to-date, MCH and FoxO1 are considered key components in the thermogenic effect of leptin [105, 106]. Mice lacking both leptin and MCH display reduced body fat, increased body temperature, and improved cold tolerance compared with *ob/ob* mice, whereas hyperphagia seems unaffected. These observations suggest that the improved body weight control may be resulted from energy expenditure rather than restriction of food intake [105]. Mice lacking FoxO1 in SF-1 neurons of VMH present improved body weight and glucose tolerance due to increased energy expenditure, suggesting that inhibition of FoxO1 may also be involved in leptin-regulated energy balance and glucose homeostasis [106].

Glucose and Lipid Metabolism

As mentioned above, *ob/ob* mice exhibit hyperglycemia, steatosis, and insulin resistance in addition to overt adiposity. Many of these adverse metabolic homeostatic and insulin sensitivity responses can be reversed by leptin supplementation [35, 36, 107, 108]. Interestingly, further studies revealed that leptin-offered beneficial effect on glucose/lipid metabolism is independent of its regulation of food intake or body weight control. First, leptin-induced improvement in glucose homeostasis occurs prior to weight loss in *ob/ob* mice [36]. Second, low dose of leptin, which does not reduce food intake or body weight, normalizes hyperglycemia in *ob/ob* mice [35]. Third, pair-fed *ob/ob* mice, which are fed the same amount of food as leptin-treated *ob/ob* mice, experience less reduction in glucose and insulin levels compared with the leptin-treated *ob/ob* mice, suggesting a relatively minor role for food restriction in recapitulating the metabolic action of leptin [36].

The beneficial effects of leptin on glucose and lipid metabolism seem to be mainly regulated centrally via CNS. Disruption of LepR in the peripheral tissues does not have much significant influence on glucose and lipid metabolism [34]. Nonetheless, targeted deletion of LepRb in the POMC and AgRP neurons leads to overt hyperinsulinemia and insulin resistance [90, 109]. Moreover, selective expression of LepRb in the POMC neurons rescues the metabolic defects in *db/db* mice [90, 109, 110]. Interestingly, centrally administered leptin improves glucose and lipid metabolism through multiple peripheral tissues, such as inhibiting glucose production in the liver, increasing glucose uptake in peripheral tissues, decreasing de novo lipogenesis and increasing lipolysis in adipose tissues, increasing fatty acid oxidation in muscles, as well as inhibiting insulin and glucagon secretion in pancreases [75, 84, 111–113]. These metabolic effects of leptin may be mediated through insulin-dependent or insulin-independent mechanism, since leptin effectively ameliorates glucose homeostasis in type I diabetic mice despite presence of insulin deficiency [114, 115].

Neuroendocrine Function

Leptin is an important signal linking energy status to the neuroendocrine axis. Leptin treatment restores levels of thyroid hormone, testosterone and luteinizing hormone in fasted mice [18]. It also synergistically interacts with glucagon-like peptide 1 (GLP-1) and cholecystokinin (CCK) to

promote satiety in the neurons of the solitary tract in hindbrain region [116]. In humans, leptin treatment increases testosterone levels, luteinizing hormone levels and pulse frequency. Not surprisingly, leptin has been indicated in the treatment for hypothalamic amenorrhea [19, 117].

Leptin Treatment for Obesity

Leptin Treatment in Human with Leptin Deficiency

Leptin deficiency in human is mainly derived from congenital leptin mutation or lipodystrophy, a disease condition with little adipose tissues. Subjects with leptin deficiency develop hyperphagia, severe obesity (hypoleptinemic type I), and diabetes mellitus [118, 119]. Leptin administration has been shown to reduce appetite, improve metabolic profile, and promote weight loss in human with congenital leptin deficiency and lipoatrophy [120–123]. In addition, leptin therapy proves to be effective for the treatment of hypothalamic amenorrhea, the cessation of menstrual cycles due to chronic energy deficiency [124]. Currently the therapeutic form of leptin includes recombinant methionyl human leptin (metreleptin), which has been approved by FDA for the treatment of congenital or acquired generalized lipodystrophy [125].

Leptin Resistance

Unfortunately, most obese subjects display elevated circulating leptin levels (hyperleptinemic type II obesity), while the sensitivity to leptin is dramatically decreased, suggesting a clinical status of leptin resistance [10, 126]. Leptin may not be effective as a weight-loss maneuver in this type of obesity as demonstrated by several clinical trials [127–129]. Several mechanisms have been postulated for the development of leptin resistance including defective transport of leptin across the blood brain barrier, impaired neuronal leptin signaling, induction of inhibitors of leptin signaling like SOCS3 and PTP1B, hypothalamic inflammation, ER stress [48, 65, 68, 130, 131]. Better understanding of the cellular mechanism of leptin resistance would be a crucial step to develop effective leptin therapy for obesity.

Potential Leptin-Sensitizing Molecules

Currently, identification of pharmacological molecules to improve central leptin sensitivity is considered one of the most effective ways to improve the efficacy of leptin. Among such, amylin is a heavily investigated leptin-sensitizing molecule. Amylin is a peptide hormone co-secreted with insulin from pancreas, which functions in glycemic regulation by promoting satiety and slowing down gastric emptying. Preclinical studies suggest that leptin and amylin act synergistically to reduce food intake and body weight gain while preventing the compensatory reduction in energy expenditure associated with weight loss [132, 133]. Amylin is capable of enhancing leptin action via up-regulating surface LepR expression and promoting leptin signaling [134]. Clinical studies support the weight-loss benefit of the leptin-pramlintide (analog of amylin) combination therapy in obese individuals [132, 135]. Nonetheless, a recent clinical trial was halted in 2011 due to the appearance of leptin antibodies in patients [136]. More molecules are reported to synergize with leptin to promote glucose and lipid metabolism in rodents including agonists for GLP-1 receptor, CCK, glucagon receptor, and clusterin [137–140]. Further studies are warranted to fully validate their efficacy and safety with regards to the leptin combination therapy in humans.

Leptin Treatment in the Maintenance of Weight Loss

With the pivotal role of leptin in energy homeostasis, recent studies suggest that leptin may play a more important role in the maintenance of weight loss rather than weight loss *per se*. During weight loss process, plasma leptin levels drop

with a prolonged energy deficit as part of the metabolic adaptation in human [141, 142]. Over time, such low leptin environment may result in resistance to weight loss and perhaps regain of body weight. Leptin treatment has proven to reverse satiation and restore thyroid hormone levels, sympathetic nerve tone and energy expenditure in leptin deficiency due to weight loss [18, 143, 144]. Functional brain imaging also shows that leptin treatment reserves weight loss-induced changes in neural activity governing the regulatory, emotional, and cognitive control of food intake [145]. All these findings seem to suggest that leptin replacement could be a promising therapy to help the maintenance of the lost weight.

Conclusion

As one of the most intriguing anti-obesity hormones identified over the past 20 years, leptin has gained sufficient clinical and scientific attention with its regulatory roles in energy homeostasis through CNS and peripheral target sites. Leptin treatment proves to effectively suppress food intake, reduce body weight and ameliorate glucose metabolism in subjects with leptin deficiency, but not in most obese individuals with high circulating leptin levels and poor leptin sensitivity. Therapeutic application of leptin for treating obesity depends on the thorough understanding of leptin action, the elucidation of the cellular mechanism for leptin resistance, the discovery of leptin-sensitizing molecules, and the solution for drug safety issues such as autoimmunity due to the formation of leptin antibody.

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Role of Neuro-Endocrine System in Obesity

5

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Energy and Life

Energy is needed for every manifestation of life such as to run various biosynthetic pathways, active transport, generation of nerve impulses, muscular contractions and motility etc. The energy is derived from the oxidation of nutrients. One of the greatest source of energy is sun (solar energy), absorbed by the plants to synthesize the energy rich chemical compounds (carbohydrates, lipids etc.). These carbohydrates and lipids are used by the human beings and other animals to synthesize their own type of compounds such as glycogen, lipids, and high energy compounds like adenosine triphosphate (ATP). ATP is an energy rich chemical used for various physiological activities such as muscular contraction (mechanical work), generation of nerve impulses (electrical work), transport against the gradient (osmotic work) etc. In plants the solar energy is converted to chemical energy, which is converted by humans and higher animals into mechanical energy, electrical energy, osmotic energy and other form of chemical energy. This confirms the first law of thermodynamics in living cells that energy can neither be created, nor be destroyed but transformed from one to the other form.

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Energy Cycle Body Mass and Obesity

Whenever the energy intake and output ratio increases, there is a conservation of energy in the body stores as carbohydrates and lipids. The normal proportion among them gets disturbed in the total body mass. This imbalance initially leads to overweight, and if not controlled causes obesity. The simple, easy and commonly used method to calculate and differentiate between overweight and obesity in human is the measurement of Body Mass Index (BMI) which is the body weight (in Kg) divided by the square of height (in meters) or Kg/m^2. According to WHO, BMI of 25 or over is overweight and greater than 30 or over is obesity [1].

In recent years the importance of obesity has drawn extraordinary attention due to its association with metabolic imbalance. Obesity is one of the most common metabolic diseases and greatest threat to the health because of the possibility of numerous complications and elevated risk such as Type 2 diabetes mellitus (T2DM), hypertension, cardiovascular disorders and cancer [2]. T2 DM in turn gives rise to several different complications (see Chap. 12). Development of effective tools for treatment of obesity by drugs or elective surgery demands complete understanding of the mechanisms of appetite control and the evaluation of disorders resulting in obesity.

Obesity is reaching to an alarming stage and in United States alone up to 33 % of adults are

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suffering from this disease [3]. In 1998 WHO has declared obesity as a chronic medical disease because of the risk of serious complications, which prompted extensive studies on its pathogenesis in order to apply appropriate treatment before the serious disorders develop [4, 5].

Gastrointestinal Hormones, Neuron Systems, Satiety and Body Weight

Our body has highly synchronized systems regulated by various hormonal and neuronal processes. It is believed that the central nervous system (CNS), particularly hypothalamic region together with other regions is involved in the feedback regulation of energy homeostasis, i.e., food intake and satiety.

The hypothalamus plays a pivotal role by exerting its influence on hunger center situated laterally and satiety center at ventromedial nucleus. Also the paraventricular and arcuate nuclei are the sites in guts and adipose tissues from where multiple hormones are released and used to regulate food intake and energy utilization.

Two distinct types of neurons in arcuate nuclei that regulate food intake are: (a) Proopiomelanocortin (POMC) neurons, activated by α-melanocyte stimulating hormone (α-MSH) which is released from arcuate nuclei and suppresses appetite at the satiety center and (b): neurons stimulated by ghrelin which induces and releases neuropeptide-Y (NPY) and Agouti Related Peptide (AgRP) at hunger center with the increase of appetite.

Arcuate nucleus integrates neural and humoral inputs and determines a physiological role in regulating appetite and satiety, such as the neural via vagal and mostly hormonal via anorexigenic (cholecystokinin, polypeptide YY, glucagon like peptide-I, oxyntomodulin, leptin and others) peptides and orexigenic enteropeptides (ghrelin and other orexins). The adiposity signaling and control of appetite is mediated through peripheral and central humoral mechanisms involving specific receptors.

When food intake is in excess the resulting unused energy is stored mostly as fat in adipocytes in subcutaneous tissues and in the intraperitoneal cavity. Recent studies show that the new adipocytes may differentiate from fibroblast-like preadipocytes at any time in life and the development of obesity in adults is accompanied by increased numbers as well as increased size of adipocytes; this contravenes earlier thinking [1]. The hypothalamus is the key region in CNS which controls the feedback mechanism of appetite and food intake, though other regions also play their roles. Nucleus Tractus Solitarius in the brain stem is the gateway for neural signals from the gastrointestinal tract to the hypothalamus feeding centers. Also the Amygdala, cortex prefrontalis, as well as area postrema have been held responsible for feeding disorders and inadequate conservation or storage of energy. In addition both the nucleus arcuatus (ARC) and the nucleus paraventricularis (PVN) are important centers [1].

Hypothalamic lesions in experimental animals and in human autopsies with morbid obesity led to "dual center hypothesis" suggesting that ventromedial nuclei (VMN) act as the satiety center and the lateral hypothalamic area (LHA) as the hunger center, that when stimulated result in hyperphagia and subsequently hypothalamic induced obesity [6, 7].

It seems that appetite center is instinctively active and only inhibited for a short term basis by the satiety center just after the meal. The destruction of feeding center in animal models leads to anorexia and cachexia. Signals from the receptors in oropharyngeal and gastric area are conveyed to nucleus tractus solitarius (NTS) in brain stem through afferent nerves. In addition to mechanical stimulation, the chemical stimulation of receptors in gastrointestinal mucosa by nutrients contributes to the peripheral signaling from gastrointestinal tract (GIT) and pancreas with orexigenic and anorexigenic properties [1].

Various enteropeptides and enteric nervous system (ENS) which have their two way connections with CNS mainly via vagal nerves and peripheral neurohormonal component reflects an active regulatory process termed "energy homeostasis" conserving the stability of the amount of the body fat stores [8–10].

The stimulation of appetite is obtained via ARC to hypothalamus by the neurons containing

neuropeptide Y (NPY) and AgRP and inhibition of appetite by neurons containing pro-opiomelanocortin (POMC) derived α-MSH and Cocaine & Amphetamine Regulated Transcript (CART) peptide to hunger centers in LHA, the satiety center in the medial hypothalamus [11]. Thus the coordination of feeding and energy expenditure in response to constantly altered energy balance is managed via NTS to CNS. Moreover, NTS itself gathers and assimilates numerous neural and hormonal impulses from peripheral organs like gastrointestinal mucosa and fat tissues and accordingly transfers to CNS.

Ghrelin

Ghrelin, a potent orexigenic hormone, released from the empty stomach; its plasma level reaches to peak in fasting and lowest after feeding, and this cycle goes on with empty and full stomach [12, 13]. Its peripheral input is routed through ARS and leads to NTS, releasing growth hormone, and regulating energy balance and its metabolic control via hypothalamus [12, 14]. Target of ghrelin are neurons in arcuate resulting in release of NPY and AgRP to express orexigenic effects in brain [11, 15]. It seems to inhibit POMC derivative α-MSH and its anorexigenic effects in the PVN [10, 11, 16]. Experiments have shown that the ghrelin is a mediator of altered energy balance [17–19]. Increased food desire, combined with increased gastrointestinal motility and gastric acid secretion, is associated with higher levels of ghrelin in plasma [20].

Exogenous ghrelin reduces release and action of leptin and vice versa, in that soon after starting of food intake leptin reduces the plasma level of ghrelin [21]. Increased levels of ghrelin in plasma in fasting and weight loss are proposed to be due to diminished or inhibitory effect of leptin and also by peptide YY (PYY). It seems as if the weight reducing effects of leptin are mediated not only centrally via hypothalamus but also peripherally by inhibiting release and actions of ghrelin. Studies of immune-neutralization of ghrelin and leptin with anti-ghrelin and ant-leptin IgG on rats suggest the existence of "Argentinian ghrelin-leptin tango" [21].

The neuropeptide orexin A (OXA) and orexin B (OXB) are implicated in stimulation of food intake [22]. Plasma levels of OXA are increased in humans during fasting, and lowered in obese as compared to normal weight subjects [23, 24]. This suggests that peripheral OXA modulates food intake as an orexigenic agent [25].

The vagal afferent receptors receiving satiety signals from GIT and hypothalamic ARC inhibit the food intake at the satiety center and inhibit the feeding center [10]. The duodeno-jejunal endocrine-I cells secrete cholecystokinin (CCK) [26–29]. This hormone has several isoforms and has five same amino acids at the C-terminal. CCK is also produced in other peripheral nerves and brain neurons, in addition to intestinal mucosa [30]. Physiological mediation of satiety is likely to be obtained by CCK and works well in connivance with the mechanoreceptors of the gut as observed during distension, after food intake, to the brain via vagal afferents. Subdiaphragmatic vagotomy thwarts the effects of exogenous CCK as was found earlier. Also CCK-receptors and vagal nerves limit food intake, and loxiglumide by blocking CCK-receptors abandons the anorexigenic activity of both the exogenous and endogenous hormone [31]. The development of tolerance to CCK and its analogues diminishes its utility as an appetite reducing agent and thus obesity on long term basis as compared to its short term use [32]. Moreover, removing the gene for CCK-receptors could not increase the appetite, instead, resulted in the decreased sensitivity of these animals to anorexigenic action of exogenous CCK [33]. Exogenous CCK injection retains its efficacy, only intermittently, tendency to overeat compensatorily occurs; thus its utility as anti-obesity therapeutic agent becomes questionable.

The control of body weight is actually a concern limited to control of adipose tissue. Adipose tissue acts as a depot for huge amount of energy. Adipocytes produce the leptin, a peripherally active appetite inhibiting hormone. Leptin acts directly on ARC neurons enhancing satiety via specific receptors (Ob-R) on afferent vagal neurons [33, 34]. Leptin is also produced in the stomach, protecting gastric mucosa against topical

irritant and as ulcerogen. It acts at least partly by increasing the blood flow due to increased production of nitric oxide (NO) achieved by the upregulation of NO synthase as well as the brain-gut axis pathways [35, 36]. Also brain gut axis is involved in releasing leptin, in sham feeling, with excitation of vagal nerves [36]. Thus it seems that gastro-protective and hyperemic effects are centrally mediated at least partly by the activation of sensory vagal fibers [37].

Gastric ghrelin antagonizes leptin release in stomach, probably through brain-gut axis, called as "leptin-ghrelin tango", and thus leptin together with insulin acts as lipostatic substance playing their roles in adiposity signaling [1, 38]. It has been observed that insulin applied intracerebroventricularly (ICV) decreases appetite and antibodies to insulin administered ICV increases appetite and body weight. Also insulin, like leptin, seems to inhibit NPY/AgRP neurons in ARC region and enhances satiety [39, 40]. Thus leptin, like insulin, induces an adiposity signal decreasing appetite via hypothalamic receptors through POMC and CART neuronal pathways stimulating satiety center, and decreasing hunger by inhibiting activity of NPY/AgRP neurons.

Conclusion

Obesity is one of the most common metabolic diseases and greatest threat of the health because of the possibility of numerous complications. Development of effective tool of treatment of obesity by drugs or elective surgery demands complete understanding of the mechanisms of appetite and satiety control and a pinpoint evaluation of disorder(s) resulting in obesity.

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Oxidative Stress and Obesity

6

Isabella Savini, Valeria Gasperi,
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Introduction

Obesity is a nutritional disorder, characterized by abnormal or excessive fat accumulation, as a result of adipocyte hypertrophy (increase in size) and/or hyperplasia (increase in cell number). It represents a serious risk to health, as it increases the likelihood of several pathologies (including metabolic syndrome, Type 2 diabetes, cardiovascular diseases, non-alcoholic fatty liver disease, cancer, sleep apnoea and gynaecological pathologies), thus reducing quality of life and life expectancy [1].

A lot of evidence has shown that obesity is a state of chronic oxidative stress, although it is not completely understood if alteration in redox balance is a trigger rather than a result of obesity [2–19]. Overfeeding, high-fat (especially rich in saturated and trans-fatty acids) and high-carbohydrate meals stimulate specific signalling pathways, promoting oxidative stress and inflammation in different cell types [20–23]. On the other hand, oxidative unbalance alters food intake [24, 25] and stimulates adipocyte proliferation and differentiation, thus playing a crucial role in controlling body weight [26–28].

Systemic oxidative stress is achieved through multiple biochemical mechanisms, including superoxide generation, endoplasmic reticulum stress, glyceraldehyde autoxidation, enhanced flux in the polyol and hexosamine pathways, and activation of redox-sensitive kinases and transcription factors [29, 30]. Noticeably, in obese individuals, oxidative stress is so closely interlinked with inflammation as to trigger a vicious circle: oxidants activate specific redox-sensitive transcription factors [including nuclear factor-kB (NF-kB) and activator protein-1 (AP-1)], which drive the expression of pro-inflammatory cytokines; these mediators, in turn, enhance production of reactive oxygen species (ROS), thus contributing to the onset and maintenance of oxidative stress [31].

Besides pharmacological approach, several strategies (weight reduction, physical activity and antioxidant-rich diet) may be taken to lower oxidative stress in obesity. Firstly, weight loss and/or physical activity increase antioxidant defences, thus decreasing oxidative markers and risks for obesity co-morbidities [32–36]. Secondly, diet rich in fruits, vegetables, fish and olive oil helps to maintain the right weight and reduce the risk of metabolic diseases [37–39]. Certain nutrients (including monounsaturated fatty acids, ω-3 polyunsaturated fatty acids, vitamins C and E, phytochemicals and probiotics) contained in such food may account for reduced oxidative stress and inflammation observed in obese subjects [40–44]. Although underlining healthy effects, nonetheless observational and human intervention studies failed to demonstrate

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the efficacy of a single dietary component [45]; rather, it is likely that the beneficial effects on reduction of oxidative stress observed in obese subjects have to be ascribed to cumulative effects of multiple nutrients.

Oxidative Stress: An Overview

In the last 40 years, vast array of data have tried to elucidate the mechanisms involved in the maintenance of redox state in humans; however, some critical issues, related to interpretation of data obtained on *in vitro* experimental models, have been raised as well [46–48]. In addition, this research field often experiences confusion about the correct meaning of some terms. Below, a brief description of concepts commonly used in studies on redox balance is given.

Free Radical

Any molecule that contains one or more unpaired electrons, with a half-life varying from a few nanoseconds (very reactive radicals) to seconds and hours (rather stable radicals).

Antioxidant

A molecule with the ability to scavenge free radicals and hence able to protect biological targets (DNA, proteins, and lipids) against oxidative damage.

Reactive Oxygen Species (ROS)

A collective term that includes radical (hydroxyl radical $^{\cdot}OH$, or superoxide $O_2^{-\cdot}$) and non-radical (hydrogen peroxide H_2O_2) derivatives of oxygen.

Reactive Nitrogen Species (RNS)

A term including derivatives of nitrogen, such as nitric oxide (NO), nitrogen dioxide ($NO_2^{\cdot}$), dinitrogen trioxide (N_2O_3) and peroxynitrite ($ONOO^-$).

Oxidative Damage

Injury caused by RO(N)S to cells and tissues.

Oxidative Stress

A term formulated by Sies in 1985, referring to a significant imbalance between RO(N)S generation and antioxidant protection (in favour of the former), causing excessive oxidative damage [48], depending on the cellular source and/or the major ROS produced. It can be sub-classified in metabolic, environmental, drug-dependent or nutritional oxidative stress [20]. Main ROS and RNS, together with their biochemical characteristics, are summarized in Table 6.1.

All these reactive species, RO(N)S, are continuously produced through cellular metabolism and also act as signalling molecules. Indeed these reactive species, if maintained below a critical threshold value, may play regulatory roles in a range of biological phenomena [49, 50]. Mitochondria are the major site of intracellular ROS production, due to electron leakage along the respiratory chain; other sources include plasma membrane systems, endoplasmic reticulum (ER), lysosomes, peroxisomes and cytosolic enzymes.

At low concentrations, RO(N)S act as secondary messengers, modulating specific signal transduction pathways that, in turn, regulate cell homeostasis, proliferation, differentiation and cell death. Moreover, RO(N)S can directly or indirectly be involved in immune-mediated defence against pathogenic microorganisms [46]. These physiological effects are mainly mediated by changes in the redox state of crucial intracellular and/or surface thiols. Indeed, the RO(N)S-triggered reversible modification of sulphur-containing amino acids represents a common post-translational mechanism for regulating the activity of enzymes, transporters, receptors and transcription factors. Spatial and temporal regulation includes covalent modification of cysteine thiols within the active and allosteric sites of enzymes, oxidation of iron-sulphur clusters, S-glutathionylation (disulfide link between protein thiols and glutathione),

Table 6.1 Main reactive oxygen/nitrogen species and relative features

RO(N)S	Reaction	Description
$O_2^{\bullet-}$ (*superoxide*)	$O_2 + e^- \rightarrow O_2^{\bullet-}$	Oxygen with an extra electron. Produced by: mitochondrial electron transport chain; NADPH oxidases; xanthine oxidase; LOX; COX; NADPH-dependent oxygenase.
H_2O_2 (*hydrogen peroxide*)	$2O_2^{\bullet-} + 2H^+ \rightarrow 2H_2O_2 + O_2$	Formed by the action of SOD. Intracellular signalling. Low intrinsic toxicity.
HOCl (*hypochlorous acid*)	$H^+ + Cl^- + H_2O_2 \rightarrow HOCl + H_2O$	Formed by the action of MPO. It inhibits bacterial DNA replication by destroying anchorage at the membrane. Highly oxidizing.
HO• (*hydroxyl radical*)	$HOCl + O_2^{\bullet-} \rightarrow HO^\bullet + O_2 + Cl^-$ $HOCl + Fe^{2+} \rightarrow HO^\bullet + Fe^{3+} + Cl^-$ $HOCl + Cu^+ \rightarrow HO^\bullet + Cu^{2+} + Cl^-$ $H_2O_2 + Fe^{2+} \rightarrow HO^\bullet + Fe^{3+} + OH^-$ $H_2O_2 + Cu^+ \rightarrow HO^\bullet + Cu^{2+} + OH^-$ $H_2O_2 + O_2^{\bullet-} \rightarrow HO^\bullet + O_2 + Cl^-$	Produced spontaneously by HOCl with $O_2^{\bullet-}$ or metal ions and by H_2O_2 through Fenton reactions. Highly toxic.
ROO• (*peroxy radicals*) ROOH (*organic hydroperoxide*) RO• (*alkoxy radicals*)	$RH + O_2 \rightarrow R^\bullet + {}^\bullet OH$ $R^\bullet + O_2 \rightarrow ROO^\bullet$ $ROO^\bullet + RH \rightarrow R^\bullet + ROOH$ $ROOH \rightarrow RO^\bullet + HO^-$	Produced by the attack of oxygen radicals on unsaturated lipids (RH).
NO (*nitric oxide*)	L-arginine + O_2 + NADPH → L-citrulline + NO + $NADP^+ + e^-$	Formed by the action of NOS. Free radical scavenger. At physiological concentrations, it acts as intracellular messenger. It conjugates with GSH Long half-life.
$ONOO^-$ (*peroxynitrite*)	$NO + O_2^{\bullet-} \rightarrow ONOO^-$	Formed through the action of SOD. It reacts directly with proteins containing transition metal centres.
N_2O_3 (*dinitrogen trioxide*)	$^\bullet NO + \cdot NO_2 \leftrightarrows N_2O_3$	Strongly oxidizing agent. It causes nitrosylation of phenols.

RO(N)S reactive oxygen/nitrogen species, *COX* cyclooxygenase, *GSH* reduced glutathione, *LOX* lipoxygenase, *NOS* nitric oxide synthase, *SOD* superoxide dismutase, *MPO* myeloperoxidase

S-nitrosylation (reaction between NO and thiol radical), and S-nitrosation (reaction between nitrosonium ion and protein thiolates). Conversely, RO(N)S over-production (often coupled with impaired antioxidant defences) can damage DNA, lipids and proteins; thus potentially being harmful to living organisms and being causative of several pathologies, including metabolic alterations, cardiovascular and neurodegenerative diseases, and cancer [51].

To keep RO(N)S at correct levels, tissues possess antioxidant molecules working in synergy to minimize free radical cytotoxicity. The main endogenous antioxidant compounds include: (i) enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase, glutathione S-transferase, catalase, thioredoxin reductase, peroxiredoxins (Prx), NAD(P)H:ubiquinone oxidoreductase (NQO1), heme oxygenase-1 (HO-1) and paraoxonase-1 (PON-1); (ii) low molecular weight molecules, such as urate, glutathione, ubiquinone and thioredoxin; and (iii) some proteins (ferritin, transferrin, lactoferrin, caeruloplasmin) able to bind and sequester transition metals that may trigger oxidative reactions. Exogenous antioxidants, coming from diet, include: vitamin C, vitamin E and a broad spectra of bioactive compounds (such as phytochemicals); other important nutrients are certain minerals (zinc, manganese, copper and selenium) that are crucial for the activity of antioxidant enzymes [50].

Biomarkers of Redox State

Oxidative stress can be evaluated by direct assessment of free radical production or by indirect methods that assess end-products of oxidative damage to proteins, lipids and nucleic acids in blood and urine (Table 6.2).

Direct measures of free radicals, carried out by electron spin resonance (ESR) or by immuno spin-trapping methods are difficult and expensive; therefore, even if promising, they mostly are inapplicable in human research [52]. Oxidative damage to proteins is normally assessed by measuring plasma protein carbonyls, 3-nitrotyrosine, advanced glycosylation end products (AGEs) and advanced oxidation protein products (AOPPs). Indicators of lipid peroxidation are F2-isoprostanes, malondialdehyde (MDA), oxidized LDL (oxLDL), thiobarbituric acid reactive substances (TBARs) and 4-hydroxynonenal (4-HNE). Some biomarkers (such as F2-isoprostanes) are highly sensitive, while others (such as TBARs) are much less sensitive and specific. Furthermore, F2-isoprostanes reflect both acute and chronic oxidative stress. DNA oxidative damage is usually evaluated by measuring urinary 8-hydroxy-2′-deoxyguaine [53–56]. Several studies also employed NADPH oxidase or myeloperoxidase activities in neutrophils. The first enzyme is a plasma membrane enzyme catalysing the mono-electronic reduction of exogenous oxygen using NADPH as an internal electron donor (thus producing $O_2^{-\cdot}$), while the second enzyme is heme-containing protein catalysing the reaction between chloride and H_2O_2 (thus generating the potent oxidant hypochlorous acid) [57].

Another method, widely used to investigate oxidative stress in various diseases and in postprandial responses, is ROS generation by isolated mononuclear cells [22]. Other promising biomarkers of oxidative stress include urinary levels of allantoin (produced by the oxidative breakdown of urate), acrolein-lysine and dityrosine [56]. Finally, a stable, sensitive and inexpensive method to assess changes in oxidant levels is the measurement of total oxidant status (TOS), which is based on the oxidation of ferrous ion to ferric ion in the presence of oxidative species in the acidic medium. By this method, additive effects exerted by different oxidant molecules can easily be determined at the same time [58].

Plasma antioxidant profiles may be useful in conjunction with other biomarkers to measure the levels of oxidative stress. The most widely used biomarkers of the antioxidant state are serum concentrations of antioxidant molecules (retinol, carotenoids, vitamin E, vitamin C, glutathione, uric acid), minerals (selenium and zinc), as well as antioxidant enzyme (SOD, catalase, glutathione reductase, PON1). Another useful biomarker is the total antioxidant capacity (TAC), which evaluates the integrated action of some plasma antioxidants (uric acid, protein thiols and vitamin C) [20]. Finally, quantitative proteomic is emerging as an additional approach to simultaneously evaluate any change taking place in different members of the antioxidant enzyme network [59].

Evidence for Obesity-Related Oxidative Stress in Humans

Substantial cross-sectional studies have outlined the presence of altered redox state in obese subjects and redox imbalance has been demonstrated by the way of increased oxidative stress biomarkers and/or decreased antioxidant defences, both in obese children and adults.

Impairment of body defences in obese subjects may arise either from inadequate intake of antioxidant micronutrients and phytochemicals, from metabolic alterations leading to modifications in the endogenous antioxidant machinery, or from enhanced requirements due to RO(N)S over-production. Currently, the relationship between body mass index (BMI), body fat, and antioxidant defences is still an open question, especially concerning the expression and activity of antioxidant enzymes [34, 60–63]. Controversial data, however, may be explained in terms of time-window, as tissues, at the onset of obesity, increase the activity of antioxidant enzymes in order to counteract oxidative stress, but, as obesity goes on, the antioxidant apparatus is progressively depleted.

In recent years, particular attention has been given to the assessment of redox state in obese

Table 6.2 Common markers used to measure oxidative stress in tissue and/or body fluids

Oxidative effects	Biomarker	Characteristics
Lipid peroxidation	F2-IsoPs	Specific and stable products of arachidonic acid peroxidation.
	MDA	End product of the polyunsaturated lipid peroxidation pathway. Capable of binding to proteins and forming stable adducts, also termed advanced lipid peroxidation end products.
	TBARs	By-product of lipid peroxidation, estimated by using thiobarbituric acid as a reagent. Assay product estimate of MDA formation.
	4-HNE	Primary α, β-unsaturated hydroxyalkenal produced by lipid peroxidation. 4-HNE protein adducts are typically more stable than MDA protein adducts.
	Ox-LDL	LDL is the major transport protein for cholesterol in human plasma. Its oxidation is catalysed by transition metal ions, free radicals, and some oxidizing enzymes. When oxidized, it is specifically recognized by macrophages, leading to foam cell formation.
Oxidative damage to proteins	Protein carbonyls	Derived from oxidative cleavage of the protein backbone, direct oxidation of amino acids (such as lysine, arginine, histidine, proline, glutamic acid, and threonine), or binding of aldehydes produced from lipid peroxidation.
	3-nitrotyrosine	Product of nitration of tyrosine by reactive nitrogen species.
	AGEs	Products derived from the reaction between carbohydrates and free amino group of proteins. The most common are the very unstable, reactive pentosidine and carboxyl methyl lysine.
	AOPPs	Uremic toxins formed during oxidative stress through the reaction of chlorinated oxidants (such as chloramines and HOCl) with plasma proteins. Indicators of nitrosative stress.
	Acrolein-lysine	Derived from the attack of acrolein (the most reactive aldehyde produced from lipid peroxidation) with lysine.
	Dityrosine	Formed by free-radical attack on tyrosine residues, resulting in generation of tyrosyl radical, which in turn yield the stable cross-linked product dityrosine.
Oxidative damage to DNA	8-OHdG	Oxidized derivative of deoxyguanosine of nuclear and mitochondrial DNA.
	8-OHG	Oxidative derivative of guanosine.
Activation of anti-oxidant enzymes	NADPH oxidases	NADPH oxidase family of ROS-generating enzymes with different subcellular localizations. They are differentially expressed and regulated in various tissues.
	MPO	Heme-containing enzyme that generates the potent oxidant HOCl in activated neutrophils.
Others	GSSG/GSH ratio	It evaluates the increased oxidation of glutathione. Under normal conditions, reduced GSH constitutes up to 98 % of cellular glutathione.
	TOS	It evaluates overall oxidant molecules. It is based on oxidation of Fe^{2+} to Fe^{3+} in the presence of various oxidative species.
	Allantoin	Produced by the oxidative breakdown of urate, the terminal product of purine metabolism.

4-HNE 4-hydroxynonenal, *8-OHdG* 8-hydroxy-2′-deoxyguanosine, *8-OHG* 8-hydroxyguanosine, *AGEs* advanced glycosylation end products, *AOPPs* advanced oxidation protein products, *F2-IsoPs* F2-isoprostanes, *GSSG/GSH ratio* reduced/oxidized glutathione, *MDA* malondialdehyde, *MPO* myeloperoxidase, *Ox-LDL* oxidized low-density lipoproteins, *TBARs* thiobarbituric acid reactive substances, *TOS* total oxidant status

children and adolescents, with or without the simultaneous presence of metabolic alterations (insulin resistance and steatosis), since these patients show higher risk to early develop obesity-associated chronic diseases. Moreover, children and adolescents often have poor intakes of vegetables and fruit, as well as micronutrient deficiencies (iron, zinc, vitamins A, E and C), that may contribute to oxidative stress [4].

A significant inverse relation has been found between adiposity and serum concentrations of carotenoids and vitamin E, in Mexican-American children (8–15 years of age), included in the 2001–2004 U.S. National Health And Nutrition Examination Survey (NHANES). The finding has been confirmed in NHANES III (as well as in separate studies carried out in the United States, Brazil, France, and Italy) that pointed out lower serum levels of lipophilic vitamins in overweight or obese children and adolescents with respect to normal-weight counterparts(despite similar daily intakes of fruit and/or vegetables) [11, 64]. These differences seem to be not gender-specific, since similar results have been obtained in boys and girls [11]. Also vitamin E and C levels appear to be inversely proportional with body fat, abdominal fat and waist/height ratio, in 197 Mexican school-aged children. In addition, low concentrations of zinc, vitamins A and E appear to be positively correlated with insulin resistance and inflammation in overweight or obese children [8]. Deficiencies in selenium and zinc have also been reported in children with central adiposity [65, 66]. Finally, a relationship between glutathione homeostasis and obesity has been proven: a significant reduction in total, reduced and oxidized glutathione as well as in glutathionylated proteins has been found in 30 obese children [5].

As mentioned before, less clear are investigations carried on antioxidant enzymatic activities. Sfar and colleagues reported increased SOD activity in 54 obese healthy children (aged 6–12 years), while GPx and CAT activities appeared unaffected [9]. Conversely, Sun's group documented a decrease in SOD activity, associated with increased MDA levels and NADPH oxidase activity, in 93 overweight adolescents [10]. Similarly, lower thiol content and SOD activity (paralleled by enhanced GPx1 and catalase activities) have been found to be related to central obesity, in 156 children and adolescents (47 lean, 27 overweight and 82 obese subjects). This cohort also showed inverse relation between PON1 activity and central obesity. All these associations were gender dependent: PON1 catalytic activity appeared to be sensitive to oxidative stress in girls, while being modulated by inflammation in boys [16]. Accordingly, Agirbasli reported a negative correlation between BMI and PON1 catalytic activity, while Torun found that PON1 activity significantly increased in 109 obese children and adolescents (either with or without steatosis) [12, 17].

Juvenile overweight and obesity is also linked to high levels of oxidative stress and inflammation markers [67, 68]. Pirgon and co-workers found decreased TAC values in obese adolescents (either with or without steatosis), increased oxidative stress index (TOS/TAC ratio) and insulin resistance [69]. Decreased TAC and increased oxidative stress was also found in 25 Caucasian obese children [70]. Conversely, Torun's group reported comparable oxidative stress indexes in obese and lean children, and increased TAC measurements in obese children with non-alcoholic fatty liver disease (NAFLD) [12].

Central obesity, triglycerides and insulin correlated also with oxidative stress markers. A positive correlation between AOPPs and obesity has been found in children and adolescent; this marker also correlated with glucose/insulin ratio and HDL-cholesterol [71, 72]. In 112 overweight and obese children (7–11 years old), F2-isoprostane concentrations were positively linked to body mass index (BMI), waist circumference, insulin resistance, and dyslipidemia, while being inversely associated with fitness (peak of oxygen consumption: VO_2max) [73]. Similar results have been obtained in a study enrolling 82 African American and 76 White American youth (8–17 years old) [68]. In a cross-sectional study, severely obese Caucasian children (7–14 years old) showed enhanced levels of AOPPs and inflammatory markers [72].

Mineral and vitamin deficiencies are often detected in obese adults [74–76]. Studies on Coronary Artery Risk Development in Young Adults (CARDIA) showed a strong inverse relationship between BMI and serum carotenoids (α-carotene, β-carotene, β-cryptoxanthin, zeaxan-

thin/lutein) [77]. The multicentre prospective population study of diet and cancer in Europe (EPIC) reported inverse correlation between plasma vitamin C concentrations and central fat distribution [78]. As obesity goes on, a linear rate of deficiency of vitamins A, B_6, C, D and E has been noted [79].

Several experimental and clinical trials have shown that the catalytic activity of antioxidant enzymes is often reduced in adult obese subjects, although available data remain ambiguous and unconfirmed. Indeed, obese individuals with insulin resistance appear to have lower plasma SOD activity and higher GPx activity than healthy, lean controls [80]. In addition, serum GPx activity seems to be positively correlated with weight reduction [63]. Accordingly, several studies underlined an inverse relationship between BMI and antioxidant enzyme activities (especially SOD, catalase, PON1 and GPx) [13, 61, 62, 81, 82].

In a population-based (3042 Greek adults) study, an inverse relationship was found between waist circumference and TAC, regardless of variations in, sex, age, physical activity, smoking, and dietary habits [83] Comparable reduction in TAC measurements (together with low levels of vitamins C and E and high levels of hydroperoxides and carbonyl proteins) was observed in young and old obese patients, and signs of oxidative stress were aggravated in older adults [84].

Concerning biomarkers of oxidative stress, levels of F2-isoprostane, protein carbonyl, TOS, oxLDL and TBARs have been shown to be positively associated with BMI and waist circumference in adults [2, 3, 14, 82, 85, 86]. In addition, endothelial dysfunction and endothelial NADPH oxidase activity were found to be associated with central adiposity markers (waist circumference or waist-to-hip ratio) [87]. Interestingly, association of central adiposity markers with oxLDL and TAC is more evident in women, thus suggesting that changing the gynoid to android phenotype may lead to an unfavourable redox state in young women rather than in men [88].

Recently, several studies have focused on the relationship between obesity and redox state during pregnancy. In a prospective case-control study, obese pregnant women showed increased inflammation and oxidative stress (low levels of vitamins B_6, C, E, and folate, high levels of GSSG/GSH ratio, C-reactive protein and IL-6), with respect to lean pregnant women. Newborns from these obese mothers, however, did not show significant changes in oxidative stress and inflammation [89]. On the other hand, dysregulation of redox balance in the mother-placenta-fetus axis has been reported by Malti's group; maternal, foetal and placental tissues coming from obese women (pre-pregnancy BMI > 30 kg/m^2) showed higher oxidative stress (MDA, carbonyl proteins, O_2^-, NO) and lower antioxidant defences (GSH and SOD activities), if compared to control pregnant women, and variations of redox balance were also observed in newborns from these obese mothers [90].

In obese women, oxidative stress may also be associated with gynaecological disorders. A systematic meta-analysis showed increased SOD activity, decreased GSH levels and decreased PON1 activity in patients with polycystic ovary syndrome [91]. Also localised oxidative stress and insulin resistance (in abdominal adipose tissue) seem to play a crucial role in the pathogenesis of this syndrome [15].

In conclusion, conflicting results emerging from cross-sectional and intervention studies in obesity field are difficult to interpret. However, they could be explained in terms of the use, in each investigation, of single or only few, insensitive, non-specific markers of redox state [53]. The best and unambiguous results demonstrating the relationship between oxidative stress and obesity have been obtained when several oxidant and antioxidant molecules were considered together or when urinary isoprostanes (the best available biomarker of lipid peroxidation) were measured.

Mechanisms Underlying Oxidative Stress in Obesity and Oxidative Stress-Induced Diseases

Mechanisms Underlying Oxidative Stress

Oxidative stress is clearly connected with obesity, although it is not fully understood the real cause-effect relationship. Nutritional overload (especially after consumption of high-fat high-carbohydrate meals, as well as of high

Table 6.3 Potential mechanisms accounting for oxidative stress in obesity

Obesity-associated conditions	Metabolic changes	Effects on redox/inflammatory systems
Hyperlypidemia	ATP accumulation in mitochondria. Mitochondrial DNA damage	ROS overproduction.
		Pro-inflammatory cytokine increase. Endoplasmic reticulum stress.
Adipose tissue dysfunction	Adipose tissue macrophage infiltration	ROS overproduction.
		Pro-inflammatory cytokine increase.
		Nrf2 deletion.
		Antioxidant enzymes decrease.
		Endoplasmic reticulum stress.
Hyperglycemia	Increased glycolysis and tricarboxylic acid cycle	ROS overproduction
	Increased polyol pathway	NADPH depletion
	Increased AGEs	Stimulation of NF-kB, NADPH oxidases and iNOS
	Activation of PKC	Stimulation of NF-kB and iNOS.
		Aberrant expression of specific microRNAs.
	Increased hexosamine pathway	Thioredoxin inhibition.
		Endoplasmic reticulum stress.
		Pro-inflammatory cytokine increase.
Endothelial dysfunction	Chronic inflammation and monocyte recruitment	Activation of NADPH oxidases, xanthine oxidase and iNOS.
		ROS overproduction.
		Pro-inflammatory cytokine increase.
Hyperleptinemia	Increased mitochondrial and peroxisomal fatty acid oxidation. Monocytes/ macrophages activation	ROS overproduction.
		Pro-inflammatory cytokine increase.
Genetic variants (SNPs)	Altered activity of GPx, PON1, catalase, peroxiredoxins, SOD, NADPH oxidases, PPARγ, PGC1α, Nrf2	ROS overproduction.
		Antioxidant enzymes decrease.

AGEs advanced glycosylation end products, *iNOS* inducible nitric oxide synthase, *PKC* protein kinase C, *ROS* reactive oxygen species, *SOD* superoxide dismutase, *GPx* glutathione peroxidase, *PON1* paraxonase 1, *PPARγ* peroxisome proliferator activated receptor γ, *PGC1α* PPARγ co-activator 1α, *Nrf2* nuclear factor E2-related factor 2, *SNPs* single nucleotide polymorphisms

dietary saturated fatty acids and trans-fatty acids) leads to oxidative stress by different mechanisms [23]. On the other hand, oxidative stress could play a causative role in the development of obesity, by altering food intake and stimulating adipocyte proliferation and differentiation [24–28]. Several factors contribute to obesity-associated oxidative stress, including abnormal post-prandial ROS generation, low antioxidant defences, hyperleptinemia, tissue dysfunction and chronic inflammation [2–22, 92, 93]. In this context, it should be recalled that a vicious circle can be established: ROS activate redox sensitive transcription factors [including nuclear factor-kB (NF-kB) and activator protein-1 (AP-1)], which in turn promote over-expression of inflammatory cytokines that lead to exacerbation of ROS production [31] (Table 6.3).

In obese subjects, the adipocytes surpass to non-physiological limits and become unable to

function as an energy storage organ; therefore, fat is improperly accumulated in heart, muscle, liver and pancreas, where it can trigger these organs' dysfunction. In particular, adipose tissue dysfunction contributes to the onset of oxidative stress, by increasing expression of adipokines (MCP-1, -2, -4, and macrophage inflammatory protein (MIP) -1α, -1β, -2α) that trigger macrophage infiltration and subsequent overproduction of ROS and inflammatory cytokines [94, 95]. Simultaneously, the activity of the redox-sensitive transcription factor, nuclear factor E2-related factor 2 (Nrf2) becomes impaired. As a result, the expression of Nrf2 downstream targets (antioxidant and phase II detoxifying enzymes) is inhibited, leading to the weakening of the body antioxidant defences [96]. Also bioavailability of antioxidant molecules may be impaired, as is the case with vitamin C. Also, sodium-dependent vitamin C transporters expression has been shown to be modulated by metabolic and/or oxidative stress, thus affecting cellular uptake and the overall homeostasis of this vitamin [97].

Additionally, intracellular triglyceride accumulation triggers lipotoxicity, by inhibiting the adenosine nucleotide translocator (ANT) leading to ATP accumulation into mitochondria. Mitochondrial ADP fall reduces the speed of oxidative phosphorylation and mitochondrial uncoupling promotes electron leakage and ROS generation. High fat diet-induced mitochondrial dysfunction also triggers the endoplasmic reticulum (ER) stress. The ER is a cytosolic organelle that participates in the regulation of lipid, glucose and protein metabolism, apart from being at the site where protein folding occurs. ER stress observed in obesity basically results in impairment of protein folding leading to production of misfolded proteins which activate abnormal "unfolded protein response" (UPR). In turn this stimulates ROS production, with subsequent systemic release of free fatty acids and inflammatory mediators, lipid droplet creation and hepatic cholesterol accumulation [98, 99].

Ectopic-fat deposition also inhibits glucose transport and insulin signalling in skeletal muscle, thus promoting insulin resistance [62, 100]. Hyperglycaemia is another condition promoting oxidative stress, by enhancing oxidative degradation of glucose; the resulting increase in proton gradient across the mitochondrial inner membrane leads to electron leakage and $O_2^{-\cdot}$ production. As a result, glycolytic metabolites are shifted to four alternative pathways: (i) glucose is redirected into the polyol pathway; (ii) fructose-6-phosphate is redirected into the hexosamine pathway; (iii) triose phosphates produce methylglyoxal, the main precursor of advanced glycosylation end products (AGEs), and (iv) dihydroxyacetone phosphate is converted to diacylglycerol, thus activating protein kinase C (PKC) [101]. These four pathways induce oxidative/nitrosative stress, by different mechanism. Activation of the polyol pathway leads to NADPH depletion, glucosamine-6-phosphate derived from the hexosamine pathway induces oxidative and ER stress, and AGEs and PKC stimulate ROS/RNS production by activating NADPH oxidases and NF-kB [102, 103]. In particular, NF-kB is a transcription factor whose downstream targets are pro-inflammatory cytokines (TNF-α and IL-6), inducible nitric oxide synthase (iNOS), adhesion molecules (E-selectin, intercellular adhesion molecule-1 and endothelin-1), and some microRNAs (miR). Aberrant expression of these NF-kB-responsive genes may account for increased oxidative/nitrosative stress and inflammation, as well as for enhanced adipogenesis (for example, modulation of miR-103, miR-143, miR-27a and miR-27b has been recognized as condition leading to adipose hypertrophy and hyperplasia) observed in obese individuals [104–106]. Finally, oxidative stress is exacerbated by inflammatory mediators that worsen insulin signalling, thus intensifying hyperglycaemia [6].

A relevant source of ROS can also be represented by endothelial dysfunction, commonly found in obesity, due to chronic inflammation and dysregulation of adipocyte-derived factors. Activation of endothelial NADPH oxidase (triggered by cytokines, hormones, elevated intraluminal pressure and hypertension) increases ROS levels, thus aggravating vascular injury [107].

Among adipocyte-derived factors, the hormone leptin plays a crucial role in obesity-associated oxidative stress. Hyperleptinemia

increases mitochondrial and peroxisomal fatty acid oxidation, with subsequent stimulation of ROS production via the mitochondrial respiratory chain [92, 108]. In addition, it stimulates activation of monocytes/macrophages, with production of pro-inflammatory cytokines (IL-6 and TNF-α) that intensify oxidative stress [109].

Genetic variants, such as single nucleotide polymorphisms (SNPs) in genes encoding for mediators of redox balance, represent an emerging research field in obesity. Recently, Rupérez and colleagues reviewed the current knowledge about the impact of specific SNPs on the risk of obesity or obesity-associated co-morbidities [110]. In particular, they focused on SNPs of antioxidant enzymes (GPx, PON1, catalase, peroxiredoxins, SOD), ROS-producing enzymes (NADPH oxidases) and transcription factors involved in ROS response mechanisms (PPARγ, PGC1α, Nrf2). Other genetic loci relevant for body weight regulation and oxidative stress have also been identified, including protective and susceptible SNPs in the mitochondrial control region [111], in fat mass and obesity associated (FTO) gene [112], and in the gene encoding for uncoupling protein 2 (UCP2) that leads to heat dissipation (without synthesis of ATP) and controls mitochondrial free radical production [113]. However, the expression of metabolic phenotypes is markedly affected also by environmental and epigenetic factors, thus making difficult to assess the real impact of genetically controlled heritability in human obesity.

Oxidative Stress-Induced Diseases

All the above mentioned ROS-generating conditions may play a causative role in obesity-related co-morbidities [114]. In Non-alcoholic Fatty Liver Disease (NAFLD) and Non-alcoholic Steatohepatitis (NASH), mitochondrial dysfunction, ER stress and hyperglycaemia cause excessive electron flux in the electron transport chain and ROS overproduction. As a result, fatty acid catabolism is impaired, while lipogenesis is stimulated, and, therefore, lipids abnormally accumulate in hepatocytes [115]. ROS accumulation also plays a key role in the development of metabolic syndrome, characterized by central obesity associated with two or more complications (hyperglycaemia, hypertension, dyslipidaemia), representing elevated risk factors for cardiovascular pathologies. Subsequently redox-inflammatory processes, together with visceral adiposity, disrupts downstream events of the insulin signalling pathway, thus triggering insulin resistance, which in turn promotes endothelial dysfunction, decreased vasodilatation and increased blood pressure [116]. Type 2 diabetes develops in obese individuals as a result of insulin-resistance. Impaired glucose tolerance is achieved through multiple mechanisms, all involving oxidative stress: (i) β-cells (possessing low scavenging ability) die because of chronic oxidative stress and adipokine secretion, (ii) adipocyte oxidative stress leads to production of glutathionylated products of lipid peroxidation that results in insulin resistance and inflammation, and (iii) protein oxidation and/or misfolding, resulting in proteasomal dysfunction, contribute to the onset of insulin-resistant and obese phenotype [117–119].

Circulating free fatty acids, insulin resistance, oxidative stress, mitochondrial and endothelial dysfunction are also key pathogenic factors of obesity-associated cardiovascular pathologies (including coronary and peripheral artery disease, stroke, cardiomyopathy and congestive heart failure) [95]. Elderly subjects appear to be more susceptible to obesity-associated vascular complications than younger individuals, may be because aging worsens obesity-triggered inflammation in perivascular adipose tissue, thus increasing oxidative stress and inflammation in a paracrine manner [120]. A significant correlation has been found between BMI and tumour susceptibility: obesity accounts for 14–20 % of deaths due to gastrointestinal, breast, prostate, endometrium, uterus and ovary tumours in both males and females [121].

It is now well recognized that ROS overproduction triggers DNA damage, thus leading to

genomic instability associated with activation of oncogenes and/or inactivation of tumour suppressor genes [122–124]. A recent systematic meta-analysis documented that oxidative stress, together with visceral adipose tissue, is one of the pathogenic mechanisms accounting for polycystic ovary syndrome. Indeed, abdominal adipocytes coming from patients affected by polycystic ovary syndrome show enhanced oxidative stress and impaired insulin signalling [15, 91]. Finally, oxidative stress and inflammation are involved in the pathogenesis of obstructive sleep apnea, a breathing disorder often associated with central obesity. In this disorder repeated breathing arrests lead to an ischemia/reperfusion condition, resulting in ROS overproduction that is enhanced by high levels of pro-inflammatory cytokines found in neutrophils and monocytes of sleep apnea patients [125].

Lifestyle and Nutritional Intervention to Reduce Oxidative Stress in Obesity

Natural strategies designed to increase antioxidant defences in obese subjects could be useful to prevent and treat obesity and co-morbidities. Herein, we will report recent experimental evidences concerning the effects of physical activity and diet on modulation of redox state; we will also describe potential mechanisms through which weight loss, overall diet composition and single diet components (macronutrients, micronutrients, and phytochemicals) modulate redox homeostasis.

Independent of weight reduction, physical activity exerts positive effects on oxidant/antioxidant balance. For example exercise reduces NADPH oxidase activity and ROS generation, while increasing blood levels of anti-inflammatory cytokines (interleukins 1 and 10) [126, 127]. In a retrospective analysis enrolling 108 obese, middle-aged men, exercise training without dietary restriction has been shown to improve hepatic inflammation and related oxidative stress [128]. A cross-sectional study carried out on overweight/obese postmenopausal women (45–64 years old) showed that active lifestyle (aerobic exercise for at least 30 min, three times per week) was associated with increased antioxidant enzyme activities (catalase and SOD) in peripheral blood mononuclear cells [36]. Krause and colleagues reported that aerobic exercise (at moderate intensity, three times per week) did not change body composition or aerobic fitness, but ameliorated oxidative markers in obese subjects with or without Type 2 diabetes [129]. A retrospective analysis have been conducted to determine whether exercise without dietary restriction can influence the pathophysiology of abnormal liver function in obese, middle-age men. Results showed that physical activity benefits the management of obesity-related liver diseases regardless of detectable weight reduction; in particular, these effects seem to be acquired through an improvement in hepatic oxidative stress levels and related inflammatory conditions [128]. Besides direct effects on oxidative stress, exercise is also able to reduce abnormal conditions such as inflammation and insulin resistance that underpin obesity-associated diseases. Aerobic and resistance exercise (Nordic walking) for 12 weeks without dietary intervention does not influence oxidative stress, but decreases atherogenic index in overweight or obese males (40–65 years) with impaired glucose regulation [130]. Therefore, regular exercise acts as a natural antioxidant and anti-inflammatory strategy for preventing obesity-associated complications.

Combination of regular exercise with caloric restriction potentiates the beneficial effects on redox balance. Physical activity associated with weight loss has been found to be the most efficacious approach to prevent dyslipidemia, hypertension, Type 2 diabetes, cardiovascular diseases, NAFLD and colorectal cancer, even though it is difficult to determine if the observed effects are due to exercise, weight loss or specific diet components [131, 132]. Gutierrez-Lopez et al. showed that regular and moderate aerobic exercise plus hypocaloric diet was more effective than hypocaloric diet alone in decreasing

oxidative stress markers and insulin polymerization, in 32 obese subjects [34]. Lifestyle intervention (including both exercise and diet) has been shown to be a successful approach for ameliorating endothelial dysfunction, inflammation and oxidative stress, in obese children [133].

Weight reduction obtained via caloric restriction alone has been proven to reduce the levels of protein carbonylation, AOPPs, lipid peroxidation, oxidized lipoproteins and F2-isoprostanes, as well as of inflammatory markers [33, 35, 134, 135]. In overweight and obese women, a modest reduction in caloric intake (25 % caloric restriction) is sufficient to rapidly decrease oxidative stress [33]. This finding has been confirmed by Chae's study showing that a daily 100-kcal calorie reduction was able to revert the elevated oxidative stress observed in overweight and obese individuals (3-year follow-up leading to only 5.4 % weight loss). Noticeably, lifestyle intervention has to be long-lasting, as resuming a habitual diet brings back the levels of oxidative markers to the baseline values within 3 months, in ~80 % of women [33]. The mechanisms by which lowering energy supply ameliorates metabolic functions mainly include activation of sirtuins, NAD^+-dependent deacetylases that regulate metabolism, improve antioxidant defences and dampen inflammatory activities [136]. Also the transcription factor FoxO (Forkhead box, sub-group O), which up-modulates the expression of genes involved in energy homeostasis, induces cell survival and inflammatory responses [137].

Besides weight reduction, diet quality is a key factor for redox homeostasis. Western diets (increased intake of artificial energy-dense foods and reduced intake of complex carbohydrates, fibres, fruits and vegetables) deeply contribute to oxidative stress and metabolic alterations promoting lipotoxicity [20–23, 40, 138]. Conversely, antioxidant-rich diets are effective in both reducing oxidative stress and speeding up weight loss. Indeed, Mediterranean diet (rich in whole-grains, legumes, nuts, fruit, vegetables, fish, low-fat dairy products, and olive oil as principal source of fat) and Okinawan diet (rich in unprocessed foods, vegetables, sweet potatoes with small amount of fish and lean meat) exerts protective effects against obesity and obesity-related pathologies [37, 139–141]. In particular, the Mediterranean diet (even without weight reduction) is able to reduce oxidative stress and inflammation, as well as to improve insulin sensitivity. For example, abdominally overweight men and women showed lower concentrations of pro-inflammatory cytokines after 8 weeks of a Mediterranean diet [142]. In addition, among high cardiovascular risk subjects (carrying the genetic variants rs9939609 for *FTO* and rs17782313 for *MC4R*, conferring genetic susceptibility to obesity and diabetes), those adhering to Mediterranean diet had lower rate of Type 2 diabetes [143].

Specific food or nutrients also exert positive effect on redox balance, inflammatory biomarkers and metabolic alterations associated with obesity. Animal and human studies have highlighted the protective role of mono-unsaturated fatty acids (abundant in olive oil) and ω-3 poly-unsaturated fatty acids (abundant in fish and nuts) on cardiovascular risk in overweight and obese subjects, via different mechanisms: (i) reduction of oxidative stress and inflammation, (ii) increase of antioxidant defences via the Nrf2/HO-1 pathway, (iii) prevention of endothelial dysfunction, (iv) improvement of hyperglycaemia and hyperinsulinemia [142, 144–147]. Other subsidiary dietary compounds (such as antioxidant vitamins and phytochemicals) contribute to a well redox balance, by directly scavenging ROS or indirectly modulating the activity of redox-sensitive transcription factors and enzymes, as well as by exerting anti-inflammatory actions. A diet containing food with high antioxidant capacity (such as fruits, vegetables, and legumes) is negatively associated with adiposity, oxidative stress markers, and obesity-related co-morbidities (Type 2 diabetes and cardiovascular diseases) [148, 149].

From the NHANES (2003–2006) studies, it has emerged that consumption of orange juice lowers about 21 % the risk of obesity and of about 36 % the risk of metabolic syndrome. On the other hand mandarin juice consumption up-modulates antioxidant defences in obese children,

tomato juice consumption improves plasma TAC and erythrocyte antioxidant enzymes in overweight females [150–152]. Daily consumption of grapefruit (fruit or juice) ameliorates oxidative stress in overweight and obese adults with metabolic syndrome [153]. A 24-weeks trial with unsalted pistachio nuts (20 % of total energy) leads to beneficial effects on redox state and cardio-metabolic profile of Asian Indians with metabolic syndrome [154]. The same beneficial effects on serum TAC and oxidative stress indexes have also been obtained with consumption of broccoli sprouts powder and carrot juice, in overweight and Type-2 diabetes patients [155, 156].

Antioxidant supplements (vitamins C and E, carotenoids, lipoic acid) may also be useful in primary and secondary prevention of ROS-induced health problems. Several short-term studies have shown that vitamin E supplementation resulted in significant reduction of oxidative stress and improvement of lipid state and cardio-metabolic alterations, in children and adults [157–159]. However, adverse effects have been reported as well, especially in long-term clinical trials, so that vitamin E supplementation should be carefully evaluated [160, 161]. Obese individuals and diabetic subjects often experience high rate of vitamin C deficiency and, therefore, regular consumption of vitamin C-rich foods has to be recommended [7]. Indeed, observational and interventional studies have suggested a beneficial role of vitamin C on prevention of diabetes, hypertension, stroke and heart failure, but supplementation data do not allow to univocally establish the role played by vitamin C on health outcomes [162–165]. Another vitamin deficiency commonly found in obese individuals are carotenoids (both pro-vitamin A and not pro-vitamin A carotenoids), so that these individuals may benefit from their supplementation [166]. Acting as antioxidant and anti-inflammatory agents, they modulate markers of inflammation, oxidative stress, and endothelial dysfunction, thus exerting a protective role against obesity-associated diseases [167, 168]. However, both positive and negative effects have been reported by *in vivo* supplementation studies with β-carotene, astaxanthin, β-cryptoxanthin and lycopene [169]. Interestingly, the potential of α-Lipoic acid (LA) in human therapeutics was found to bring strength in several human supplementation studies. LA increases the Nrf2-mediated anti-oxidant responses and prevents obesity-induced oxidative stress and lipoapoptosis in rat liver [170]. Administration of LA to patients with Type 2 diabetes decreases plasma oxidative products and improves insulin sensitivity [171]. Oral LA supplementation promotes body weight loss in healthy overweight/obese subjects [172, 173]. The mechanisms accounting for these positive effects not only mainly rely on modulation of redox homeostasis, but also on increased insulin sensitivity, mitochondrial biogenesis and promotion of browning process in white adipose tissue [174].

Among phytochemicals provided by food of plant origin, polyphenols constitute the most abundant and heterogeneous class and indeed, different categories (phenolic acids, stilbenes, flavonoids, chalcones, lignans and curcuminoids) can be identified on the basis of their structures. Depending on chemical structure, bioavailability and metabolism, each phytochemical exerts distinct physiological effects through multiple (sometimes overlapping) mechanisms. Referring to a more comprehensive review about the best characterized biological properties of each bioactive compound [7], here we only emphasize that polyphenols may modulate inflammation and redox state, as well as adipocyte differentiation and lipid metabolism [175]. In this way they exert protective effects on oxidatively triggered pathologies [41, 176]. Short-term clinical trials have indeed pointed out a positive role of specific compounds on obesity, glucose tolerance and cardiovascular risk factors [177–180]. A particular class deserves to be mentioned is isoflavones (genistein, daidzein and glycitein), because they are analogues of estrogens, therefore, their ability to exert anti-adipogenic and anti-lipogenic effects mainly rely on binding to estrogen receptors, thus modulating the expression of genes involved in adipose development, insulin sensitivity and fatty acid metabolism rather than only on antioxidant activity [181, 182]. However, it should be

recalled that many of the positive effects ascribed to polyphenols have been demonstrated by *in vitro* studies and *in vivo* biological relevance has not been established yet, especially considering the low bioavailability and rapid body metabolism of these bioactive phytochemicals.

Another interesting finding is that the interaction of polyphenol-gut microbiota represents an additional modulator of oxidative stress-mediated pathologies. Indeed, studies have shown that microbiota modulates the activity of different polyphenols (thus explaining the inter-individual variability observed in polyphenol supplementation studies), and, meanwhile, polyphenols change intestinal redox state (thus modulating quantitative and qualitative features of gut-microbiota) [183].

Microbial activities and gut 'dysbiosis' are involved in controlling the body weight and insulin-resistance [184, 185]. On the other hand, probiotics (healthy micro-organisms, including *Bifidobacteria* and *Lactobacilli*) and prebiotics (non-viable food components, such as inulin-type fructans, able to modulate microbiota composition) may confer health benefits for obese individuals, lowering oxidative unbalance [43, 185]. Indeed, daily consumption of probiotics has been shown to improve antioxidant parameters (TAC, enzymatic activities of SOD and GPx) and to decrease oxidative markers (MDA, oxLDL and 8-isoprostanes), both in healthy subjects and type 2 diabetic patients [186, 187].

Conclusions

Numerous investigations indicate that obesity is strictly linked to changes in redox state. Abnormal production of ROS and nitrogen species, due to unhealthy lifestyle (chronic hyper-nutrition, low quality diet and sedentary life), affects white adipose tissue, endothelium and muscle biology, thus leading to obesity-associated pathologies (including NAFLD, diabetes, hypertension, cardiovascular diseases and cancer) (Fig. 6.1).

Governmental and non-governmental organizations are developing new strategies for prevention and control of obesity, especially concerning lifestyle intervention, in order to limit morbidity and mortality rates, as well as health care costs. Approaches aimed at modulating redox homeostasis are emerging as novel tools for preventing or slowing down progression of obesity-associated pathologies. Studies on humans claim that the first goal to be achieved should be to reduce oxidative stress by combination of weight loss, physical activity and high quality diet. Obese individuals might also benefit from regular consumption of foods with high antioxidant natural compounds rather than from supplementation with antioxidant compounds. This is because of paucity of data (often controversial and not conclusive) concerning clinical trials with specific nutrients. More promising appears to be a diet rich in polyphenols, widely distributed in fruits, vegetables and some plant-derived beverages (such as coffee and tea), which are effective in counteracting weight gain and oxidative stress. Moreover, their biological activity may be enhanced by modulating composition of gut microbiota that represents a novel way of dealing with redox unbalance in overweight or obese individuals. In conclusion, the winning strategy for lowering risk factors of obesity-associated complications remains weight loss through physical activity and diet rich in fruits, vegetables and spices (containing antioxidant vitamins and phytochemicals), fish (containing ω-3 polyunsaturated fatty acids) and low-fat, fermented dairy products (especially those containing probiotics).

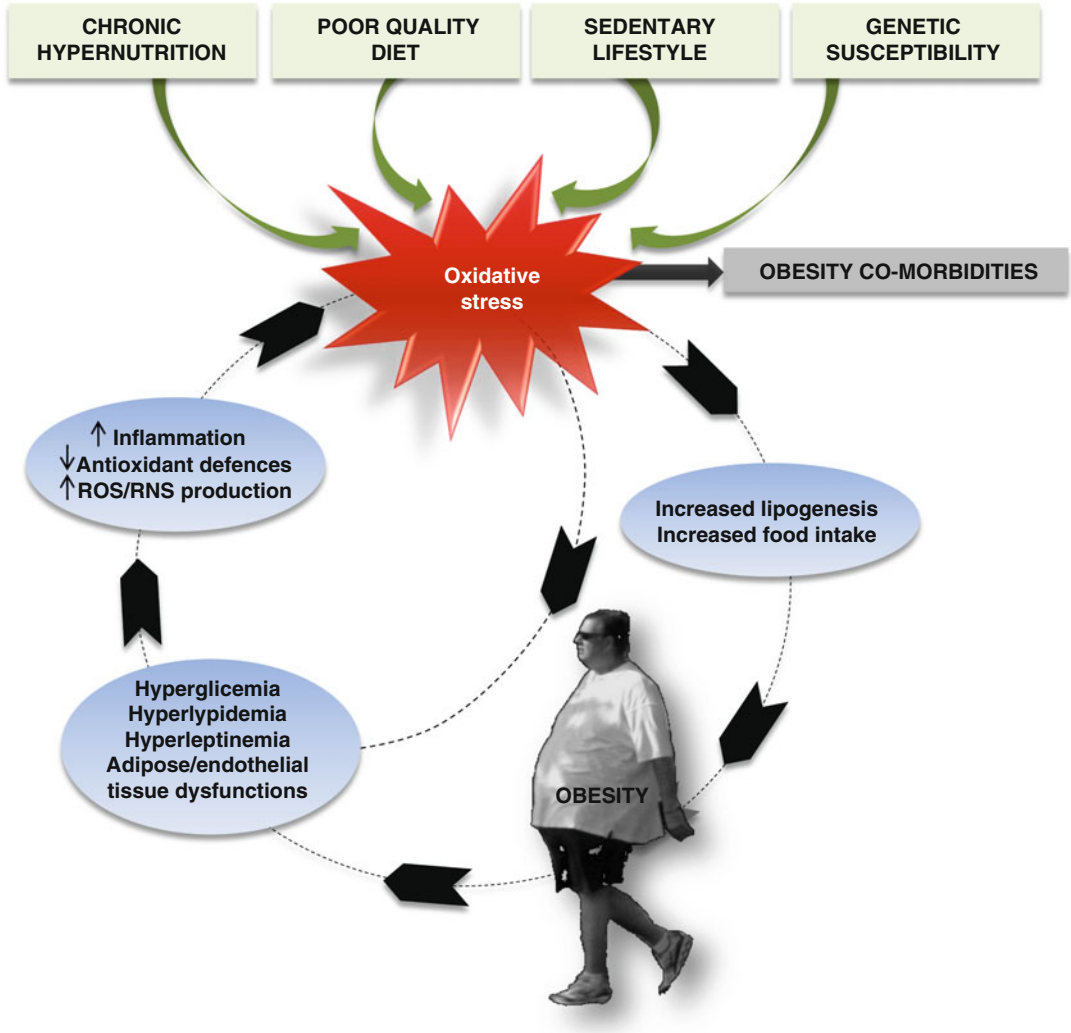

Fig. 6.1 Relationship among oxidative stress, obesity and obesity-associated diseases. Excessive caloric intake, low-quality diet and sedentary lifestyle, even before weight gain, are suggested to be primary triggers of systemic oxidative stress and inflammation; genetic variants are involved as well. A vicious circle is established: by stimulating white adipose tissue deposition and altering food intake, oxidative stress contributes to the onset and progression of obesity, as well as to development of obesity-associated diseases. Both obesity and oxidative stress trigger inflammatory conditions that, in turn, lead inexorably to a worsening of the situation (see Text for further details)

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Genetics of Human Obesity

7

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Introduction

For a considerable period of prehistory, hominines were primarily hunter-gatherers. In that period as the food was severely limited, the natural selection favored humans who had the capability of storing energy as fat. As food nowadays is relatively easily available it may be influencing our genome, resulting in a different selective process from past events. On the other hand, the changes in our environment have been occurring more rapidly than the evolution in our genetic makeup. In fact, our genetic background is not very different since around 12,000 years ago, which correspond to the beginning of the agriculture development [1]. This means that there could be a delay in the adjustment of the genetic profile to environment, and that our genetic background would be similar to the one from the time our forefathers were foragers.

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This interpretation result from the "thrifty gene" hypothesis proposed by Neel for a possible evolutionary perspective of obesity [2, 3]. Therefore, when considering the incompatibility between our modern lifestyle and our "ancient" genetic profile, it is understandable why so many people gain weight so easily. When human morphology is considered, there are profound individual differences, such as body size, hair color/form, eyes color/form, etc. These human variations were due, in part, to evolutionary forces, environmental conditions, and cultural differences. However, in all societies and subpopulations, there are both obese and lean individuals. The difference may have arisen, at least in part as a consequence of genetic factors, as is revealed by the high incidence for body mass index (BMI) (40–70 %) [4–7]. These features have been studied by anthropologists who work mainly to assess variation in physical size, shape of the body and the skull in humans using some anthropometric measures that can provide fundamental data and clues regarding the cause of human variation. A trait can reflect the activity of a single-gene (Mendelian or monogenic) or more than one gene (polygenic); both cases, being influenced by environmental factors. The polygenic multi-factorial condition reflects the additive contribution of several genes conferring different degrees of susceptibility. Accordingly, we may understand a polygenic trait as the combined action of several genes producing a "continuously varying" phenotype.

With the advent of the Human Genome Project (1990–2003), millions of DNA sequence variants

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were discovered in the human genome. This large and diverse database of polymorphism markers and the advancement of genotyping technology provided a novel opportunity to study the human genetic basis of several complex diseases through population approaches. In the studies designed for population approaches, a significant amount of individuals must be screened for a large number of polymorphisms. If a variant increases susceptibility to a specific disease of interest, we should note that it is more common among individuals affected by this condition than among non-affected individuals. Thus, through the genotyping of large number of individuals, the population genetics tools are able to highlight the genetic basis of polygenic diseases, such as obesity. This chapter provides the recent knowledge about the genetics of human obesity and covers a part of interactions between our genetic architecture linked to obesity and environmental factors.

The Genetics of Obesity

In the last three decades (from 1980 to 2013), worldwide estimate of the prevalence of overweight and obesity in adults increased ~40 %, with the same trend being observed in children and adolescents [8]. Although the prevalence of obesity is increasing in most countries in the world, partly due to ubiquitous exposure to energy rich foods and to a sedentary lifestyle, not everyone exposed to the current "obesogenic" environment (including also urbanization, education level, and socioeconomic disparities to access a healthy diet) shows unhealthy weight gain [9]. This suggests that there are marked differences in genetic factors that increase vulnerability for BMI. Indeed, evidence suggests that 40–70 % of variance in unhealthy weight gain can be attributed to individual's genetic variations [3, 7].

Moreover, emerging data imply that genetic vulnerability factors interact with environment risk, which is referred to as "epigenetic process". Whereas most scholars consider obesity to be a disorder that results from the interaction between lifestyle and genetic factors, its origin is complex, poorly understood, and most treatments are usually ineffective. Based on genetic and phenotypic characteristics we can consider three types of obesity: monogenic syndromic obesity, monogenic non-syndromic obesity and polygenic (or common) obesity.

Evidence for the Obesity Predisposition Heritability

The pathogenesis of obesity is complex and involves the interactions of several factors among nurture (environmental) and nature (genetic). The simultaneous increase in obesity across worldwide can be principally attributed to changes in the global processed food systems, and to the sedentary lifestyle of modern societies. However, at an evolutionary perspective, genes responsible for high fat accumulation could be advantageous for primitive humans to survive famine periods [3]. But nowadays in an obesogenic environment, this gene function appears to be disadvantageous.

With genetic studies attempting to address the phenotypic variations between individuals, it is not surprising to note that parental obesity is one of the important risk factors for childhood and adolescent obesity [10]. Familial aggregation studies estimate the recurrence risk of obesity within family members, comparing with the general population, it has been shown that individuals who has an obese first-degree relative are about three times more likely to develop an obese phenotype than the subjects in the lean families. For example, Whitaker et al. found that when both parents are obese the risk of childhood obesity increased twice [11]. Other studies, based on parental obesity, found a positive but small to medium effects between children's increased BMI continuing into adulthood [12, 13]. The increased risk of obesity found in families suggests that genes are involved in the development of this condition; however, it could also reflect a general parenting style due to sharing the same environment [14].

The first evidence presented that established the correlation between weight and genetics was in a study performed by Feinleib et al., using 514 veteran twin pairs, and suggesting a genetic influence in obesity risk [4]. In another study based on

this method, Stunkard et al. confirmed this result in a 25-year follow-up study [6]. For this purpose they evaluated more than 4000 monozygotic and dizygotic male twin pairs. They estimated high heritability of BMI at age 20 ($h^2=0.77$) and 45 years old ($h^2=0.84$). In another longitudinal study, Fabsitz et al. studied 514 twin adult veteran males who were of the ages of 48, 57, and 63 years [15]. They found a cumulative effect over time that explains most of the tracking in obesity. These studies were based only in male twin pairs and could represent a sex-specific effect. Nevertheless, other studies using both male and female twin pairs also found a high heritability of obesity, even higher in women (0.73) than men (0.61) [16].

Adoption studies are another way to evaluate the heritability of BMI, comparing adoptees, biological parents, and adoptive parents. Stunkard et al. performed an adoption study to compare BMI of both set of parents with those of the adoptees. They found that, despite sharing the same environment, the BMI of adopted children correlated more strongly with the BMI of their biological parents [5]. Studies based on twins could be more appropriate to assess the contribution of genetics to a given trait (as opposed to environment); in this case, individuals sharing the same genetic and environmental factors. Based on these studies the estimated genetic factors account for 40–70 % of the variations in common obesity.

We must however keep in mind that obesity is a heterogeneous condition, and it is clear that the heritability estimated figures can be influenced by environmental factors. Physical activity could be one of the most powerful influences in the heritability of obesity. Mustelin et al. were able to show that physically active subjects had reduced influence of genetic factors to develop high BMI and waist circumference [17]. Furthermore, other factors such as sex and ethnicity should be incorporated into studies to better understand the gene-environment interactions.

Monogenic Forms of Obesity

Monogenic forms of obesity are described as rare and severe early-onset obesity [18]. Its origin arose from a single gene mutation which is sufficient to cause the increased BMI. Also it represents a small number of cases appearing in childhood, and usually it is accompanied by several neuroendocrine, developmental delay and behavioral disorders. Studies performed in mouse models led to the identification of obesity-related mutations found in monogenic forms of obesity and unveiled important insights into the underlying mechanisms involved in energy homeostasis in humans [19]. Furthermore, studies based on individuals with extreme obesity and on consanguineous pedigrees have been successful in detecting mutations in human genes that cause this form of obesity [18]. Individuals affected by monogenic forms of obesity could be classified into two types based on their phenotypic aetiology.

Non-syndromic forms of obesity is found only in 5 % of the population with an extreme obesity phenotype [20, 21]. Many mutations present for this phenotype are located in a few genes that cause this severe phenotype (Table 7.1). Most of them are involved in the leptin/melanocortin pathway that plays a key role in the hypothalamic regulation of food intake [22].

Syndromic forms of obesity includes about 30 Mendelian inheritance disorders in which individuals, in addition to an extreme obese phenotype possess a distinct set of associated clinical features, such as cognitive deficit or organ-specific developmental abnormalities [23, 24]. Prader-Willi, mental retardation WAGR, Alström, Cohen and Bardet-Biel syndromes are some of the well characterized of the most common form of early-onset syndromic obesity for which the genetic basis is partially understood [3] (Table 7.2).

Genome Approaches for the Study of Common Obesity

There are several approaches to search for genetic variants for common obesity. With the advent of public databases of genetic variants and new genotyping technologies, several strategies appeared with the promise to unveil our knowledge about the genetic of obesity. Recently, the advent of the Next-Generation Sequencing

Table 7.1 Genes related with non-syndromic forms of obesity

Gene symbol	Gene name	Chromosome localization	Obesity phenotypes
LEPR	Leptin receptor	1p31	Extreme early onset obesity, hyperphagia
POMC	Proopiomelanocortin	2p23.3	Early onset obesity
PCSK1	Proprotein convertase subtilisin/kexin type 1	5q15-q21	Childhood onset obesity
SIM1	Single-minded family bHLH transcription factor 1	6q16.3-q21	Early onset obesity, hypotonia
LEP	Leptin	7q31.3	Extreme early onset obesity, hyperphagia
NTRK2	Neurotrophic tyrosine kinase, receptor, type 2	9q22.1	Obesity, hyperphagia, developmental delay
BDNF	Brain-derived neurotrophic factor	11p13	Severe obesity, hyperphagia, body weight
MC4R	Melanocortin 4 receptor	18q22	Early onset obesity, hyperphagia, increased fat mass
MC3R	Melanocortin 3 receptor	20q13.2-q13.3	Increased fat mass

Table 7.2 Most common forms of obesity syndromes

Syndrome	Additional clinical features	*Locus*
Prader-Willi syndrome (PWS)	Cognitive deficit, short stature, hypotonia, hypogonadism, and peculiar facial features	15q11.2-q12
Bardet-Biedl syndrome (BBS)	Cognitive deficit, conerod dystrophy, morphological finger abnormalities, dyslexia, renal disease	11q13, 16q21, 3p13, 15q22, 2q31, 20p12
Alström syndrome	Short stature, retinal dystrophy, diabetes	2p13
Cohen syndrome	Microcephaly, hypotonia, opthalmopathy, several facial features	8q22
WAGR syndrome	Cognitive deficit, Wilms' tumor, aniridia, genital and urinary problems	del11p
Ciliopathies	Retinal degeneration, renal disease, cerebral anomalies, congenital fibrocystic diseases of the liver and pancreas, skeletal dysplasias, diabetes	Several (> than 40 genes)

(NGS) may open new windows in the discovery of new genetic variants that predispose to the obese phenotype.

Linkage Analysis

Family-based genome-wide linkage scans the location of a disease causing *loci* by looking for genetic markers that co-segregate with disease-related phenotypes of interest within pedigrees. A number of different studies, designed on this approach, have successfully localized the cause of a rare Mendelian inheritance pattern [25, 26].

Candidate Gene Studies

The candidate gene approach has been widely used before Genome-Wide Association Studies (GWAS). In this method, researchers used selected candidate genes for specific traits or disorders with known biological function that directly (or indirectly) influence the trait/disorder under investigation. However, the main limitation of this approach concerning *loci* selection is that we need to know the function of the gene to be studied. Furthermore, candidate genes also have a low success rate, with only a few genes (~20) associated positively with common obesity [23].

Genome-Wide Association Studies

The GWAS approach has been possible due to the completion of the Human Genome Project (1990–2003), in which millions of genetic variants were discovered and catalogued into databases, and also with the advancement of chip genotyping technology conducted by the HapMap project (initiated in 2002). This method tests links between genotype/phenotype across hundreds of millions of genetic variants. Especially since 2007, an avalanche of results from GWAS emerged in the literature contributing to a major impact on our current view of the genetic susceptibility risk to common obesity.

New Approaches for the Study of Common Obesity

The advent of new approaches, such as next generation sequencing (NGS) technology provides a new way for molecular diagnosis, identifying rare variants associated with Mendelian or complex traits (such as obesity) within the whole exon or whole genome. This new method is time and cost-efficient in comparison to classical Sanger sequencing approach, and more powerful to detect mutations in novel genes not previously detected by other techniques listed [27]. Hence, since 2013 more and more studies appeared in the literature using this approach to identify genetic variants associated with obesity [28, 29].

Genes Associated with Common Obesity Discovered by GWAS

Recent GWA studies on human obesity field dramatically increased the identification of new genes associated with obesity-related traits. Common obesity is a heterogeneous condition, and unlike monogenic forms, it is expected to result from the interaction of several genes, each contributing with a small effect [30]. The first *locus* associated with obesity was identified in 2007, constituting a cluster of several single-nucleotide polymorphisms (SNPs) located in chromosome 16q12 within the first intron of the fat-mass and obesity associated (*FTO*) gene [31]. Few weeks later, another study confirmed the same intronic cluster in *FTO* gene as being significantly associated with BMI in European populations [32]. For the rs9939609, the most common *FTO* polymorphism studied worldwide, each additional risk allele (minor allele frequency) causes an increase of 1.5 kg in weight, representing approximately a 0.39 higher BMI [33–39]. After these findings the GWAS discovered many other obesity-susceptibility genes.

The *MC4R locus*, is well known for its role in the monogenic forms of obesity and was the second obesity susceptibility gene identified for common obesity [40]. The rs17782313 SNP resides in a noncoding intergenic region at chromosome 18q21, 188 kb downstream of *MC4R* and has the highest significant signal after the *FTO* gene. Another study found the rs12970134 SNP is located in the same region, 145 kb downstream of *MC4R* gene, which increases the risk of obesity among individuals of European descendants [41]. Subsequently, several SNPs in the same gene have been found associated with obesity and ubiquitously present in several European populations, African American, as well as in Asians [42–45].

Willer et al. performed a meta-analysis for BMI in Caucasians and, while confirming the association between the *FTO* and *MC4R* gene, they found six new *loci* associated with obesity including *MTCH2*, *GNPDA2*, *KCTD15*, *SH2B1*, *NEGR1* and *TMEM18* [46]. At the same time, Thorleifsson et al. discovered seven new *loci* near or in genes *BDNF*, *SEC16B*, *ETV5* and *FAIM2*, as well as in *FTO* and *MC4R* associated with obesity in a sample of 31,392 individuals from Iceland population [42].

A recent collaboration between several investigators established the Genetic Investigation of ANthropometric Traits (GIANT) [39]. This consortium expanded its genome-wide association including meta-analysis to include a total of 249,796 individuals of European ancestry. They confirmed 14 previously known obesity susceptibility *loci* and identified 18 new associated with obesity near or inside the genes: *PRKD1*, *SLC39A8*, *GPRC5B*, *MAP2K5*, *QPCTL*, *RBJ*,

LRRN6C, *FLJ35779*, *CADM2*, *TMEM160*, *FANCL*, *LRP1B*, *TNNI3K*, *MTIF3*, *TFAP2B*, *ZNF608*, *NRXN3*, *RPL27A*, *PTBP2* and *NUDT3*. Overall, by 2011, 32 genetic *loci* were found unequivocally associated with obesity by GWAS.

Most recent GIANT meta-analysis comprise 263,407 individuals of European ancestry [47]. Besides confirming the previously 32 *loci* found associated with BMI, they identified seven new *loci*, *ZZZ3*, *RPTOR*, *ADCY9*, *GNAT2*, *MRPS33P4*, *HS6ST3* and *HNF4G*, explaining an additional 0.09 % of the variance in BMI. Until now, 59 genetic *loci* have been robustly found associated with at least one obesity-related trait. More than 35 *loci* have been found associated with the increase of BMI, while other 13 *loci* have been found associated with weight-hip-ratio [48]. Other *loci* such as *LCT* gene have been found associated with BMI and abdominal obesity [49–52], and the *IRS1* and *SPRY2* genes associated with body fat percentage [53].

With the advent of new approach cost-efficient methodologies and the accumulation of more results including meta-analysis it is possible to predict that more genes are present associated with obesity phenotype. All these studies have been performed mainly in adults of European origin. However, in order to develop preventive measures it is important to extend studies in children to understand if candidate genes play any role early in life rather than in adulthood.

Common Childhood Obesity

Further studies on obesity *loci* in children will emerge as an important step for our understanding on variants which are intricately associated with obesity [43]. Moreover, understanding the genetic basis of obesity in children could be a first step to develop preventive measures in early life. In 2011, all 32 *loci* (described above) in GIANT meta-analysis of adult were also tested in a sample of children and adolescents; 1097 obese cases and 2760 lean controls (age between 2 and 18 years) of European Americans were included [54]. They found evidence of association with nine of these *loci*: *FTO*, *TMEM18*, *NRXN3*, *MC4R*, *SEC16B*, *GNPDA2*, *TNNI3K*, *QPCTL*, and *BDNF* with obesity. Overall, 28 of the 32 *loci* showed consistent effects to that found in adult obesity by meta-analysis. In a GWAS for childhood obesity in European descendants, researchers identified two new *loci,* one near the *OLFM4* and another in the *HOXB5* genes [55]. A recent study conducted by the Early Growth Genetics (EGG) consortium replicated findings on all 32 previously found *loci* and the newly *HOXB5* and *OLFM4* genes identified in childhood obesity in a Greek adolescents cohort [56]. They calculated a genetic risk score, based on all 34 *loci* and found that 27 of them showed consistent effects with those reported in adult obese subjects.

GWAS in Other Ethnic Groups

It is also important to confirm information results across different ethnic groups and not restrict studies in European populations only. It is because obesity is no longer a problem of only developed countries but also affects people living in developing countries due to changes in their life style by adopting Western life (changes in dietary habits and a more sedentary lifestyle). Furthermore, human genetic set up can vary between populations (linkage disequilibrium) and even between individuals in regards to obesity susceptibility. Several GWAS performed in East Asian populations identified *FTO* SNPs associated with BMI and obesity [57, 58]. Additionally, the association of *FTO* SNPs with obesity-related traits was also found in Japanese, Chinese, Vietnamese, and Asian Indian populations [36, 37, 59–64]. More controversial results were found for the subjects of African origin [65–67]. Monda et al. observed an association between the *FTO locus* and BMI in individuals belonging to an African ancestry. In a recent systematic review conducted within several African population groups, the researchers also observed several SNPs located in genes such as *ACE*, *ADIPOQ*, *ADRB2*, *AGRP*, *AR*, *CAPN10*, *CD36*, *C7orf31*, *DRD4*, *FTO*, *MC3R*, *MC4R*, *SGIP1* and *LEP* associated with at least one obesity-related trait [68, 69]. Reason for disparity may be due to the lack of quality studies mainly with African groups.

Regarding the extent of the effects of each additional copy of the risk allele on the *FTO locus*, differences can be observed between Asian

and African populations relative to subjects of European descent. The effect of risk allele increases BMI by 0.16 in East Asian, 0.20 in Indian Asian and 0.10 in African descendants, which is less than 0.39 observed in European descents [70]. When comparing the minor allele frequencies for *FTO* SNPs, in East/Indian Asians they range between 12 and 33 %, in African populations 7–18 %, which is still lower compared to the 42 % found in European populations [70].

In near future it would be important to increase GWAS meta-analysis to establish how strongly obesity-susceptibility *loci* are associated with these ancestries.

The "Missing Heritability" of the Genetics of Human Obesity

Since 2005, due to increased use of GWAS the enthusiasm of the scientific community for the investigation of complex disorders also increased exponentially. As described in the previous sections, GWASs have been successful in identifying several *loci* associated with the susceptibility risk of obesity. However, all together it only explains 1–3 % of the variance in BMI. Hence, there is a gap between the explained variance of BMI due to known SNPs (1–3 %) and the estimated heritability of the BMI variance (40–70 %).

The *FTO* gene still remains endowing highest effect on BMI with only 0.34 % of the total variation. An important concern about the interpretation of the results regarding GWAS is that this approach is based on the "disease-common" variant hypothesis, and variants panels were designed to cover the common genetic variants (minor allele frequency ~45 % in populations) [71]. In this form, current GWAS is not being able to identify rare variants. Recently, this and other different kinds of genetic variations were pointed as the possible source of the missing heritability genes and this is required to be explained in obesity, because the effect size could be higher in rare and low frequency alleles (<5 %) than in common variants (~45 %).

A recent novel approach called Genome-wide Complex Trait Analysis (GCTA) has been proposed to estimate variance, explained by all variants in a *loci* or in the whole genome for a complex trait rather than testing the link between a particular variant to the trait [72]. The main aim of this method is to unveil the "missing heritability" caused by the inability to detect a large number of common variants with small effects or rare variants with large effects by GWAS. In case of obesity, all together it accounts for up to 17 % of the overall BMI variance in adults [73]. In a recent analysis of twin children, Llewellyn et al., found that the additive effects of multiple common variants are 37 % of the BMI variance. In another study, the same authors, based on the same approach, suggested an increased genetic influence on adiposity during childhood [74, 75]. Therefore, it is expected that part of the missing heritability could be due to rare genetic variants, copy number variations (CNVs), and epigenetic factors. Despite all this arguments, it is clear that there still remain many variants to uncover relationship between genetics and obesity.

Rare Single Nucleotide Polymorphisms

The current arrays of genotyping technologies are designed to cover common genetic variants and not only to detect variants below 5 % frequency based on the 1000 Genome project. So, most of GWASs have been focusing in search of common genetic variants associated with BMI (>40 %), without including the rare variants. Nevertheless, the effect size of rare alleles is higher than common variants in causing disease, and in some cases with high penetrance. Blakemore et al. found a low frequency variant located in the *NAMPT* gene associated with severe obesity in Caucasian children [76]. The rs10487818 variant presents a minor allele frequency in general Caucasian population of <1 % in and was not found in African and Asian groups. However, the researchers observed a strong protective link between the minor allele, which was markedly stronger in the severely obese children compared to the class III obese adults. It is possible that the rare variants could be ethnic-group specific. Today, several studies emerged analyzing the potential effect of rare obesity-susceptibility genetic variants with

Table 7.3 Some candidate CNV *loci* found to be associated with obesity

Locus	Localization[a]	Genes overlap	Reference
2p11.2	chr2:88,422,508-88,427,650	*FABP1*	[82]
2p11.2	chr2:89,285,770-89,461,034	*None*	[82]
4q25	chr4:108,285,188-108,293,270	*None*	[84]
5p15.33	chr5:795,720-851,101	*ZDHHC11*	[82]
8q24.3	chr8:143,545,377-143,612,149	*BAI1*	[82]
10q11.22	chr10:46,338,178-46,812,351	*GLUDP2, PPYR1, GPRIN2, SYT15 BMS1P2, LOC642826, LOC643650, ANXA8L1, CTGLF7, LOC728643, LOC728657, LOC100132646, FAM25B, LOC100133189*	[82, 84, 86]
10q11.22	chr10:47,011,183-47,145,122	*LOC340844, LOC728684*	[84, 86]
10q26.3	chr10:135,178,653-135,227,268	*CYP2E1*	[87]
10q26.3	chr10:135,092,863-135,146,259	*CYP2E1*	[87]
11q11	chr11:55,130,596-55,210,165	*NEGR1*	[86]
11q11	chr11:55,130,596-55,210,165	*OR4P1P, OR4V1P, OR4P4, OR4S2, OR4C6*	[84]
11q13.4	chr11:72,307,637-72,353,420	*PDE2A*	[83]
15q11.2	chr15:24,803,304-24,808,624	*PWRN1*	[88, 90]
16p11.2	chr16:30,907,928-30,914,880	*CTF1*	[83, 89]

[a]Chromosome position is based on genome build hg18

obesity that can explain part of the missing heritability [77–80]. However, it will be possible that undiscovered common variants themselves might explain the missing fraction of genetic of human obesity.

Copy Number Variations

Copy number variations (CNVs) result from deletions and duplications of chromosomal segments constituting a major source of the individual humans' variation as single-nucleotide polymorphisms. Some of them encompass large parts of genes, with the replicated or deleted copies having a potential functional effect. This common type of genomic variability has been suggested as a possible cause for the missing heritability. Currently, several large (>500 kb) and rare (<1 kb) CNVs have been reported linked to obesity including 16p12.3, 16p11.2, 11q11, 10q11.22, etc. [80, 90] (Table 7.3). Some of these CNVs are in strong linkage disequilibrium with adjacent SNPs [82, 85]. The most established CNV associated with obesity correspond to a chromosomal deletion of at least 593 kb at 16p11.2. Heterozygotes for this CNV have been significantly associated with obesity in Caucasian individuals with severe early-onset obesity and cognitive deficits [89]. This deletion was absent from healthy non-obese controls and accounted for 0.7 % of morbid obesity cases (BMI ≥40 kg/m^2), with an odds ratio of 43.0, demonstrating the strong effect of rare variants [89]. Bochukova et al. identified several CNVs that contribute to obesity in a Caucasian sample, including the 16p11.2 [83]. An interesting result observed was the fact that all 16p11.2 deletions found in a sample of 1062 patients with severe obesity encompass several genes including the *SH2B1*, which is known to play a role in the leptin and insulin signaling [83]. Sha et al. found one CNV at 10q11.22 that contribute to 1.6 % of BMI variation and covering the important *PPYR1* obesity-related gene, that was a key regulator of energy homeostasis and food intake [82].

In a sample of children and adolescents from the German population, 20 CNVs were found to be directly linked with obesity, with one region (11q11) that covers three olfactory receptor genes *OR4P4*, *OR4S2* and *OR4C6* [86]. These genes interact with odorant molecules in the nose,

giving a perception of smell by neuronal response of the olfactive stimuli. Furthermore, Sun et al. found that the CNV *locus* 8q24.3 playing significant roles in obese Chinese children [81]. However, they failed to achieve any significant association with the well-reported 10q11.22 and 16p.11.2 *loci* in their sample. This result could be due to environmental and cultural difference between Asian and Caucasian populations, and these CNVs obesity-associated genes could have different expression. CNVs are still poorly studied in the context of obesity. However, studies in this field at least were able to demonstrate that they could play an important role in the missing heritability that still needs to be explored.

Epigenetic Factors

Epigenetic is defined as the study of heritable changes, which affect gene function but do not involve changes in the DNA sequence [91]. These factors include genomic DNA methylation, changes in chromatin organization by histone modifications, and non-coding microRNAs (microRNA) [92]. In a simple analogy, it is like genetics refers to the genes "writing", while epigenetics to the genes "reading". So, in the same genetic sequences, gene expression may vary due to inter-individuals differences, which could be programmed by environmental factors.

Epigenetic markers can change during lifetime and have a heterogeneous distribution in tissues. DNA methylation is a well-known epigenetic marker. It has a methyl group at the carbon-5 position of cytosine, at the CpG dinucleotides position, and is usually associated with gene silencing in the promoter regions [91, 93]. The *Agouti* mouse viable yellow (A^{vy}) model is one of the best-studied examples on how early environmental exposures interact with epigenetic gene regulation influencing the phenotype [94, 95]. The murine *agouti* gene influences DNA methylation at early developmental phase, affecting coat colour, which correlates with adult body weight. When the *agouti* gene is kept in the "*off*" position (by attaching methyl groups to prevent transcription), mice have a brown fur and slim healthy, whereas when the same gene is turned "*on*" (unmethylated) the mice present a yellow fur and an obese phenotype. Interestingly, there is a wide variation in individual coat colour and obese phenotype varying due to the mother's diet as well [96, 97]. This phenomenon occurs by epigenetic modifications of *agouti* gene in early developmental phase. Basically, the phenotype variations are caused by DNA methylation patterns that are acquired during early embryonic development and passed over through the female germline that results in stable intergenerational transmission [98–100].

Several other studies have been performed based on the link between obesity and DNA methylation. Using a genome wide approach, obesity has been related to changes in DNA methylation status in peripheral blood leukocytes of lean and obese adolescents in the *UBASH3A* and *TRIM3* genes [101]. Godfrey et al. found that 31 CpGs with higher methylation levels at birth strongly correlated with greater adiposity in later childhood [102]. Analyzing the methylation profile on a genome-wide scale by sampling DNA from peripheral whole blood, Almén et al. observed that individuals with the rs9939609 polymorphism risk allele affects the methylation status of sites related to genes *KARS*, *TERF2IP*, *DEXI*, *MSI1*, *STON1* and *BCAS3*; showing that *FTO* gene may influence the methylation level of other genes [103]. In a recent study, Zhao et al. observed that the hyper-methylation of the promotor of the *SLC6A4* gene was associated with an increase in BMI, body weight and waist circumference [104]. Xu et al. by analyzing 470,000 CpG sites in adolescents found a differential variability in CpG sites, which was more variable in obese than in lean individuals, constituting an important feature in obesity related to methylation [105]. Nevertheless, most of DNA methylation sites found until now associated with obesity is required to be confirmed. Studies based on this marker undoubtedly will permit to establish an epigenetic basis for human obesity.

Studies based on pre-conceptual, *in utero*, and postnatal developmental environment showed also to have an important impact in long-term risk for adult-onset obesity by a set point of adaptive changes. Environmental conditions experienced *in utero* may have a life-long effect in the propensity to develop obesity that constitutes a

"critical period". As previously reported in the heritability section, there is an important association between maternal obesity and childhood obesity. Relton et al. presented evidence that some DNA methylation patterns varies at birth and showed its association with BMI, fat mass and lean mass at the age of 9 years [106]. This observation suggests that variation in DNA methylation patterns at birth in multiple target genes may influence body size in childhood. Moreover, maternal diet can alter later the child's adiposity, accompanied by epigenetic changes in genes controlling the energy homeostasis. Parental preconceptional environmental exposures could also have an effect on the health status of the offspring in later life. In two recent studies regarding parental obesity an association has been observed between DNA methylation profiles at *MEST*, *PEG3*, and *NNAT* genes in children born from obese parents, when compared with children born from non-obese parents [107, 108]. These results points to a pre-conceptional influence of parental life-style or over-nutrition in the reprogramming of imprint marks during gametogenesis and early development [107, 108]. Hence, experienced perinatal events are important in defining the epigenetic marks that will persist until the adult age. However, our knowledge about mechanisms underlying maternal nutritional environment that induces changes in their offspring remains largely unknown.

Continuous advances in research show promising results about the implication of epigenetics mechanisms in the etiology of obesity. Epigenetics has shown that our genes *per se* are not the only factor to determine our phenotype and that our behaviors can alter the expression of our genotypes. Rönn et al. observed a change in the level of several DNA methylation sites, which were altered in response to a 6-month exercise intervention [109]. This result showed that our behavior can modulate the susceptibility to develop obesity. Despite the high number of DNA methylation candidate genes and some epigenome-wide association studies (EWAS), most of the associations have not yet been confirmed by other samples whether those CpGs are reliably associated with obesity.

Interaction Between Genetics and Lifestyle Factors

The population based genetic profile is only a small portion of the susceptibility risk to develop the obese phenotype. In addition to genetic variants, other mechanisms could lead to differences in obesity risk in individual subjects. Interactions between environment factors and genes are another potential explanation for the unexplained heritability. The exposure to an environmental factor should increase the magnitude of relative risk if a genetic susceptibility is present (gene-environment interactions, see epigenetic section). Furthermore, several studies found evidences of the cumulative effect of common genetic variants that predispose to obesity with lifestyle factors.

Gene-Gene Interaction (Epistasis)

The study of the heritability of complex traits can be difficult as it may involve a single gene or interactions between several genes. Approximately 20,000 genes are present in human genome with a set of complex interactions among genetic *loci* to produce phenotypic characteristics. Some of the best examples of interaction between two or more genes to produce traits are: *Rose-comb* and *Pea-comb* alleles in chicken, flower color in sweet peas, or flower petal color of *Primula* plant [110, 111]. These simple examples covering Mendelian inheritance have been more successful in identifying the genetic cause of the phenotypic variability than complex traits such as diabetes, obesity and hypertension, which could result from the contribution of a considerable number of *loci* [112].

In the past most GWASs on obesity were focused on the association of a single-*locus*, in which each variant was tested individually with specific traits without studies on gene-gene interactions. Speliotes et al. performed a GWAS discovering 18 new *loci*, and confirming 14 known obesity-susceptibility *loci* with BMI [39]. These authors tested a SNPxSNP interaction but found no evidence of association after multiple test correction. One reason for this lack of success in genetic studies of complex disorders may be due to the specific failure to take into account the existence of interactions between *loci* [113].

Although major interest can be seen on studying the relationship between gene-gene interactions in complex disorders, few studies can be found on the influence of epistasis on obesity risk. In a sample of women with bulimia nervosa, Kaplan et al. analyzed the possible role of *BDNF*/*DRD4* gene-gene interactions [114]. They found that individuals with both Met66 allele of *BDNF* and 7R allele of *DRD4* had higher BMI than individuals without those variants. Also two studies conducted in the Chinese population investigated and found an interaction and contribution to obesity risk including abdominal obesity of several variants located in the peroxisome proliferator-activated receptors (PPARs) in their contribution [115, 116]. Using a genome-wide association scan for the effect of epistasis on BMI in four European populations, Wei et al. found eight epistatic pairs that could explain a proportion of the BMI variation, and Young et al. found one Gene-Gene interactions (*PRKD1-FTO*) after multiple correction test in a sample of European descendant adolescents on BMI [117, 118].

Evidence is available that epistasis can help to understand the quantitative effects of gene interactions of complex genetic networks. Furthermore, interactions between genes result from a long evolutionary process. However, the study of epistasis related to complex traits is not easy due to the putative high number of possible genes interactions.

Link Between Nutrition and Genomics

Nutrition appears to be one of the most important factors contributing to the obesity susceptibility risk. It is clear that an increase in food intake along with sedentary life style brings high risk for the obesity. Furthermore, there is some evidence that food consumption can modify patterns of gene expression influencing the phenotype [119]. The recent research continues trying to understand the variability in metabolic response to diet and food quality (nutrigenomics).

Human diet has been suffering from a profound alterations marked by innovations in food technology (processed food). Moreover, nutrients that are being complicated by several bioactive compounds with molecules carrying components from the external environment may affect the process of gene expression when we consume them [120, 121]. It is well known that several dietary components can modulate epigenetic phenomena by inhibiting enzymes such as DNA methyltransferases and histone deacetylases [119]. Furthermore, several studies found an interaction between genetic variants on nutrient requirements (nutrigenomics). For example, Ortega-Azorín et al. found a gene-diet interaction of the *FTO* rs9939609 and *MC4R* rs17782313 polymorphisms with adherence to the Mediterranean diet on type 2 diabetes, in which this type of diet counteracts the genetic predisposition [122]. Steemburgo et al. observed that individuals carrying both minor alleles of the rs9939609 polymorphism were positively associated with a higher intake of total fat and low-fiber consumption, independent of BMI [123]. Obesity susceptibility genes, *FAIM2*, *FLJ35779*, *FTO*, *LRRN6C*, *RBJ*, and *SEC16B*, were found to interact with dietary carbohydrates to increase BMI [124]. Other *loci* such as *ADRB2* and *MC4R* were also pointed for relationship with carbohydrates intake [125].

The periconceptual *in utero* and postnatal developmental environment can also play a role on long-term risk for adult-onset obesity by a set of adaptive changes. Breastfeeding has recently been pointed to protect against childhood obesity and the authors observed an association between DNA methylation of *LEP* gene with early life environment [126].

Despite the increased number of studies showing that nutrients indeed influence epigenetic modifications (e.g. genistein, curcumin, tea polyphenols, etc.) the interaction of nutrients with biological systems remains mostly speculative.

Link Between Physical Activity and Genomics

Physical activity is another important component involved in the complex etiology that influences obesity. The practice of a regular exercise could be an important factor for preventing and reducing weight gain, as well as other health and psychological benefits. Several studies found an interaction of *FTO locus* with physical activity is important in the obesity-susceptibility putting emphasis that a moderate or active physical

activity attenuates the association of *FTO* variants with increase BMI [127–131]. A meta-analysis conducted by Kilpeläinen et al. observed that the minor risk allele of the *FTO* rs9939609 polymorphism increased the odds ratio of obesity by 1.23-fold/allele, but this increased is attenuated by 27 % in physical active individuals (p interaction = 0.001) [132]. Similar result was found in another meta-analysis conducted by Ahmad et al. that combining 12 polymorphisms showed a significant genetic-risk-score and physical activity interaction effect in obesity (p interaction = 0.015) [133]. These results support the notion that individuals with moderate or higher levels of activity may attenuate the influence of obesity susceptibility polymorphisms on BMI.

Interestingly, some studies provide evidence that the propensity to be active can have involvement of genetic components in both animals and humans [134]. Studies based on family aggregation observed that in a family with more active parents, children have tendency to be more active than children in inactive parents [135]. Some variants have been found associated with inactivity such as variants located in the *MC4R* gene have been found to be related to inactivity, using a self-reported physical inactivity questionnaire in French-Canadian families and Mexican-Americans [136, 137]. The Gln223Arg variant located in the *LEPR* gene was also found associated with lower 24 h energy expenditure and physical activity levels in individual homozygotes for the Arg223 allele when compared to Gln223 allele in Pima Indians populations [138].

These are only few examples about a possible interaction between some genetic variants and variation in physical activity. More studies are needed to identify *loci,* which could be implicated in this interaction to reveal and help to understand the causes that contribute to the development of the obese phenotype. However, these results indicate that it is important to practice a regular activity level to maintain a healthy weight.

Drug-Genotype Interaction

Drug therapy option for obesity could be suggested for subject with a BMI >30 with existing co-morbidities such as diabetes, dyslipidemia or hypertension [139]. In the last one decade, the concept of "pharmacogenetics" emerged as a field investigating if the consumption of certain drugs was affected by the genetic variation of individuals [140]. This new field of investigation focuses the attention towards the study of genetic variants within one or more candidate genes for links with pharmacologic phenotypes. It was found that ingestion of certain bioactive compounds interacted with some functional variants and could alter the response to pharmacotherapy affecting drug metabolism, drug transport or drug targets [139, 140].

Currently available drugs in the market for controlling obesity, approved for continuous use in the United States of America (USA) are: orlistat (Xenical®, Alli®), lorcaserin HCL (Belviq®), phentermine and topiramate extended release (Qsymia™) [139]. Orlistat alters metabolism by inhibiting the gastro-intestinal absorption of triglycerides and Lorcaserin HCL and Phentermine act centrally as an appetite suppressant [139, 141, 142]. Recently, the US Food and Drug Administration (FDA) approved the glucagon-like peptide-1 (GLP-1) agonist Liraglutide (trade name Saxenda®, Novo Nordisk), initially used for the treatment of type 2 diabetes, which on clinical trials was found to have significant effect on reductions in body weight due to its appetite-suppressing effects [143].

It is possible that in future such pharmacologic intervention can become a powerful tool for obesity control. Based in the personalized genetic profile it could be possible to determine which sub-populations will respond optimally to which particular drug. This field may open an important area of research with the necessity to identify differences in drug response and tolerability, and investigate gene regulation, epigenetic modifications, and DNA-protein interactions that could explain individual differences in responses to drugs beyond genetic variation.

Bariatric Surgery

Generally, in patients with a BMI greater than 35 and suffering from severe obesity-related co-morbidities, after failing diet control, exercise, and

drug therapy, a surgical intervention could be an option for losing weight. However, some patients present a significant weight gain after surgical intervention. There are several guidelines and procedures that surgeons/gastroenterologists need to follow before a possible surgical treatment of obesity due to the associated risk [144]. We will not detail about surgical intervention strategies, which have been reviewed elsewhere as well in this book in chapter 23 and in reference [145]. However, below we present about a possible relation between certain genetic variants and the success rate to maintain weight loss after surgery.

It is now well established that genetics factors play in the etiology of obesity. There is a high degree of inter-subject variability for surgical outcomes, so genetic profile should be taken into account in patients undergoing bariatric surgery [146]. Generally, patients submitted to surgical intervention have a durable weight loss [147]. However, despite its effectiveness after the intervention not all patients maintain the healthy weight or obtain the same clinical benefits. Several studies emerged linking specific variants in response to bariatric surgery. Moore et al. found that patients carrying a rare *MC4R* allele associated with obesity, lost less weight after surgery than non-carrier patients [148]. After performing a follow-up study, de Luis et al. observed that individuals homozygous for the rs6923761 G allele (*GLP-1R* gene) showed higher weight loss after a biliopancreatic diversion than individuals carrying the A allele [149]. Furthermore, Hatoum et al. found a significant association of the 15q26.1 *locus* with weight loss after Roux-en-Y gastric bypass surgery [147]. In another study using the same intervention, 17 variants were found associated with weight loss 2 years after the surgery [150]. Hence evidences exists regarding the use of genetic variants to identify response to surgical procedures [147, 151, 152]. In a complex disorder such as obesity, the identification of genetic contributors could be useful to select those individuals who will obtain required weight-reducing effects to benefit and not subject them to go to an invasive technique. However, these results need to be interpreted with caution, as there are inadequate data available.

Gut Microbiota and Obesity

The human intestine is colonized by a variety of microorganisms, which are collectively known as microbiota. This complex community contains more than 100 trillion bacteria in the gastrointestinal tract that co-evolved and co-adapted in response to environmental selective pressures over hundreds of millions of years [153]. The gut microbiota live in a perfectly mutualism relationship with its host, which is beneficial to both organisms as well human. Although certain conserved microbial species are common among the hosts, however individual person seems to have distinct and variable species of gut microbiota probably due to our difference in lifestyle. Several studies showed that the human gastrointestinal tract is colonized by microbiota during and shortly after birth, and subsequently influenced by various factors, such as age, sex, stress, surgery, medication, nutrition, and the genetics of the individual [154] (Fig. 7.1).

Numerous metabolic functions of microbes in gut enable the digestion of food components, such as humans cannot digest certain fibers but bacteria present in the gut have the enzymes glycoside hydrolases and polysaccharide lysate which can breakdown polysaccharides of plant cell wall [155, 156]. Recently, an altered gut microbiota has been suggested to be critical for the development of obesity [157]. Also several human studies have demonstrated a link between the gut bacteria and obesity [158, 159], which it is not surprising when we know that this microbial community can contribute to the host with their genetic makeup. Furthermore, diet is one of the principal factors linked to obesity, having an important impact in the composition and activity of intestinal bacteria. Several studies have found that childhood obesity is higher when both parents are obese, and some of them are attribute to a higher predisposition when the mother has an obese phenotype [11–13]. Also it has been shown that gut microbiota can be inherited from mothers to their offspring [160]. In addition Turnbaugh et al. observed that obese individuals have an altered gut microbiota when compared to lean individuals [161]. This factor could be important to take into consideration for global increase of obesity occurring in the last three decades.

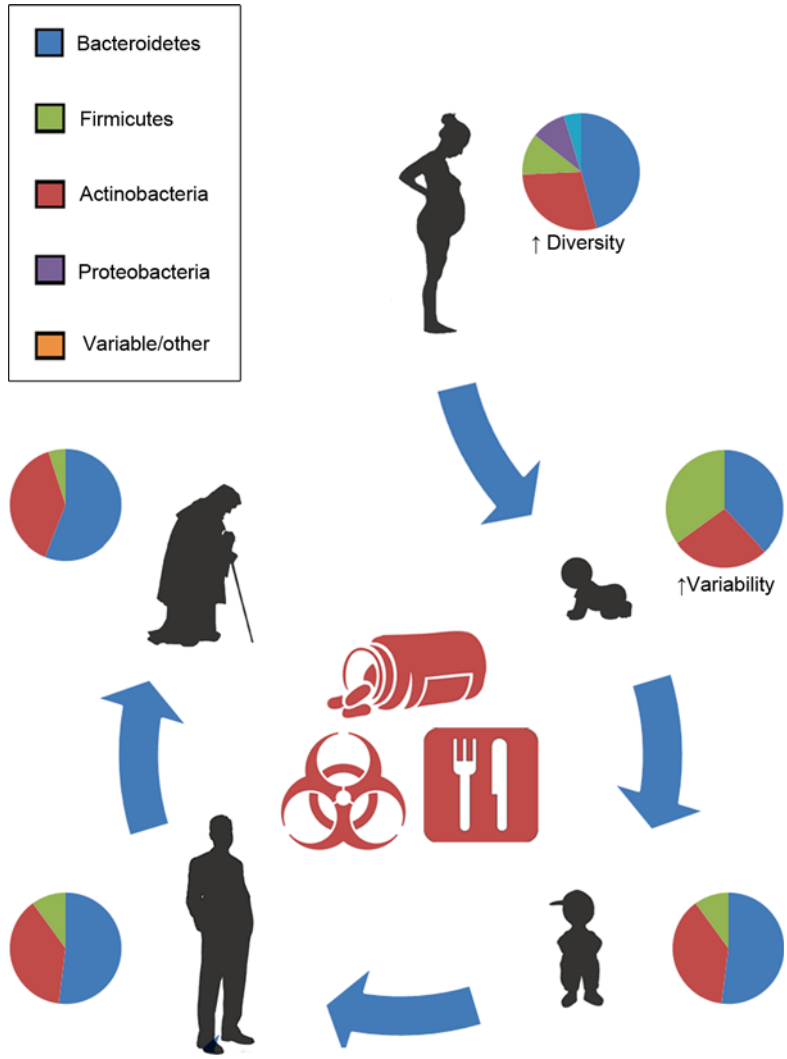

Fig. 7.1 The characteristics at phylum level of the human intestinal microbiota throughout the life cycle. The composition of gut microbiota changes in response to several environmental factors (e.g. diet, antibiotics, bacteria, etc.) and life stages. Prenatal exposure (pregnancy stage) affects and modulates the newborn gut microbiota and is characterized by higher diversity. There is a complex interaction between mother and child, and maternal behavior can negatively influence the newborn gut microbiota composition (e.g. fatty diet, weight gain, stress, smoking, drugs, etc.). On the other hand, infant stage is characterizing by a greater variability and converges into its final adult composition, remaining mostly stable throughout human life. In elderly individuals (>65 year) significant changes in the composition of the gut microbiota have been observed. Some factors such as stress, immune responses, inflammation, and increased susceptibility to infections which can increase the consumption of antibiotics are pointed out

Ley et al. found in a leptin-deficient *ob/ob* mouse model differences in the ratio of *Bacteroidetes* and *Firmicutes* (two of the most dominant species), comparing obese *versus* lean mice [160]. Obese mice presented an increase in *Firmicutes* and a decrease in *Bacteroidetes*. Similar results were found in human gut microbiota between obese and lean individuals [162]. So, if gut microbiota is different between obese and lean individuals, and was inherited from mother to their children, the BMI of mother before pregnancy could be an indicator of part of the missing heritability in childhood obesity.

In a recent study, Parks et al. investigated the interactions between obesity traits, gene expression and gut microbiota in response to a high-fat/high-sucrose diet in mice [163]. They observed a relationship between genotype and gut microbiota plasticity during high-fat/high-sucrose feeding. After a surgical intervention, Damms-Machado et al. investigated gut microbiota composition and dietary weight loss; they found a moderate alteration of the intestinal microbiota after a laparoscopic sleeve gastrectomy [164]. This modification could be explained by weight loss and dietary food restriction mostly due by reduced fiber consumption. Furthermore, treatments based on antibiotics have a real effect on the gut microbiota [165]. However, our knowledge about how the genetic basis affects gut microbiota and interacts with obesity remains limited.

Conclusion

Common obesity results from the interaction of several internal and external factors. Since 2007, with the discovery of the first *locus* associated with common obesity, more than 55 *loci* were found associated with an obesity-related trait and many more are still to be discovered. Rapid developments in genotyping technology in recent years have led to an increase in our understanding of the genetic influences on obesity. At the same time, the progresses on sequencing technology in recent years have become promising to discover new possible variants associated with obesity susceptibility risk. Probably the combination of common with rare, low allele frequency and CNVs may contribute to significant increase in the knowledge of obesity risk. Furthermore, in common obesity both genetic and environmental factors may contribute to susceptibility of developing the obese phenotype, but it is unclear how these factors interact in their influence to the risk. The interaction between genetic or environmental mechanisms may differ among cultures, which result from differences in behavior, diet, environment, and social structures that can influence obesity. Further studies based on genetic epidemiology are needed and probably will be a hot topic in obesity research in the coming years.

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Obesity and Coronary Heart Disease

8

Helena Tizón-Marcos and Paul Poirier

Introduction

Obesity is a chronic disease that is increasing in prevalence worldwide. Based upon data collected for the National Health and Nutrition Examination Survey (NHANES) between 2011 and 2012, the prevalence of obesity in adults in the United States is 34.9 % [1] and worldwide overweight/obesity is though to be 36.9 % in men and 38 % in women [2]. Obesity is an independent risk factor for all-cause mortality as well as for cardiovascular disease (CVD) and its management (decrease in adipose tissue depots) lowers the incidence of ischemic heart disease [3–7]. Of importance, obesity shares common pathway with other metabolic-inflammatory processes leading to atherosclerosis thus increasing the incidence of all related atherosclerosis diseases [8].

Classically, obesity is classified by the body mass index (BMI) ratio. This is an easy tool that uses two anthropometric measurements commonly used: 1- weight divided by 2- height in meters squared (kg/m^2). This worldwide used index classifies overweight subjects in two categories: (i) overweight (subjects with BMI between 25 and 29.9 kg/m^2) and, (ii) obese (BMI $\geq$ 30 kg/m^2). Obese subjects are then graded into three classes according to BMI; (i) 30–34.9 kg/m^2, (ii) 35.0–39.9 kg/m^2 and, (iii) $\geq$40 kg/m^2. More classes have been added to the list in order to characterize very severe obesity which has been named "super-obese" ($\geq$50 kg/m^2) and "super super-obese" ($\geq$60 kg/m^2) individuals (Table 8.1a, b) [9]. However, and as detailed later, BMI may not be the best indicator of obesity prognosis and indices of regional distribution of adiposity may better predict cardiovascular risk [10].

Several large epidemiological studies have reported the link between obesity and CVD. The definition of CVD includes angina, myocardial infarction (MI), heart failure and sudden cardiac death. The Nurses Health Study, that followed more than 100,000 women from United States, showed increased mortality with increased BMI; women with a BMI >32 kg/m^2 had a relative risk of death from CVD fourfold those women with BMI <19 kg/m^2 [11]. These findings were later supported by the Framingham Heart Study in which men participants were followed during 30

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Table 8.1a Class of obesity using body mass index

Underweight	BMI <18.5 kg/m^2
Normal or acceptable weight	BMI 18.5–24.9 kg/m^2
Overweight	BMI 25–29.9 kg/m^2
Obese	BMI ≥30 kg/m^2
Grade 1	BMI 30–34.9 kg/m^2
Grade 2	BMI 35.0–39.9 kg/m^2
Grade 3	BMI ≥40 kg/m^2 (severe, extreme, or morbid obesity)
Grade 4	BMI ≥50 kg/m^2 (super obese)
Grade 5	BMI ≥60 kg/m^2 (super super obese)

Table 8.1b Threshold for waist circumference

		Men (cm)	Women (cm)
Europid IDF		94	80
Caucasian WHO	(Increased risk)	94	80
	(Higher risk)	102	88
United States AHA/NHLBI (ATP III)		102	88
Health Canada		102	88
European ESC		102	88
Asian (including Japanese) IDF		90	80
Asian WHO		90	80
Japanese Obesity Society		85	90
China Cooperative Task Force		85	80
Middle East, Mediterranean IDF		94	80
Sub-Saharan African IDF		94	80
Ethnic Central and South American IDF		90	80

IDF International Diabetes Federation, *WHO* World Heart Association, *AHA* American Heart Association, *NHLBI* National Heart, Lung and Blood Institute, *ESC* European Society of Cardiology

years; the mortality of overweighed men was fourfold those with normal weight [12]. NHANES registry followed more than one million inhabitants of the United States during 14 years and found that high BMI was predictive of cardiovascular death [13]. Obesity, in particular abdominal obesity, is one of the modifiable risk factors influencing the incidence of first MI through all ethnic groups and gender [14]. As the prevalence of obesity has been increasing in the last decades, there is an expected increase in atherosclerotic complications incidence primarily from ischemic heart disease.

Pathophysiology

Atherosclerosis has been shown to begin early in childhood and progresses with increasing age. Accelerated or prompt atherosclerosis is probably the key to understand the fact that obese subjects are more prone to die at younger ages from CVD. This datum is supported by postmortem examinations of young individuals dying from accidental injuries and sudden death. In a series of 243 subjects younger than 40 years who died suddenly, coronary artery disease was responsible for 37 % of deaths in subjects 20–30 years of age and 80 % of subjects dying suddenly at 30–40 years of age [15]. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study analyzed coronary arteries from autopsy materials of more than 2800 subjects aged 15–34 who died of external injuries. Subjects with higher BMI were more prone to have higher degree of left anterior descending artery stenosis and intimal and thin cap lesions [16]. A series of 40 autopsy studies of boys aged 13–19 years showed that intima thickness and density of macrophage foam cells in atherosclerotic lesions were correlated with increased visceral fat [17]. These two studies emphasized the importance of the regional distribution of

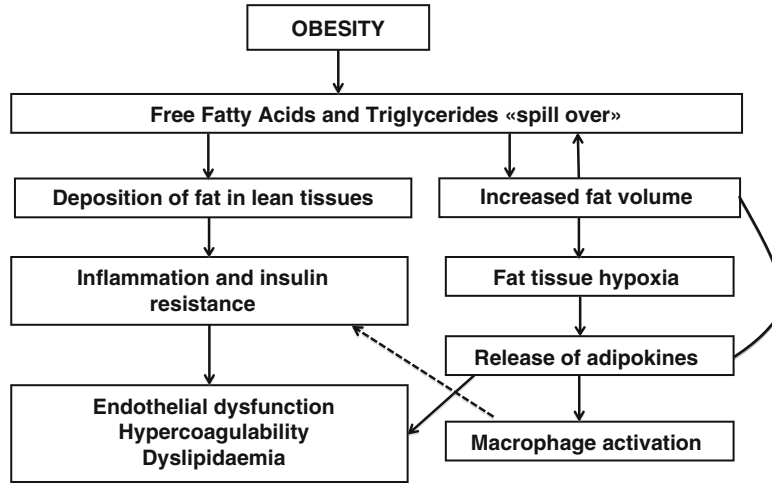

Fig. 8.1 Interactions between obesity and atherosclerosis processes

excess adiposity and the link between excess abdominal fat and more complex coronary lesions in the youth. The FATE study and the Dallas Heart Study documented the relationship between surrogates of subclinical atherosclerosis (carotid intimal-media thickness and coronary artery calcium) with abdominal obesity as assessed by the waist-to-hip ratio [18, 19]. Moreover, decreased endothelial dependent vasodilation, a marker of early atherosclerosis, has been shown in obese subjects and was correlated with visceral fat diameter measured by ultrasound [20]. Abdominal fat, and in particular visceral fat measured by magnetic resonance imaging, was correlated with a worse metabolic profile in young and apparently healthy adults [21]. The InterHeart study showed that waist-to-hip ratio was the strongest anthropometric measure associated to MI even when adjusting for gender, age and ethnicity [22]. In addition to its importance as an independent risk factor for coronary atherosclerosis, obesity, defined by BMI, but more specifically abdominal fat depots, usually assessed in clinic by waist circumference, waist-to-hip and/or waist-to-height ratio, promote metabolic abnormalities of numerous cardiovascular risk factors that may accelerate atherosclerotic processes.

Non-ectopic fat (or subcutaneous fat) appear to be less metabolically deleterious since its primary role is one of energy storage [23]. In contrast, excess abdominal visceral adipose tissue has been associated with known pro-atherosclerotic factors like insulin resistance, increased triglycerides and apolipoprotein B levels, low high-density lipoprotein cholesterol and increased small dense low-density and small dense high density lipoprotein levels, high blood pressure and a prothrombotic state [24]. Therefore, common pathophysiological pathways involving systemic inflammation and lipid metabolism relate obesity to accelerated atherosclerosis. In a state of positive energy balance, free fatty acids and triglycerides are initially stored in adipose tissue. Adipocytes expand and become mature as the pressure of storage increases. Once the normal site of adipose tissue depots becomes saturated and no more storage can be permitted, the adipocytes contain return to the circulation as free fatty acids. This "spill-over" results in an ectopic deposition of fat with preference in lean viscera (liver, kidney), muscle (skeletal muscle, myocardial/epicardial) and also perivascular (Fig. 8.1).

Adipose tissue has not only the role of energy reserve of the human body but also acts as an endocrine organ that controls the deposition of new ectopic fat and its homeostasis through the production of molecules/hormones/adipokines. The deposition of ectopic fat may induce a combined state of inflammation, insulin resistance and adipokines production influencing cardiometabolic risk [25]. Adipokines secreted by adipose tissue are also involved in the modulation of some of the steps promoting atherosclerosis such as endothelial dysfunction, hypercoagulability and dyslipidemia [26]. These cytokines

may be classified in two main groups such as beneficial adipokines (adiponectin and omentin) and deleterious adipokines (TNF-α, IL-6, plasminogen activator inhibirot-1, adipocyte fatty acid-binding protein, lipocalin-2, chemerin, leptin, visfatin, vaspin and resistin). The levels of "bad" adipokines are upregulated in obesity, particularly in the presence of abdominal obesity, contributing to the inflammatory profile [27, 28]. These adipokines promote specific actions such as: (i) induce cellular changes in macrophages, that become active while secreting pro-inflammatory factors and, (ii) induce a miss-match in the oxygen supply to ectopic adipose tissue leading to hypoxia that perpetuates the inflammatory state and metabolic disease [29–31] (Fig. 8.1).

Among visceral fat depots, the epicardial adipose tissue surrounds the heart and is in close contact to the coronary vessels. This tissue is involved into myocardial energy supply, thermoregulation and interacts with the cardiac autonomic nervous system influencing the regulation of coronary vessel motion and lumen diameter [32]. Epicardial adipose tissue shows greater inflammatory cell infiltrate (macrophages) than subcutaneous adipose tissue and produces highly atherogenic and inflammatory adipokines in patients with coronary artery disease [33]. As well as the intra-abdominal fat, epicardial adipose tissue is probably involved into subclinical atherosclerosis processes through increased arterial stiffness and increased intima-media thickness [34]. Furthermore, epicardial adipose tissue thickness and volume is correlated with the incidence and severity of coronary artery disease and coronary calcification [35]. Also, epicardial adipose tissue does correlate with the percentage of necrotic plaque tissue, low-density lipoprotein levels and micro-vascular dysfunction even in the absence of symptomatic coronary artery disease [36, 37].

Evaluation and Treatment

Stratification Strategies

Standard treadmill stress test with continuous electrocardiography and non-invasive blood pressure determination may be of limited value in obese patients due to several factors. Firstly, the electrocardiogram may depicts specific alterations in obese patients due to the increased distance between the heart and the electrodes but also due to structural changes secondary to a more horizontal position (false positive Q-waves in the inferior leads that disappear with the standing position), left ventricle (LV) overload and LV enlargement [38, 39]. Secondary, obese patients have impaired aerobic capacity and most fail to achieve the age-predicted heart rate in order to have a valid diagnostic stress test [40, 41]. As well as for elderly patients, modified protocols have been designed to increase exercise time. However, these modified protocols achieve lower metabolic equivalents, lower heart rates and lower pressure-rate products [42]. Stress echocardiography is a useful technique if a good echocardiographic window can be achieved. As in non-obese patients, the presence of detected myocardial ischemia, is an excellent predictor of adverse events [43]. The use of contrast agents may help to improve the acoustic window and increase diagnostic accuracy [44]. Single-photon emission tomography (SPECT) in obese patients has a good sensitivity for the detection of myocardial ischemia. However, photon attenuation through adipose tissue and decreased signal-to-noise ratio despite higher doses may impair its accuracy. In fact, there is conflicting data regarding the prognostic value of a negative SPECT test in obese patients [45]. The positron emission tomography (PET) scan has a high accuracy to detect ischemia in obese patients. A normal rubidium PET imaging ruling out myocardial ischemia is highly predictive of low cardiac events [46]. However, issues concerning the availability of the radiotracer and the ionizing radiation pose important limitations to its widespread use. Coronary computed tomography angiography (CTA) has been suggested for the assessment of patients with intermediate risk of coronary artery disease, those with electrocardiographic abnormalities or those unable to exercise due to its high negative predictive value [47]. However, image quality in obese patients is still suboptimal despite higher radiation doses

administered (2–5 mSv with a 120 kV energy) compared to less obese patients [48]. Also, the need to test for ischemia and not only anatomy would make CTA a second line of option for stratification. Nevertheless, new scanners with better resolution and shorter acquisition times may improve the quality of diagnostic images and dual-source energy may add functional information to the anatomical one. A recent international registry has shown that BMI was positively associated with the prevalence of coronary artery disease and increased number of segments with atherosclerotic plaque [49].

Cardiovascular magnetic resonance imaging can assess ventricular function, rest and stress perfusion and viability in a single examination. Relative to alternative techniques, stress cardiovascular magnetic resonance imaging has high spatial and temporal resolution and is not limited by acoustic windows or image acquisition. Scanner with wider-bores (70 cm) and higher capacity weight scanners are progressively available to study severely obese patients. Recent data show that stress cardiovascular magnetic resonance imaging is feasible and the main cause of failure (mainly claustrophobia) is manageable. Cardiovascular magnetic resonance stress ischemia is a powerful predictor of myocardial infarction and cardiovascular death [50].

Treatment Strategies

Invasive early strategies in acute coronary syndromes have shown to improve cardiovascular prognosis [51, 52]. Stratification tools commonly used in clinical cardiology have partially integrated blood markers or anthropometric measurements involved in inflammation and metabolic disorders [53].

Coronary Angiography and Percutaneous Treatment

Obese patients are increasingly being studied in cardiac catheterization laboratories. Maximum weight supported by the new equipment is up to 250 kg and vendors facilitate equipment to comfortably fit the patient within the table range. Radial access is definitely preferred in obese patients for coronary angiography and intervention because of lower bleeding rates, lower vascular complications, faster re-empowerment and mobilization and eventually shorter hospital admissions [54–56]. Echography guided artery puncture may be useful in obese patients who require femoral access. Higher BMI are associated with higher radiation dose during the procedure despite similar procedural times and contrast doses than non-obese patients [57]. Quality image acquisition may be improved with newer X-ray tubes and upgraded image acquisition protocols avoiding non-diagnostic views with high radiation dose. Other studies report higher incidence of contrast induced nephropathy and hemodialysis requirements after coronary angiography in obese patients showing the importance of adequate hydration prior the procedure, use of non-ionic contrasts and saving-contrast protocols [58]. Despite all measures, obesity is still independently associated with a greater in-hospital mortality rate [59].

Obesity was thought to be a protective factor after coronary angioplasty. This was coined the "obesity paradox". However, recent larger registries show that obese patients have still increased mortality and that longer follow up are required to understand the whole impact of obesity on cardiovascular health [31, 60]. Obese patients treated with bare metal stents had increased rates of binary restenosis, repeated revascularization and major cardiac events at 9-months follow up compared with those treated with first generation drug-eluting stents [61]. Repeated target vessel revascularization and acute stent thrombosis are still increased in obese patients treated with a third generation drug eluting stent [62]. However, in the absence of contraindication of prolonged dual antiplatelet therapy, a drug eluting stent is preferred over a bare metal stent [63]. Intravascular ultrasound and optical coherence tomography may help to size the vessel and assess the immediate result of a percutaneous revascularization procedure if angiography is not optimal. Bioabsorbable scaffolds may confer

additional benefits in different subsets including obese patients. Despite the fact that the prevalence of obesity is "epidemic", there is paucity of data about percutaneous revascularization on this specific group of patients. As an example, obesity does not account for the Syntax or Syntax II Scores to evaluate the risk and major cardiovascular events comparing percutaneous versus surgical treatment [64, 65].

Surgical Revascularization

As obesity is steadily increasing, the need for surgical revascularization in obese patients also increases [66]. Obesity remains a challenge for surgical myocardial revascularization due to the complex management of the pre-procedural conditions, intra-procedural use of drugs and pump and post-procedural complications. There is conflicting evidence about the mortality of obese patients undergoing surgical myocardial revascularization. Initial reports showed increased mortality especially in severely obese patients [67]. However, more recent studies show similar mortality of obese patients compared to non-obese patients [56, 68]. Different registries have still show the association of obesity and several periprocedural complications such as renal failure, respiratory failure, arrhythmias as atrial fibrillation, deep sternal wound infections and, greater intraoperative transfusion rates [69–72]. Newer surgical approaches, pharmacology and technology have been implemented to minimize the risk of obese patients. Concentration of cases in specialized-high volume centers may increase specialization and decrease complications. Off-pump coronary by-pass surgery shows increased benefit in obese patients compared to on pump procedures [56, 73, 74].

Pharmacotherapy

Anticoagulation and dual antiplatelet therapy has been considered as a cornerstone therapy in patients with acute coronary syndromes and thienopiridines have demonstrated clinical benefit in large randomized controlled trials [75, 76]. Obese patients show increased markers of inflammation including increased baseline platelet activation and variable response to different antiplatelet agents, including increased platelet reactivity while under treatment with aspirin [77, 78]. This pro-aggregation state is even more accentuated in obesity and patients with diabetes [79]. The impact of obesity on thienopyridines remains controversial. As well as with aspirin treatment, greater platelet reactivity under clopidogrel treatment has been shown in patients with increased BMI [56]. Insulin resistance, increased intracellular calcium and oxidative stress may influence the response of obese patients to clopidogrel [80, 81]. The meaning of increased platelet reactivity and its final clinical net effect or clinical relevance has yet to be determined. Patients receiving ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial had no significant difference in the primary endpoint of death from vascular causes, MI or stroke in obese patients compared to normal weight or overweight patients [76]. Recent studies observed the association of greater platelet reactivity under prasugrel treatment and BMI whereas there is no such association with ticagrelor [82, 83]. In addition, prasugrel has poorer action, reflected in higher platelet reactivity, in obese patients with metabolic syndrome [84]. Data on anticoagulation in obese patients and acute coronary syndromes are scarce. A large registry that examined in-hospital complications of severely obese patients who underwent percutaneous intervention showed that obesity was associated with a greater mortality rate than non-obese but also that obesity seemed to protect against major bleeding [59]. There is no standard dosing of unfractioned heparin in patients with weights above 100 kg who undergo both percutaneous and surgical interventions for myocardial ischemia [85]. Heparin dosage is based on body weight assuming that all tissues, both perfused and less-well perfused (as fat), assume the same metabolic rate. This may be the cause of increased bleeding rates during surgical interventions in obese patients [72]. The dosage of heparin is therefore suggested to be calculated through lean body mass in

obese patients [86]. During percutaneous intervention, bivalirudin shows benefits only in obese patients who undergo femoral access in terms of transfusion of blood units [56, 87].

Conclusions

Obesity is a highly prevalent chronic disease that is an independent risk factor for cardiovascular mortality and also interacts with other risk factors to accelerate atherosclerosis. Visceral adipose tissue is an active pro-inflammatory organ that combined with other CVD risk factors, increases the prevalence of subclinical coronary artery disease and the incidence of acute coronary syndromes at younger ages. Regional adipose tissue indices allow more accurate stratification of cardiovascular prognosis. Newer technologies allow better study and stratification of obese patients with coronary artery disease. Both percutaneous and surgical revascularization strategies have finally improved to enhance immediate and mid-term results to this increasingly growing and aging population.

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Obesity and Diabetes

9

Shamim I. Ahmad

Introduction

Diabetes

Diabetes mellitus commonly known as the "disease of sugar" occurs due to a number of biochemical impairments in which the level of glucose in blood stream remains relatively higher in compare to non-diabetic persons. It is an irony that in several countries especially in South Asian countries diabetes is not considered a disease. It is because diabetes is not manifested in any kind of immediate threat of death such as heart failure, cancer and even fever, headache or sickness. They should realise that diabetes is a *Silent and Slow Killer.*

There are several different types of diabetes mellitus (DM) including autoimmune or Type 1A diabetes mellitus (T1DM), Idiopathic or Type 1B, Type 2 diabetes mellitus (T2DM), Gestational diabetes, Maturity onset diabetes of the young (MODY), Fulminant diabetes, DM due to: genetic defects of insulin action, diseases of the exocrine pancreas, other endocrinopathies, infection and drug or chemical induced DM [1].

In a recent study, George et al have introduced a new type of diabetes called "Lean Diabetes mellitus". It includes those diabetic patients who have body mass index (<25). Their studies of lean patients from developing countries included the history of childhood malnutrition, poor socioeconomic status and relatively early age of onset and absence of ketosis at withdrawal of insulin. Extension of their studies in US showed that the lean diabetes is not rare there especially among minority population. Indeed these patients were normally males, have higher prevalence of insulin use, indicating the rapid β cell failure. Moreover it was assumed that they might be suffering more from cardiovascular mortality than adult obese diabetic patients. Further genetics, autoimmunity, acquired and behavioural factors have been discussed [2].

Out of several different types of diabetes mentioned above, in this chapter will be addressed only the two major types: T1DM, previously known as insulin dependent diabetes or juvenile onset diabetes; which is an autoimmune disorder involving the destruction of β cells produced by pancreas by $CD4^+$, $CD8^+$ T cells and macrophages infiltrating the pancreatic islets. The onset of this class of diabetes normally occurs at an early age and genetics and certain environmental factors have been associated with its onset [3].

T2DM on the other hand is more complex and two main biochemical alterations have been associated with this type of disease: (i) progressive reduction of insulin secretion and its action (also commonly referred as insulin resistance) and (ii) progressive β cell failure which is an important

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feature of this class of diabetes and rarely progresses to a point where the patient, unlike T1DM, becomes totally dependent on insulin (to be discussed in detail later).

T2DM is mostly prevalent in obese people although it is not necessary that every obese subject will develop this disease (the subject of this chapter). Non-obese person developing this type of diabetes has some insulin resistance in addition to a deficiency in insulin production and release. It is yet to be worked out in obese T2DM subjects as to what is the percentage contribution of insulin resistance versus insulin production and release. It is highly likely that this percentage may be varying from one individual to other suffering from this disease and hence may be very difficult to come to a final figure.

Another point to be noted is that it is more a myth than a fact that *diabetes is a result of consuming too much sugar.* We do not have any scientific proof for it. However, it is true that consuming too much sugar can increase weight which is an important risk factor for T2DM.

Prevalence of Diabetes

Out of all these different types of diabetes two of them are more common: T2DM which prevails in about 85 % of the total diabetic patients and T1DM prevailing in about 10 % of the total. The rest of the types prevail in about 5 % of the patients. Interestingly the gestational diabetes is usually short lived persisting during the pregnancy and then usually vanishes after the child birth [4].

With the advent of industrialization worldwide and the staggering rise in obesity, diabetes has gained its title as a global epidemic. Also it is very difficult to reach an accurate measure of prevalence for the reason that the standard and method of data collection and calculation varies widely in different countries. According to the availability of current prevalence data for diabetes and estimated data for future, one thing for sure is clear that it is significantly on increase. Also according to estimation, at any one time only about 50 % of the diabetic patients remain undiagnosed for up to 10 years; even then in many cases it is diagnosed accidently.

The change in life expectancy and lack of improvement in health care are in part responsible for the astonishing rise in the incidence of diabetes. If the trend will continue many countries worldwide will face a significant increase on the burden of healthcare, as patients with diabetes are prone to both short-term and long-term complications and premature death (for more see below).

According to an estimate for 2010, globally there were more than 380 million people (amounting to about 7 % of the population) suffering from diabetes. In Britain alone, the 2012 survey showed that there were about 2.8 million people suffering from this disease. Furthermore the speculation was that by about 2025, if no cure found or proper care for control applied this population may reach to 440 million [5].

According to National Diabetic Fact Sheet 2011, in US, there were 25.8 million (or 8.3 %) of the population suffering from diabetes and according to an estimate that around further 7 million were remaining undiagnosed [6].

The GULF News in a recent report presented that: “There are 368 million people in the world currently suffering from diabetes and it is expected to rise to 679 million by 2035” if no treatment found or better control measures applied. Furthermore according to International Diabetes Federation report the GCC countries were heading the list.

They further reported that 7 of the top 20 countries with high prevalence of diabetes are from the MENA (Middle East and North Africa) region. The news further adds that within the MENA region it is the Kingdom of Saudi Arabia which, due to wealth driven from oil, leads with almost 24 % of its population suffering from diabetes in Kuwait (23.1 %), Bahrain (21.9 %), Qatar (19.8 %) and UAE (19 %).

Referring further to the GULF NEWS it is shown that, despite a slew of diabetes health awareness campaign, the prevalence of diabetes in GCC region is soaring rapidly and primarily it is caused due to the change in life style and food. This newspaper further states that lack of exercise

and unhealthy food, primarily based on fat, sugar and carbohydrates, is the important reason leading to increased obesity and diabetes. The forecast, according to GULF NEWS, is that the obesity rate is not only increasing but expected to become worse in the Middle East countries [7].

As it has been well established that body overweight and obesity to be the most important reasons for DM and as the prevalence of obesity has been escalating rapidly (especially in industrialised nations), it will not be long that this disease will take the form of epidemic.

Risk Factors for Diabetes

Although a single best predictor of diabetes is obesity and almost 90 % of people suffering from T2DM have been found to be either overweight or obese, a number of other well-defined risk factors especially for T2DM include sedentary life style, smoking and unhealthy diet (such as consumption of high fat content food, high sugar containing drinks and low fibre containing meals). Other risk factors include: increasing age, ethnicity, gender, pre-diabetes, pregnancy, stress, certain medications, certain viral infections, polycystic ovarian syndrome, genetic or family history of diabetes, history of gestational diabetes and high cholesterol in blood [5].

A recent meta-analysis showed that the risk of developing T2DM is 30–40 % higher for regular smokers, compare to non-smokers. In contrast, exercise and dietary control has been found to be most effective in preventing the onset of this type of diabetes. About the age and diabetes it is clear that as the age increases so is the chance for the development of T2DM. An age distribution recorded for the diabetes is: less than 2 % (age, 16–34) 5 % (age, 35–54) 14.3 % (age, 55–74) and those over 75 (16.5 %). Family history and hence genetic makeup is another important risk factor for diabetes specially T2DM. Also it is interesting to note that the frequency of diabetes varies in different ethnicity, for example the incidence in the South Asian countries (India, Pakistan and Bangladesh) has been estimated at around 10–12 % of the population whereas in Europe it is about 4–5 %. Genetic makeup, and the era in which the key genetic mutation affecting diabetes has occurred, may explain this variation. Variation has been registered even within the same country for example within United Kingdom the variation noted in England (5.4 %) Northern Ireland (3.7 %), Scotland (4.1 %) and Wales (4.9 %) [5].

According to a report in BALANCE (May-June 2012), although about 85 % of the T1DM occurs without family history, the risk among close family is about 15 times higher than in the general population. About gender, it has been noted that the men carry higher risk of developing diabetes than women. The reason postulated is that the men on the average carry more abdominal fat than women. A misconception among men that "having fatter belly is a normal growing process" must be discouraged [5].

Environmental factors associated with diabetes are: a variety of viral infection, cow's milk, certain toxins, rice consumption in certain cases and vitamin D deficiency [5].

Sign and Symptoms of Diabetes

They includes: *polydipsia* or excessive thirst, *polyuria* or excessive passing of urine, *delayed wound healing, polyphagia* or excessive hunger or appetite, *weight loss and erectile dysfunction* [5].

Consequences of Diabetes

DM, normally occurs due to a number of biochemical and genetic dysfunctions, in which the level of glucose in blood stream remains relatively higher in compare to a non-diabetic person. This increase in sugar can damage a number of body organs as well as the systems. This includes damage to eyes (retinopathy), kidney (nephropathy), vascular system (cardiovascular disease, including ischemic heart disease including atherosclerosis and dyslipidemia, cerebrovascular disease, peripheral arterial disease), impairment of immune systems leading to somatic and autonomic neuropathy (also causing

low defence against invading microbes and gastroparesis), damage to neurone systems (causing numbness in peripheral organs), periodontal disease, diabetic foot (leading to foot amputation) and pancreatic cancer [8].

Obesity

Obesity and Overweight

Prior to 2007 obesity was considered by World Health Organization (WHO) as a simple risk factor and a manifestation of consumer society. In 2007 this organization recognised obesity as a disease and it was based on several developments including epidemiological data, progress in pathological concept and increase in health expenditure due to obesity, as well obesity associated diabetes [9].

Obesity and overweight can be defined as accumulation of excessive or abnormal amounts of body fat which can lead to a number of health problems including some serious ones.

Measurement of Obesity

Obesity is determined by measuring body weight and the height and from this is determined the Body Mass Index (BMI). The calculation is carried out by measuring the person's weight in kilograms divided by the square of his height in meters (kg/m^2). If the person's BMI is under 18.5 then he is considered underweight, between 18.5 and 25 is healthy weight, between 25 and 30 is overweight, between 30 and 35 is grade 1 obesity, 35–40 is grade 2 obesity and 40 or more is morbidly obese. Every person with BMI of 25 or above may be carrying the risk of developing diabetes.

An example of BMI calculation is: Weight in kg/height in m^2.

Suppose the body weight is 95 kg and the height is 1.8 m then

$95/1.8 \times 1.8 = \text{BMI is } 29$

BMI measurement is a standard method to determine if a person is overweight or obese and has been accepted globally to classify this health issue. It is important to note that this calculation is not valid for children.

Prevalence of Obesity and Overweight

According to WHO estimation the global prevalence of overweight persons in 2014 was more than 1.9 billion adults of 18 years or over and of these 600 million was obese. This makes around 39 % of adults of above 18 years overweight and 13 % of them obese. Since 1980 worldwide obesity has more than doubled. Out of this 13 % obesity figure, estimated data show that 11 % of them were men and little higher (15 %) women. Furthermore, in 2013, 42 million children under the age of 5 were overweight or obese. If we go back to the figures in 2014 of adult population of 18 years, the overall population of overweight men comes to 38 % and of women 40 %. Furthermore, globally at least 2.8 million people are dying each year from being overweight or obesity, and according to WHO, most of the world's population live in countries where overweight and obesity kills more people than underweight. Another record shows that since 1980 till now the population of overweight people globally has reached to the double figures [10].

Reasons for Global Increase in Obesity

One fundamental reason for the overweight and obesity is the change in the life style, and this change in the last 3–4 decades came with improvement in economy and earning. Industrial improvement and high income led to the culture of fast food and availability of cheap transportation brought significant changes in life style specially eating more than required and little or no exercise. The changes in life style also includes consumption of more energy rich food (such as food with high in fat and sugar) and spending less energy for example working at the environment with little or no physical movement, change in

the modes of transportation and increasing urbanization. To sum up, the consumption of energy rich food and lack of adequate dispensing of energy are the fundamental cause of obesity and overweight which has now reached to the pandemic stage [11].

As shown above the oil producing and developing countries have become rapidly and significantly more affected than the developed countries. An example is the rate of increase of childhood obesity and overweight which has become more than 30 % higher than that of developed countries. In United Kingdom it is reported that this country has the highest number of overweight people (1 in 5 or 20 % of the population) and one in 15 (or 6.6 %) are obese. Furthermore, it is estimated that if no effective control measures applied, in the next 20 years the population of obese adult will rise to 260 million which is about 73 % of the population. Also for UK it is estimated that as the T2DM is closely linked to obesity, in 20 years' time there will be an additional 1 million people to be suffering from diabetes and obesity and there associated diseases such as heart disease and cancer [12, 13].

Consequences of Obesity

Metabolic syndrome has been given an umbrella titles for a large number of diseases and syndrome [14, 15].

A number of these are clearly responsible to cause overweight and obesity and a number of others may be tangentially associated with them. Below are presented these syndromes and readers are advised to consult about those missing in this book using appropriate materials.

Metabolic syndromes linked with obesity, presented in this book are:

- Cardiovascular diseases such as stroke (Chap. 8), sleep apnoea (Chap. 10), gastro-oesophageal reflux (Chap. 11), certain gastrointestinal disorders (Chap. 12) non-alcoholic fatty liver disease (Chap. 13), chronic kidney disease (Chap. 14), Polycystic ovary syndrome (Chap. 15), osteoporosis (Chap. 16), certain types of cancers (Chaps. 17 and 18), depression (Chap. 19) and T2DM (this chapter).

Those missing are: rheumatoid arthritis, chronic renal disease, hyper tension, and adiposopathy.

Those which are tangentially associated: Alstrome syndrome, autism, gout, chronic obstructive pulmonary disease [16, 17].

Association Between Obesity and Diabetes

It is now clear that obesity and T2DM go hand in hand. Many obese people specially at their late age either suffer from diabetes or from prediabetes condition which means they are likely to suffer from this disease at a later stage in life. In addition, from the past 2–3 decades a new trend has started appearing that due to increased obesity in children, they too have started suffering from T2DM [18–21].

This information confirms a link between obesity and diabetes. Unhealthy diets, lack of physical activity and sedentary behaviour have been postulated to be the the most common reasons for obesity linked diabetes in children too. Furthermore social environments as well economic, psychological and cultural factors also play important roles in it.

An interesting issue associated with obesity and diabetes is that if a person is carrying excessive weight around the belly he carries more chances of developing T2DM. It is because the fat cells in the abdominal region lead to android obesity which mostly progresses to diabetes and atherosclerosis. Hence this kind of obesity has been branded as diabetogenic and atherogenic obesity [22].

Abdominal fat cells contribute mostly to the development of diabetes because they release more pro-inflammatory cytokines such as plasma leptin, tumour necrosis factor α, and non-esterified fatty acids; also their levels remain elevated in obese subjects. The elevated levels of

these hormones can make the body cells less sensitive and irresponsive to the insulin by disrupting the function of insulin responsive regions in cells. Also obesity triggers alterations to the body's metabolism that causes the fat cells in adipose tissues to release high levels of fatty acids, glycerol, certain hormones and other factors that are involved in the formation of insulin resistance. In T2DM, besides insulin resistance, dysfunction of β cells (usually partial) from pancreatic islets also can occur. A combination of these two can lead to failure to control blood glucose levels which entail being usually higher known as hyperglycaemia, hence T2DM [23].

Getting full information about the cause and mechanism of various types of diabetes (especially T2DM) is still at the research stage and we have to go some distance before entire mechanisms for each kind of diabetes will be fully understood. Studies so far have identified a number of gene mutations inflicting diabetes and a number of factors that promotes it. We now know that T1DM, for which the patients have to depend on insulin treatment, suffer from the total loss of the ability of pancreas to produce insulin or produce at the quantity much less than required, is mostly caused due to gene mutation (see Chap. 7 for detail).

Control of Obesity and Its Effects on Diabetes

Diabetic glycaemic control and insulin resistance can be controlled by reducing obesity. However, control and even treatment of obesity is much more difficult and weight reduction usually been seen to be transitional. After the weight reduction, normally obese people become relaxed and soon after they start gaining the weight again. Another report suggests that weight reduction cannot be carried out by dietary control alone. For successful weight reduction, low calorie diets, regular low impact exercise associated with education including behavioural techniques are important for sustainable weight reduction. Weight reducing medications such as orlistat or sibutramine (these are more useful when obesity is linked with diabetes) can be beneficial when given alongside the other measures described (see Chap. 27).

Bariatric surgery is an alternative method which has been shown to have more lasting effects on weight reduction. Out of two types of common bariatric surgeries, Rox-en-Y gastric bypass and Sleeve gastrectomy the former has been considered to be more effective than the latter and hence more commonly applied (see Chap. 23 for detail). Although weight reduction in obese subject may be helpful in reducing the probability of suffering from diabetes, unfortunately this method cannot be applied with lean people suffering from T2DM; for them other methods such as exercise plus restriction from sugar consumption and/or medications or insulin injection remain the only choice.

Cost of Treating Obesity and Diabetes

The cost of controlling obesity *per se* does not drain as much resources from the national budget as much the obesity related diseases such as heart disease, musculoskeletal disorder and cancer. In addition the treatment of T2DM and its associated complications, such as nephropathy, heart disease and leg amputation remains very costly. Furthermore, with rising number of overweight, obesity and T2DM, both in adults and in children, the future of national health budget can become alarmingly high and this is required to be addressed as soon as possible.

Overlapping Biochemistry of Obesity and Diabetes

It is well documented that the abdominal fat plays a major role in the development of metabolic syndromes including T2DM. The deposition of abdominal fat has been linked with abnormal glucose and lipid metabolism as well resistant to the action of insulin in skeletal muscles, liver and fat. Also are involved a cascade of proteins and hormones described below.

It is therefore important to know how abdominal adiposity can imbalance the normal metabolism. Interestingly this disruption not only affects the lipid and glucose metabolism but also other metabolic as well as immune pathways. The latter leads to chronic inflammatory state and this process in turn targets critical organs and tissues and disrupt systemic homeostasis.

Insulin Signalling Pathway

Insulin signalling leading to glucose uptake by skeletal muscle and fat tissues is a complex and an intricate process involving a number of hormones, enzymes and factors: these include: insulin receptor located at the cell membrane region, insulin receptor substrate (IRS), phosphatidylinositol 3-kinase (PI3K), Akt/protein kinase B (PKB/Akt), atypical protein kinase C (aPKC) lambda and zeta, Glut-4 vesicle, glut-4 as glucose transporter, AS160 kDa Akt substrate (AS160), PTP (protein tyrosine phosphatase) and PTEN and few more .

Roughly explained, in non-diabetic subjects the process starts from insulin molecule binding to insulin receptor located at the cell surface in that one end is exposed to the cell surface and the other inside the cell. The attachment of insulin to its receptor elicits receptor's autophosphorylation and activation of the receptor tyrosine kinase. This results in tyrosine phosphorylation of IRS, located inside the cell in the cytoplasmic region [24, 25].

The phosphorylation of IRS leads to activation of P13K. Subsequently occurs the activation of PKB and aPKC lambda and zeta, each of which is serine threonine kinase [26].

Activated Akt then phosphorylates AS160, which stimulates the translocation of insulin mediated GLUT-4 from intracellular vesicle to the plasma membrane [27, 28].

Here activated GLUT-4 binds to the exogenous glucose molecules and transport it inside of the cell. In essence the physiological regulation of insulin action is controlled by the balance between phosphorylation and dephosphorylations in which P13K plays a key role. In T2DM patients P13K activity has been found to be decreased leading to insulin resistance [29, 30].

Besides the above mentioned pathway for insulin uptake, involving a number of proteins, enzymes and hormones, a set of other factors and hormones are involved in maintaining proper glucose homeostasis and their impairment may lead to obesity and diabetes. Below selected ones playing important roles are described.

Adipose Tissue: In human this tissue is made up of fat cells which are noted to be a major endocrine organ producing a number of hormones. Adipose tissues are derived from lipoblasts and are made up of adipocytes. It is an important structure plays one of the most important roles in controlling the whole body glucose homeostasis in both normal and disease states. They store energy in the form of lipids and also modulate glucose homeostasis. Adipose tissue produces and releases a variety of hormones and proteins collectively known as adipokines.

Those adipokines associated with tissue inflammation or having pro-inflammatory function are called cytokines. These include heterogeneous cellular infiltrates monocyte/macrophages, neutrophils, B lymphocytes, T lymphocytes and some others. Results show that in severely obese patients and in fatty liver disease the expression of these cytokines is 100–1000 times higher than in liver. If weight loss is rapid, these pro-inflammatory cytokines are greatly eliminated in the adipose tissue.

In T2DM patients low grade inflammation is a common feature due to increased concentration of circulatory inflammatory cytokines [31–33].

The two kinds of adipose tissues are white and brown adipose tissues:

White adipose tissue: this tissue is mainly involved in energy homeostasis and some other physiological functions. Also they produce and excrete a number of important proteins known as adipokines. This includes leptin, adiponectin, resistin, retinol binding protein-4 (RBP4) and also pro-inflammatory cytokines such as tumour necrosis factor α (TNFα) and interleukin-6 (IL6). In obese subjects adipose tissue mass is increased

and this plays significant roles in development of insulin resistance and other metabolic complications associated with obesity to promote T2DM and obesity related other diseases. Also from adipose tissue are secreted in high concentrations non-esterified fatty acid, glycerol, certain hormones and pro-inflammatory cytokines. They interact with insulin signalling leading to low grade inflammation and obesity. Research has shown that dysfunction of adipose tissue plays a crucial role in the induction of insulin resistance in T2DM [34–38].

Also cardiovascular disease in obese persons has been associated with adipose tissues. Other adipokines include chemerin, plasminogen activator inhibitor-1 (PAL-1) and visfatin (see Chap. 8).

Brown adipose Tissue plays important role in obesity in that, rather than storing energy; it is involved in its dissipation. This is carried out through heat production rather than storing triglycerides and hence used in reducing obesity [39].

Adiponectin: Adiponectin, also known as adipoQ coded in human by ADIPOQ gene. It is a collagen like protein and is involved in regulating whole body glucose level as well breakdown of fatty acid. It is a 244 amino acid protein and secreted exclusively from adipose tissue into the blood stream. It is heavily present there relative to many other hormones. This is another important hormone involved in modulating a number of metabolic processes including enhancing inhibition of hepatic glucose output as well as glucose uptake and utilization by fat and muscle. Additionally it has been shown that adiponectin is involved in insulin-sensitizing activity and alters glucose metabolism through stimulation of pancreatic insulin secretion; hence imposing a positive effect on balancing the weight and reducing various metabolic syndrome including adiposity, insulin resistance and T2DM [40, 41].

Leptin: This is the first described hormone mostly secreted from white adipose tissue and used in most important signalling function for the regulation of food intake and energy homeostasis. Hypothalamus is signalled by leptin for quantity of fat stored. It also signals for food intake and involved in high energy expenditure thus indirectly promoting insulin sensitivity (for detail see Chap. 4 and Ref. [42]).

Free fatty acid: The modulation of whole body glucose homeostasis is assisted by free fatty acid (FFA). Derived from triglycerides or phospholipids, it is an energy compound and when it is metabolised they produce large quantities of adenosine tri phosphate (ATP). FFA can be used by several types of cells in heart and skeletal muscle (especially striated muscle) in liver and endothelial cells as a source of energy, in addition to glucose. Here excessive lipolysis through increased FFA oxidation is followed by reduced glucose utilization. FFA also generates low grade inflammation in these organs through activation of nuclear Kappa B resulting in release of several inflammatory cytokines which most likely are contributor to T2DM. This compound is increased in obese patients and a major contributor of diabetes. Additionally adipocytes are capable to synthesise and store triglycerides during feeding, as well to hydrolyse and release triglycerides as FFA and glycerol in the circulation. Thus adipocytes are a kind of gatekeeper for FFA that can circulate in the blood and enter in the skeletal muscles [43, 44].

Another role of FFA has been that it increases serine phosphorylation of IRS protein (see above) thereby impairing insulin signal transduction.

Ghrelin: This hormone is synthesised and secreted mainly by gastric and pancreatic cells and is involved in satiety – in that it stimulates appetite and reduced after the meal and hence regulates energy balance. Hence plays a positive role in keeping the weight under balance. Research on the importance of ghrelin as anti-obesity drug is ongoing and in future this work may play an important role in obesity and T2DM control [45, 46].

Obestatin: It is a 23 amino acid amidated peptide coded by the same gene as ghrelin. Initially it was suggested as an opponent of ghrelin for food

intake and body weight gain through interaction with its receptor GPR39. Later it was found that the effect of obestatin is not different from ghrelin especially for the cardiovascular regulation. This finding is largely still debated and hence obestatin's biological roles remain elusive. More recent finding, however, clearly indicates that obestatin is a multifunctional peptide, exerting multitude of effects such as stimulation of cell proliferation, survival and differentiation, influence on glucose and lipid metabolism as well as anti-inflammatory and cardio-protective actions [47, 48].

Retinol binding protein-4: another adipokine acting as carrier of retinol (vitamin A alcohol) in blood; also involved in insulin signalling pathway. Although data are still controversial it is suggested that this protein (secreted by adipocytes) plays roles in insulin signalling pathway and more studies required for understanding its role in controlling obesity [49, 50].

Tumour Necrosis Factor-α: this is a pro-inflammatory cytokine produced by adipocyte and is known to play an important role in obesity by impairing insulin action via disturbing insulin signalling. The disruption of insulin signalling occurs at the stage of serine phosphorylation of IRS-1 and down regulation of GLUT-4 expression, also by inhibiting the insulin-induced glucose uptake thus contributing in insulin resistance [51].

Plasminogen activator inhibitor-1: another hormone associated with adipocytes, secreted from endothelial and mononuclear cells, hepatocytes and fibroblast and acts as proinflammatory cytokine. Besides its association with increased risk for cardiovascular disease, it is also involved in insulin resistance in T2DM [52, 53].

Glucagon: This is a key hormone secreted from islet α cells of pancreas and its main function is to control in blood levels of glucose, in the fasting state by increasing its level. In normal person when the blood sugar level goes down below the required level, pancreas releases glucagon, induce liver to convert stored glycogen into glucose; a process known as gluconeogenesis. This results in increased plasma glucose level. Subsequent release of insulin from pancreas occurs and glucagon production is inhibited. Insulin allows glucose to be taken up and be used by the insulin dependent tissues. Glucagon also reduces satiety and increases energy expenditure through central and peripheral mechanisms, indicating that activation of signalling through glucagon receptor may be used to control obesity. In T1DM patients the secretion of glucagon can predispose to hypoglycaemia. On the other hand in T1DM as well in T2DM patients it can induce hyperglycaemia due to hyperglucagonaemia [54, 55].

Mechanism for Insulin Resistance

This occurs due to impairment of insulin signalling pathway (see above) in targeted tissues such as skeletal muscle and fat tissue. It also involves increased glucose production from liver and defect in insulin secretion from pancreas. T2DM patients may also suffer from reduced synthesis of insulin from β cell in pancreas [56–58].

In non-diabetic subject the blood glucose level is monitored and kept in balance at targeted tissues by inhibiting the glucose production from the liver cells. In diabetic patients, in insulin resistant condition, the targeted organs do not properly response to insulin leading to hyperglycaemia or increased blood glucose level and an increased requirement of insulin from β cells. Thus insulin resistance is a major contributor to T2DM and diabetes associated complications.

Obesity, a Main Mediator of Insulin Resistance

Obesity plays key roles in increasing the risk of developing insulin resistance and hence T2DM. However, although progression of T2DM occurs more frequently in obese human compared with lean individuals, it seems likely that genetic factor(s) also plays roles. It is evident from the fact that not every obese patient suffer from T2DM but in certain population, lean

subjects do develop T2DM suggesting that genetic and/or environmental factors also play a part in the development of this disease [59].

In minor population insulin resistant individuals can be found but they do not suffer from diabetes; it is because their glycaemic control may be maintained by compensatory increase in insulin secretion by pancreatic β cells.

Endoplasmic Reticulum and T2DM

Over the past few years a new research finding appeared in which it has been shown that that endoplasmic reticulum (ER) plays important roles in unfolding, folding and misfolded proteins under physiological and pathological conditions. Additionally ER adapts to endogenous and exogenous stressors by employing its protein-folding ability by applying its protective processes such as autophagy and antioxidant responses. These functions are essential for cellular balanced homeostasis and its loss has been associated with the development or pathology a number of human diseases including insulin resistance and diabetes [60, 61].

Accumulation of unfolded and misfolded proteins interferes with the ER function and triggers ER stress response. In normal condition ER stress is to maintain ER homeostasis, restore ER function and protect stressed cells from apoptosis by coordinating gene expression, protein synthesis and accelerating protein degradation.

Prolonged or chronic ER stress, on the other hand, plays opposite roles in that it leads to cell damage, apoptosis and resulting tissue injury. If the demand from the unfolded proteins is sustained the ER can coop it through an adaptive signalling called Unfolded Protein Response (UPR). This response is critical for the survival and functioning of pancreatic β-cells. Any dysfunction in this UPR can contribute to the pathogenesis of T2DM. Although activation of factor 6 (AFT6α), spliced X-box binding protein1 (sXBP1), and phosphorylation of eukaryotic initiation factor 2 (EIF2α) have been implicated with the regulation of UPR molecule, exact mechanism is still to be fully elucidated. In the β cells of T2DM, the expression of ATF6 and sXBP1 has been found to decline suggesting that UPR plays an important role in the decline of islet function in T2DM [62].

Also the activation of the UPR impairs the calcium and redox homeostasis; together with oxidative stress they influence the vital mitochondrial function. Calcium released from the ER increases the production of mitochondrial reactive oxygen species (ROS). In turn these toxic agents participate in inducing a number of diseases including several neurodegenerative diseases, stroke, metabolic disorders, cancer, diabetes and cardiovascular disease.

Furthermore, it is proposed that as soon as the ER finds excess nutrients that come in need of processing, storing and utilization, it sends an SOS signal. The signal is for the cell to dampen their insulin receptors. This leads the insulin losing their ability to reduce the blood sugar and hence diabetes develops [63, 64].

Proinsulin is the precursor of insulin and to maintain its demand pancreatic β cells produce 30–50 % of the total cellular protein from these cells. This puts pressure on the β cell secretory pathway specifically ER. The proinsulin undergoes its initial folding including formation of the two disulphide bridges. However, up to 20 % of the proinsulin can fold and the rest remains misfolded. The misfolded proinsulin is degraded by the ER associated degradation (ERAD) and autophagy, associated with usually no enhanced synthesis of proinsulin by the β cells. However, in certain pathological conditions, proinsulin misfolding increases and this results in the accumulation of misfolded proinsulin in the ER and resulting diabetes. Thus a tight links exists between proinsulin misfolding, UPR and β cell failure leading to T1DM and T2DM [65].

Another recent study reports the ER and mitochondria, which play roles in numerous cellular processes, are critical contributors of whole body homeostasis. These two organelles seem to physically and functionally be interconnected via mitochondrial associated membranes (MAMS). In addition, mitochondrial dysfunction and UPR are involved in determining insulin resistance leading to T2DM. Mechanisms interplaying

between mitochondrial dysfunction and UPR and its relevance to control glucose homeostasis remains to be further explored [66, 67].

So What Can Be Done to Minimise the Obesity and Diabetes Related Complications?

At Personal Level

Avoid the myths: that: (i) obesity and diabetes are not diseases; they are and a slow killer (ii) by eating a lot of sugar you can develop diabetes; it is not strictly true, however, by eating lot of sugar you can develop obesity and this in turn can lead to diabetes (iii) if you are lean or underweight you will not develop diabetes; you may develop it (iv) if you have eaten sweets such as a bar of chocolate or barfi (an Asian sweet) and that you have taken additional anti-diabetic medication, you can bring back your sugar level to the stage where you had before consuming the sweet; may not be true.

Gain knowledge about these two diseases as much as possible because the author believes that *Knowledge about disease is as valuable as treatment at least in case of obesity and diabetes.*

Do not leave all the responsibilities over your doctors and specialist nurse; for these diseases take selected responsibility specially for running the daily life. In that:

Bring about changes in the life style to live healthily life. This should include eating healthy diet and regular exercise. Avoid sugary and fatty food as much as possible. A balanced food is: a small amount of good quality protein rich diet such as fish, chicken meat, yoghurt, fat- reduced cheese; reasonable amount of carbohydrates (found in pasta, bread, rice, potato etc.); and plenty of fresh salads and reasonable amount of fresh fruits.

At Parental Levels

Parent and caretakers: to prohibit young children from eating high calories food such as loaded with fat and sugars. Also avoid consuming fast food rich in fat and sugar (also known as junk food).

Promote regular exercise and indoor activities rather than spending lot of time in front of TV programmes, TV games and chatting, using electronic devices, mobile telephones etc. Studies have shown that prevention of TV watching for 1 week can reduce a child's waist size by an average of 2.3 cm.

At Educational Level

Schools, colleges and universities: ought to take relevant responsibility to educate children and young adults for these two important diseases so that when they come to sensible age they could understand better the long-term consequences of these ailments and help-themselves more effectively to have a healthier and longer life.

At Social Level

Join specialised society running locally or at national level. Many societies at local and national level can be found at Internets. Find and join them and obtain benefits from their information bulletins and help desks.

If unavailable try to create one at your local level. Your organised society/club will be responsible to spread information within the community and through education bring awareness in them. It may also include such community programmes as screening for blood glucose level and Body Mass Index.

Lecture and seminars: Organise lectures and seminars by specialists with good publicity to attract good attendance.

Use of health clubs and gymnasia: Health clubs and gymnasia should provide free entrance to the patients suffering from any of these diseases. Involve local council for the support.

Use the media: Produce TV programmes to educate people for diabetes and obesity and how

they can be managed effectively. Ask government to spare fund to start a new *health channel* (if already missing) or at least assign a slot in one of the existing channel for presenting regular health programmes.

Campaign: for food industry and fast food companies to improve further their products and take those products out of the system known as the "junk food". Also the super markets to introduce and identify the shelves specifically displaying healthy food and food for diabetic patients.

At Governmental and International Levels

Government: as enforced for the certificate of Ministry of Transport (MOT) test, Ministry of Health ought to introduce certificate for Ministry of Health (MOH) test and this ought to be subsidised wherever required. This will not only reduce the National Health Services budget due to improved control of the disease but improve the quality of life due to better control on associated complications. Additionally at international level the WHO should support with more funding to minimise these two diseases – otherwise according to the prediction of the global escalation of the disease, it can become an uncontrollable pandemic in twenty-first century.

Conclusion

No doubt that obesity and diabetes are closely related diseases. Several types of diabetes have now been identified of which two types are more common; these are T1DM and T2DM and a significant number of obese people are T2DM patients. T1DM usually starts early in the life, is insulin dependent for diabetes control due to total (or almost total) loss of insulin synthesis from the pancreatic β-cells. T2DM on the other hand is more complex and more prevalent (about 85 % of the total diabetes) and normally starts late in life. Genetic mutations seem to play important roles in T1DM whereas environmental, biochemical and physiological factors are involved in determining T2DM. Beside reduction in synthesis of insulin another physiological factor playing role in T2DM is insulin resistance.

The correct level of glucose in blood is very important because not only being an important energy supplier, it plays vital role in driving many important biochemical reactions in the body. In non-diabetic subjects the level of glucose in blood is maintained intricately involving a number of enzymes and hormones but mainly by the insulin. Insulin helps transporting the sugar inside of the cells. In diabetic patients this intricacy is lost due to imbalance in insulin level. Hence diabetic patients can suffer high levels of glucose retained in the blood than needed (hyperglycemia) or low levels than needed (hypoglycemia) and they both can become heavily problematic.

Diabetes still remains an incurable disease but can be controlled by adequate care, knowledge and treatment. Obesity on the other hand in many cases is controllable and to avoid obesity related diabetes it is important that care should be taken to overpower obesity. In addition both these diseases are on rapid increase and speculation is that if no significant control measures taken or effective treatment found, the likelihood is that both diseases can reach to pandemic level in the near future. A number of measures have been proposed in this chapter and it is urged to the National Health Service throughout the world that they should take these two diseases more seriously to avoid the burden of heavy expenses as well relieve the public from the suffering.

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Obesity and Breathing Related Sleep Disorders

10

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Introduction

The increasing prevalence of obesity mostly in the developed world has lead to an increase in the occurrence of breathing disordered during sleep. As the obese people, due to consumption of too many calories, suffer from hypertension, dyslipidemia, coronary heart disease, peripheral vascular disease (both, venous and arterial), diabetes mellitus, osteoarthritis and gout, they carry an increased risk of morbidity and mortality from these acute and chronic medical conditions. Here we are concerned with the consequence of obesity on respiratory diseases such as obstructive sleep apnea and hypopnea syndrome characterized by repeated airway collapse during sleep [1, 2]. Sleep-related breathing disorder (SBD) is a term used to describe a spectrum of respiratory disturbances that occur during sleep and comprises OSA, central sleep apnea (CSA), and obesity hypoventilation syndrome (OHS) [1]. OSA remains an important medical condition because of its high prevalence and its association with numerous cardiovascular and non cardiovascular consequences if left untreated. Alveolar hypoventilation in obesity results from complex interactions between obesity, ventilatory mechanics, central ventilatory control, sleep apnea and degree of FEV_1 abnormality [3]. OSA and OHS and CSA are often the frequent basic cause in the pathogenesis of hypoventilation in the obese subject [4]. They may be generated as a consequence of hyperventilation response that follows obstructive apnea. Moreover, there is a subset of patients in which obesity is associated with hypoventilation correlated with hypercapnic-OSA, hypercapnic-OSA & OHS and OHS without OSA.

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Effects of Obesity on Sleep

Obesity is associated with anatomic alterations that predispose to upper airway obstruction during sleep. These alterations may included excessive adiposity around the pharynx and chest. In the former, increases in neck circumference and fat deposited around the upper airway may narrow down the airway. It is known that the upper airway is more easily compressed and is higher in obese people compared with non-obese individuals. In these people the pharynx is not expanded by extending mandible. As for the

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chest, obesity and especially central obesity have been associated with reductions in lung volume, which leads to a loss of caudal traction on the upper airway, and an increased risk in pharyngeal collapse; thus obesity in the neck and thorax increases continuous positive airway pressure requirements and produce a greater severity of sleep apnea. Thus, obesity imposes mechanical loads on both the upper airway and respiratory system that predispose to upper airway narrowing, collapse, and airflow obstruction during sleep [5, 6]. Obesity also is associated with structural defects that compromise the airway, but the correlation is not linear. Greater obesity does not correlate with degree of apnea and it is difficult to measure local adiposity. There may be anatomical deformities in the nose, uvula, or tonsil which become critical when obesity is involved. The mechanisms causing these elevations in upper airway mechanical loads in obesity are not well understood. It needs to be said that more is known about therapy than pathogenesis in this kind of disorders. The pattern of obesity plays an important role in the ventilatory consequences. FEV_1 is sometimes moderately reduced in patients with severe or massive obesity, but the FEV_1/VC ratio is normal in the absence of associated bronchial disease. These effects may be mediated by circulating adipokines, which influence body fat distribution and CNS activity. As patients with sleep apnea lose weight, improvements in upper airway function and disease severity are likely to reduce according to the weight loss as well relative changes in protective and pathogenic adipokines, as shown below [5].

Obesity also induces an inflammatory state directly, because adipose tissues are abundant source of pro-inflammatory cytokines, including tumor necrosis factor (TNF-α), IL-6, as well as the pro-fibrogenic adipokine leptin [7]. In addition, adipose tissue elaborates humoral factors that may act centrally on the regulation of upper airway neuromuscular control. Leptin has been demonstrated to stimulate CO_2 ventilatory responses in mice [8, 9]. Its action is antagonized by other adipose-related factors, namely the soluble leptin receptor (sOB-R) and C-reactive protein (CRP), which bind circulating leptin and can decrease its central nervous system (CNS) uptake and action. Levels of sOB-R and CRP are elevated in sleep apnea compared with matched control patients and decline with weight loss and the loss of visceral compared with central adiposity. There is also evidence that neurohormonal changes such as leptin resistance may have a fundamental role in ventilatory control of obese patients with hypercapania [7, 10]. It has previously been observed that serum leptin was a better predictor for the presence of OHS in obesity than BMI or calculated body fat mass [10]. Central leptin resistance (indicated by increased circulating leptin levels) may not just reflect a resistance to the satiety effects of leptin but also a resistance to the respiratory stimulatory effects. Alternatively, the increased leptin levels in OHS relative to eucapneic OSA with obesity may reflect a compensatory rise to counter hypoventilation [10]. Current evidence indicates that sleep apnea is associated with fundamental disturbances in upper airway mechanical and neuromuscular control and suggests that a combined defect is required to produce sleep apnea [11].

Obstructive Sleep Apnoea

Obstructive sleep apnea is characterized by temporary but intermittent episodes of upper airway obstruction resulting in cessation of breathing or reduction in tidal volume in sleep. Apnea termination requires arousal and the resulting frequent awakenings lead to daytime symptoms such as daytime sleepiness, and impaired concentration [12], snoring, hypoventilation, hypoxemia, leading to sleep fragmentation, poor sleep, mood problems, and poor quality of life. Several risk factors, including obesity, gender differences, age, familial factors, enlarged tonsils and adenoids, and craniofacial abnormalities (retrognathia and micrognathia) have been associated with an increased prevalence of obstructive sleep apnea in the general population. Among these, obesity is one of the strongest sleep apnea risk factors. It has been shown that OSA is present in more than 50 % of a population of adult obese patients with a mean Body Mass Index (BMI)

higher than 40 [13]. Nocturnal hypoventilation seems to be present in more than 29 % of severe obese population. There is a relationship between body weight change and Apnea-hypopnea index (AHI): a 10 % weight gain has been shown to predict an approximate 32 % increase in the AHI; a 10 % weight loss predicted a 26 % decrease in the AHI, and a 10 % increase in weight predicted a six fold increase in the odds of developing moderate to severe SBD [11, 14]. OSA is common, under-diagnosed and treatable syndrome. In developed countries, it is reported to affect between 3 and 7 % of middle-aged men and 2–5 % of women. Furthermore, it has been reported that OSA is present in about 6 % of population between the ages of 50–70 years [15]. OSA is more common in men than in women. This has been attributed to differences in anatomical and functional properties of the upper airway, differences in craniofacial morphology and fat deposition, and different ventilatory responses to arousal from sleep. Central obesity accounts for the strong male predominance of this disorder, whereas peripheral adiposity may protect women from developing sleep apnea [5].

In addition to fat distribution pattern in the upper airway, upper airway anatomy and function may also contribute to gender differences in OSA. Upper airway collapsibility is greater in males than in females. Some reports support that upper airway resistance during sleep is higher in males than in females [16, 17]. Hormonal status may also have impact on sleep apnea susceptibility, particularly in women. Postmenopausal women demonstrate increase in sleep apnea prevalence and severity compared with premenopausal women [18, 19].

Obesity Hypoventilation Syndrome

Clinically OHS is considered to be a severe form of obstructive sleep-related breathing disorder in obese patients. Obesity hypoventilation syndrome (OHS), formerly described as "Pickwickian syndrome" is characterized by the combination of obesity (BMI >30 kg/m^2), daytime awake hypercapnia (partial pressure of arterial carbon dioxide ($PaCO_2$) >45 mmHg at sea level) and hypoxemia (partial pressure of arterial oxygen (PaO_2) >70 mmHg at sea level) in the presence of sleep-disordered breathing without other known causes of hypoventilation, such as severe obstructive or restrictive parenchymal lung disease, kyphoscoliosis, severe hypothyroidism, neuromuscular disease, and congenital central hypoventilation syndrome [20].

It is estimated that 90 % of patients with OHS also have OSA [21] because approximately 1.5 % of the United States population has severe obesity and OSA, and 10–20 % of the severely obese patients with OSA have OHS. The prevalence of OHS among the general adult population in the United States is estimated to be 0.15–0.3 % [22]. The prevalence of OHS is 11 % in patients with known OSA and 8 % in bariatric surgical patients [23]. OHS is a disease entity distinct from simple obesity and OSA. Patients in whom OHS is diagnosed consume greater levels of healthcare resources than eucapnic patients with OSA [24]. In order to confirm the diagnosis of OHS, other pulmonary, thoracic, metabolic or neuromuscular diseases accounting for the gas anomalies should be excluded [25]. Daytime hypercapnia is the distinguishing feature of OHS that separates it from simple obesity and OSA. OHS is usually associated with OSA and pulmonary hypertension. Major clinical features are hypersomnolence, dyspnea and headache in combination with polycythemia, cyanosis and right heart failure [11, 25]. Compared to similarly obese individuals without daytime hypercapnia, patients with OHS have significantly impaired respiratory system mechanics with a restrictive ventilatory pattern [26]. In addition to alveolar hypoventilation, also ventilation–perfusion mismatching secondary to pulmonary atelectasis contributes to hypoxemia in OHS [27].

There are three leading hypotheses for the pathogenesis of chronic daytime hypoventilation in OHS: (i) impaired respiratory mechanics because of obesity, (ii) leptin resistance leading to central hypoventilation, and (iii) impaired compensatory response to acute hypercapnia in OSA.

Compared with obese patients with eucapnia, patients with OHS demonstrate four main clinical features: (i) more severe upper airway obstruction, (ii) impaired respiratory mechanics, (iii) blunted central respiratory drive, and (iv) increased incidence of pulmonary hypertension [23].

The Relationship Between OSA and OHS

There are many similarities between OHS and OSA and the clinical presentation is similar: excessive daytime sleepiness, fatigue and/or morning headaches. Furthermore, 11–15 % of obese OSA patients present with hypercapnia, and a majority of the hypercapnic obese manifest OSA. Hypercapnia is more frequent in obese than in non-obese OSA subjects [28].

Patients with OSAS typically have normal control of breathing (without daytime hypoventilation) and for them obesity is not a necessary condition. Patients with OHS are morbidly obese, have hypoventilation during being awaken with increased arterial PCO_2 and decreased arterial PO_2, as well as nocturnal hypoventilation [12].

The mechanisms by which OSA may induce hypercapnia are not well understood. It may be that hypercapnia in OSA develops as a consequence of a reduced inspiratory effort against an obstructed airway. Therefore, ventilatory load compensation (the normal response to maintain alveolar ventilation in the face of mechanical impediments) is impaired in OSA. This impairment may be the result either of an inability of fatigued muscles to recover between apneic episodes or of diaphragmatic dysfunction as a consequence of periodic hyperventilation episodes following apneas [29]. Also, there may be depressed ventilatory response to chemical stimuli (bicarbonate, carbon dioxide, oxygen, pH etc.) producing a reduction in compensatory ventilation. The maintenance of eucapnia during sleep requires a balance between CO_2 loading during apnea and CO_2 clearance in the intervening period. Thus hypercapnia occurs when, after an apnea, the amount of ventilation is insufficient to eliminate the CO_2 loading that occurred during apnea. Whether this type of blunted response is a consequence of increased load or represents a protective adaptation to chronic hypoxia, hypercapnia and sleep fragmentation is unknown. The hypothesis that OSA is a part of OHS has not been yet accepted. While OSA can exist with or without hypercapnia, hypercapnia in obesity patients is a defining feature of OHS. Furthermore, in these patients hypercapnia persists after eliminating apneas and hypoapneas after continuous positive airway pressure (CPAP) ventilation. In fact some authors proposed calling the condition Obesity Hypoventilation Syndrome 'OHS without OSA'. For them, this entity may be diagnosed in two situations: hypercapnia in obese patients without OSA or COPD (OHS without OSA); and persistence of hypercapnia in OSA patients who are receiving CPAP, OHS with OSA) [30, 31]. Multivariate analysis showed that hypercapnia was associated independently with HCO_3 levels and daytime oxygen saturation, and these parameters had high sensitivity and specificity in predicting OHS [32]. Evidence suggests that elevated bicarbonate levels and decreased oxygen saturation in obese OSA patients should prompt clinicians to exclude OHS [33]. Moreover, routine measurement of serum bicarbonate in obese patients can be a useful screening tool for early diagnosis of OHS and/or sleep disordered breathing [22, 23]. Further studies have shown considerable similarities between obese subjects with only elevated base excess or raised bicarbonate and no daytime hypercapnia and those obese patients with hypercapnic chronic respiratory failure. This supports the concept that obesity-related hypoventilation is a clinical spectrum. Metabolic compensation in the presence of eucapnia probably identifies subjects with early OHS at the milder end of the spectrum. Thus an obese patient with an isolated increased base level or raised bicarbonate should not be dismissed as normal. Whether early detection of obesity-related hypoventilation makes a difference in the long term needs to be tested in appropriate randomized controlled trials [34, 35].

Morbidity and Mortality

Obesity and OSA are associated with a spectrum of co-morbidities such as coronary artery disease, heart failure, stroke and metabolic syndrome, which result in increased morbidity and mortality. Furthermore, patients with OSA are at increased risk of developing postoperative complications including arrhythmias and hypoxemia. Several studies showed that patients with OHS may experience higher morbidity and mortality than patients who are similarly obese and have OSA. The mortality rate in patients with untreated OHS is high [23, 36].

Diagnosis

An essential requirement for correct diagnosis of OSA is a correct anamnesis, recording the family history (history of OSAS) and personal antecedents such as tonsillectomy/adenoidectomy in childhood, alcohol intake, the use of muscle relaxant drugs, obesity, etc. It is also important to establish the profession of the patient, since in some professions OSAS constitutes a medical emergency. A proper physical examination is also required including height, weight, BMI, cardiovascular evaluation and exploration of the upper airway (nasal passages, oropharynx and hypopharynx, and larynx). The clinical examination should be complemented by radiological study in the form of either conventional lateral X-rays or a multidimensional X-ray study, which will reveal the craniofacial anatomical alterations predisposing to OSAS [2]. The diagnosis of OSA is established by polysomnography (PSG) which monitors the sleeping state, respiration, electrocardiogram, movements of the legs, oximetry and snoring. In addition, PSG records the distribution of the stages of sleep, the number of awakenings, the number of apneas or hypo-apneas, the starting time of sleep, and the hours of efficient sleep (hours asleep/h in bed) [37]. The gold standard is monitoring by polysomnography in a sleep laboratory. This modality uses multiple biometric recording devices to accurately quantify the number of apnea (a 90 % reduction in tidal volume lasting 10 s) and hypo-apnea (a reduction in tidal volume of 50–90 %, lasting 10 s accompanied by 3 % decrease in oxyhemoglobin saturation) episodes occurring during the experimental night's sleep. PSG also provides the apnea/hypo-apnea index (AHI); in this context apnea is very serious and can only be treated surgically when AHI >30, while AHI 15–30 defines moderate apnea, and an AHI score of <15 indicates mild apnea [37–39]. The Epworth Sleepiness Scale (ESS), arousal index (per hour frequency of arousals from sleep), minimum oxygen saturation (during sleep), the multiple sleep latency test (measurement of how quickly a subject will fall asleep during the day), the quality of life measure Functional Outcomes Sleep Questionnaire and compliance (measured as time per night using the device) are required to complete the diagnosis.

Screening, such as the validated Stop-Bang questionnaire, can identify patients at high risk of OSA. The screening tool can further be complemented by the presence of low SpO2, increased $PaCO_2$, and serum HCO_3 level to identify patients at high risk of OHS. Before major elective surgery, these patients should be referred to sleep medicine for polysomnography and CPAP titration. An echocardiogram should be done to assess right ventricular function and pulmonary hypertension [23].

Treatment Options

The management of the treatment must include attempts to improve lifestyle of the patient and decrease obesity. The goals should be to treat respiratory sleep disturbances, diurnal hypercapnia as well as hypoxemia that may persist after correcting alveolar hypoventilation. NIV may be planned as first-line treatment to manage acute or sub-acute respiratory failure in these patients. In stable hypercapnic patients therapeutic choice will depend on two factors: underlying diagnosis (presence or absence of OSA) and severity of hypercapnia.

The recommended CPAP treatment to maintain upper airway patency, eliminates apnea and hypo-apneas and restores daytime eucapnia [41]. If hypercapnia persists, despite adequate CPAP treatment, patients require augmentation of ventilation during sleep rather than simple stabilization of the upper airway, so it is recommended to use NIV [41, 42]. Some published series identified greater BMI and more severe hypoventilation as predictors of lack of response to CPAP [42].

In patients with $PaCO_2$ >50 mmHg, the initial therapeutic choice may be NIV [43]. If, after some time under NIV, the patient becomes eucapnic, and sleep studies confirm OSA, it is advisable to switch off to CPAP (after performing a full-night titration to identify optimal pressure level). If the patient remains eucapnic, long-term CPAP may be carried out [39, 40]. Otherwise the patient may be switched back to NIV. In cases in which sleep studies do not show significant OSA, NIV will be the therapeutic choice. In this case, hypercapnia may be considered as obesity-related only, but additional causes such as COPD need to be sought.

Therefore the proposed management of obese patients with sleep-related breathing disorders should be:

- in eucapnic OSA patients use CPAP in addition of oxygen therapy if hypoxemia coexists;
- in hypercapnic OSA patients try CPAP and if this corrects the hypercapnia, continue this therapy, if not, switch to NIV;
- in case of pure OHS without OSA start NIV in addition an oxygen therapy if hypoxemia coexists;
- in case of OSA and unknown OHS, try to start NIV and switch to CPAP if a normalization of parameters is obtained by CPAP; (in this case if the patient remains eucapnic we have a hypercapnic OSA patient.) If after the switch the patient has hypercapnia again is very likely to have OSA + OHS, so return to NIV [41–43].

Conclusion

Obesity sleep related breathing disorders are largely under-diagnosed and the health-related costs are higher than those related to obese patients only. Although nocturnal positive airway pressure therapies represent first-line treatment and are effective in improving patient outcomes, there is a need to offer combined treatment strategies and to assess the effect of multimodal therapeutic strategies on morbidity and mortality.

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11 Gastro-Oesophageal Reflux Disease and Obesity: Pathophysiology and Putative Treatment

Waleed Al-Khyatt and Syed Yousuf Iftikhar

Introduction

Gastro-oesophageal reflux disease (GORD) is described as group of symptoms and or mucosal injury that happen as a result of reflux of gastric content into the oesophagus. Obesity is well established risk factor for developing GORD and its related complications e.g. oesophagitis and Barrett's oesophagus. The surgical management of GORD in obese patients is still a matter of debate among surgeons. Nevertheless, as there is substantial association between visceral fat and the pathophysiology of GORD, most would agree that treatment of GORD in obese and none obese patients can be entirely different. Proper understanding of the pathophysiological mechanisms underlying GORD in obese patients is essential for planning of management and achieving a successful outcome.

Gord and Obesity: Is There a Link?

The Montreal classification system defined GORD as "a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications" [1]. It is often associated with reduced quality of life, significant morbidity, and increased risk of developing oesophageal adenocarcinoma [2]. GORD is a common but costly to treat medical condition [3]. It has been estimated that the annual cost of using of proton pump inhibitors is nearly $13 billion in the United States alone [4]. The prevalence of GORD has witnessed significant increase over the last three decades. In their systematic review in 2005, Dent et al found the prevalence of at least weekly heartburn or acid regurgitation ranges between 10 and 20 % in Western countries [5]. In 2014, another updated systematic review on the epidemiology of GORD found that the prevalence is shifting towards increase reflux burden mainly in developed countries and the Middle East [6]. The incidence of GORD is approximately 0.5 % per year in the UK and US populations, and 0.84 in UK paediatric patients aged 1–17 per year [6].

Overweight (BMI >25 kg/m^2) and Obesity (BMI >30 kg/m^2) are common in Europe and the United States as well in Middle Eastern Countries [7, 8]. The obesity epidemic is considered as one of the biggest public health concerns facing in those countries across the globe. The prevalence of obesity has more than doubled in United States over the past 3 decades [9]. Among all known risk factors predisposing to or increasing the risk of developing GORD, obesity comes on the top of the list.

Obesity plays an important role in the development of GORD [10, 11]. The increased prevalence

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of obesity has also corresponded with a parallel increased prevalence of GORD [10, 11]. Moreover, the link between obesity and GORD is clear on all measures of the disease including clinical symptoms, erosive oesophagitis, acid oesophageal exposure, and complications such as Barrett's oesophagus and oesophageal adenocarcinoma [11–18]. Several epidemiological studies suggest that obese patients have 2–2.5 fold increased risk of heartburn and/or regurgitation (the hall mark of GORD) [4]. For instance, a cross-sectional study conducted in an age- and sex-stratified random sample of the population of Olmsted County in Minnesota showed that a high BMI (>30 kg/m^2) was associated with frequent (at least once a week) reflux symptoms [odds ratio (OR) 2.8; confidence interval (CI) 1.7–4.5] [19]. In the UK, a cross-sectional study was designed to examine the relation between BMI and GORD in a large sample representative of the population of England using the data of the Bristol *Helicobacter* project randomised controlled trial (10,537 subjects, aged 20–59 years) [20]. The study concluded that obesity significantly increased the likelihood of suffering from GORD and that obese people were almost three times as likely to suffer from GORD as those with normal weight. In a multivariate survival analysis on data gathered from the National Health and Nutrition Examination Survey showed that for an increment of BMI of 5 kg/m^2 clearly associated increased hospitalisation from GORD with a hazard ratio of 1.22 [21]. Similarly, a dose-dependent relationship between increasing BMI and frequent reflux symptoms was also observed in another large study [22]. Those observations were also confirmed in two subsequent meta-analyses [23, 24]. Hempel et al found the risk for GORD symptoms, erosive oesophagitis, or oesophageal adenocarcinoma increased with overweight or obesity compared with normal BMI [23]. Similarly, Coley et al in another meta-analysis suggested that there is a moderate positive association between elevated BMI and GORD within studies from the United States and that the prevalence of GORD rises with increasing BMI [24].

Besides above epidemiological studies, several pathophysiological studies have investigated the possible link between obesity and GORD [25–29]. It appears that it is not merely increased body weight *per se* rather body fat distribution is an independent risk factor for the severity of GORD associated symptoms and/or mucosal damage [26, 27, 30–32]. In a cross-sectional study of 204 patients underwent 24-h pH-manometry [28], El-Serag et al showed that Obesity (BMI >30 kg/m^2) and increased waist circumference (compared with BMI <25 kg/m^2) were associated with a significant increase in the number of reflux episodes, long reflux episodes, time with pH less than 4 and a calculated summary score in almost in each time period during pH measurements [28]. Hence, they suggested that obesity operates to increase the risk of GORD at least partly by increased abdominal obesity [28]. Similarly, two large Korean cohort studies found abdominal obesity rather than increase BMI is as independent factor for the erosive oesophagitis [18, 33]. The importance of central adiposity as a key factor in the pathogenesis of erosive oesophagitis, Barrett's oesophagus, and oesophageal adenocarcinoma was reaffirmed in a recent meta-analysis [26]. It was found that central adiposity may have a BMI-independent effect on the risk of oesophagitis and Barrett's oesophagus which further suggesting the importance of visceral abdominal fat in the pathogenesis of oesophageal inflammation and metaplasia [26]. Moreover, it was observed that central adiposity, and not overall obesity, has a GORD-independent effect on the risk of Barrett's oesophagus [26]. There was also a trend towards a dose-response relationship between the degree of central adiposity and the risk of erosive oesophagitis and Barrett's oesophagus, further strengthening the possibility of a causative association between these phenomena [26].

The Mechanisms of Gastro-Oesophageal Reflux in Obesity

Normal Anatomy and Physiology

In order to understand the mechanisms behind the development GORD in obese patients, it is essential to present first the normal anatomical and

Table 11.1 Structural and physiological components of antireflux mechanisms

Antireflux component	Description
Lower oesophageal sphincter (LOS)	The distal 2–5 cm of the oesophagus normally has a high resting pressure (10–35 mmHg). This comprises the intrinsic part of the LOS
Right crus of diaphragm	It functions as an external sphincter by compressing the gastro-oesphageal junction and increasing LOS resting pressure
Intra-abdominal oesophagus	It is exposed to positive pressure within the abdomen which adds a compressive effect on the distal oesophagus and LOS
Angle of His	It is a sharp angle between the gastric cardia and distal oesophagus which acts as a flap valve or pinchcock
Mucosal rosette	It is formed by clustering of the lower oesophageal mucosa at the gastro-oesophageal junction
Phreno-oesophageal ligament	It stabilises the distal oesophagus in the oesophageal hiatus and thus limits upwards shift of the oesophagus during periods of increased intra-abdominal pressure
Adaptive pressure changes	During increased intra-abdominal pressure or inspiration, there is reflex increase in LOS pressure and this further enforced by contraction of diaphragmatic hiatus
Oesophageal clearance mechanism	These are reflex secondary oesophageal contraction which happens upon irritation of oesophageal mucosa by acid and gastric contents reflux
Oesophageal mucosal defence mechanisms	These are classified into pre-epithelial, epithelial, and post-epithelial physiological defence mechanism

physiological factors (Table 11.1) which prevent reflux of gastric contents into the oesophagus.

The oesophagus is a muscular tube with a primary function of food passage from the hypopharynx to the stomach. The gastro-oesophageal junction (GOJ) is structurally and functionally designed to ensure that the acid secreted by the most proximal gastric mucosa flows towards the stomach and not up onto the oesophageal squamous mucosa. Among the principal factors in maintaining this function of GOJ, the lower oesophageal sphincter (LOS) plays a major role in anti-reflux mechanisms [34]. LOS is defined as the distal 2–5 cm of the oesophagus which has a high resting pressure ranging between 10 and 35 mmHg (measured manometrically) [35–37]. It consists of two components: intrinsic and extrinsic parts. The intrinsic part of LOS is made of upper clasp-like semicircular smooth muscle fibres and lowers sling-like oblique fibres which blend into the cardia of the stomach. The upper part of the LOS normally lies in the diaphragmatic hiatus, while the lower section is intra-abdominal [34]. This intra-abdominal part is exposed to a positive pressure within the abdomen and in turn has compressive effect on the distal oesophagus and LOS [34]. The pressure gradient between the oesophagus and the stomach is 10 mmHg (5 mmHg intra-thoracic pressure and 5 mmHg intra-gastric pressure). This pressure gradient increases during inspiration. The right crus of the diaphragm forms most the oesophageal hiatus. It acts as an external sphincter by compressing the GOJ and increasing LOS resting pressure during inspiration. The distal part of oesophagus is also covered by the visceral peritoneum and the phreno-oesophageal ligament at the level of diaphragmatic hiatus. The phreno-oesophageal ligament is a fibrous layer of connective tissue originating from the transversalis fascia on the abdominal surface of the diaphragm [38]. It has been suggested that transversalis fascia may have a role to play in stabilising the distal oesophagus in the oesophageal hiatus and thus limiting the superior shift of the oesophagus during periods of increased intra-abdominal pressure [38]. Between the gastric cardia and distal oesophagus a sharp angle (Angle of His) is present, which acts as a flap valve or pinchcock in preventing reflux of gastric contents into the oesophagus [34]. In addition other anatomical and physiological anti-reflux mechanisms are present, like the mucosal rosette

of the upper stomach and GOJ which prevents the acid secreted by the most proximal gastric mucosa from flowing upwards onto squamous mucosa of the distal oesophagus [39]. Moreover, the presence of gastric contents within the oesophagus stimulates a secondary peristaltic waves which clear the refluxates back into the stomach [39]. Finally, the oesophagus has some mucosal physiological defence mechanisms which are collectively known as 'tissue resistance' [40]. These mucosal factors are divided into pre-epithelial, epithelial, and post-epithelial defensive elements. The pre-epithelial protective mechanism is provided by the oesophageal buffer layer which is augmented by the presence of saliva. The epithelial factors include: tight cell junctions, a protective electrochemical gradient and sub-mucosal glands which secrete bicarbonate and provide further protection from acid induced mucosal damage. The post-epithelial components compromise the presence of adequate blood supply and the ability of regeneration of damaged epithelium [40].

Pathophysiological Mechanisms Predisposing to GORD in Obese Patients

As demonstrated above, there a strong clinical association between abdominal obesity and GORD. Various pathophysiologic mechanisms have been proposed that likely lead to the development of GORD in obese patients. In non-obese patients, the most common cause of the GORD is the increased periods of transient lower oesophageal sphincter relaxations (TLOSRs) [39, 41]. TLOSRs have been found to be substantially higher in overweight and obese subjects during the postprandial period which was accompanied with increased postprandial GORD and oesophageal acid exposure [13]. Moreover, the frequency of TLOSRs was strongly correlated with both BMI and waist circumference [13]. Hence, It has been suggested that dysfunction of TLOSRs may be the early disruption in functional integrity of the anti-reflux barrier in obesity and heralds the development of hiatus hernia and other motility dysfunction [13]. A weak LOS has also been found to have a significant correlation with increased acid exposure and reflux exposures in morbidly obese subjects [42]. Nevertheless, it has been found that increased intra-abdominal pressure is main pathophysiological factor which increases the risk of GORD in obese patients [43, 44]. As a result of this increased intra-abdominal pressure, obesity (mainly visceral fat) leads to altered gastro-oesophageal pressure gradients in a way that would promote the retrograde flow of gastric content into the oesophagus [43, 45]. It was also found that the association between BMI and oesophageal acid exposure was stronger during the supine period compared to the upright position. One potential explanation is that the influence of increased intra-abdominal pressure found in obese subjects may be maximal in the supine position. This altered pressure stress also results in a reduced LOS pressure, increased TLOSRs period, impaired oesophageal motility and oesophageal clearance mechanisms [44, 46]. Moreover, elevated intra-abdominal pressure increases the risk of developing hiatus hernia which on its own results in significant disruption of GOJ and increases the risk of reflux episodes [46]. In addition, obese subjects tend to consume a large high caloric meals leading to delayed gastric emptying, changes of LOS resting pressure, fundic distension, and hormonal changes (e.g., cholecystokinin, ghrelin), favouring the occurrence and perception of gastro-oesophageal reflux episodes [44].

In addition to its mechanical effects, there are also obesity related hormonal changes which increase the prevalence of reflux symptoms and/or mucosal inflammation. For instance, the decrease of the anti-inflammatory adiponectin or the increase of the pro-inflammatory leptin or other cytokines may explain the highest prevalence of erosive oesophagitis or Barrett oesophagus in obese subjects [18]. There is a lower synthesis of sex hormone binding globulin and increased synthesis of oestrogens in the adipose tissue which have been associated with the development of GORD symptoms [47].

Investigations and Diagnosis

As discussed above, reflux symptoms are common among overweight and obese patients [42]. Clinical symptoms of GORD are classified into oesophageal and extra-oesophageal syndromes according to the current Montreal classification [1]. Typical symptoms comprise heartburn, acid brush, intermittent dysphagia, and regurgitation (volume reflux). Atypical symptoms include cough, chest pain, asthma, dental erosion and poor oral hygiene, hoarseness of voice, recurrent laryngitis, tonsillitis and sinusitis [1]. Reflux symptoms are far less sensitive and specific for diagnosis of GORD [48]. Nearly one third of patients with reflux symptoms have a normal endoscopic examination [49]. Conversely, 20 % of those with objective findings of reflux oesophagitis and or Barrett's oesophagus are asymptomatic [50]. It has also been found that only 70 % of patients with clinical diagnosis of GORD, based on clinical symptoms and endoscopic findings of grade I and II oesophagitis had abnormal reflux scores on 24-h pH monitoring [48, 51]. Moreover, the incidence of heartburn and regurgitation was similar between those patients with normal pH scores and those with abnormal scores [48, 51]. Nevertheless, symptoms evaluation is essential as it has significant impact on the likelihood of success of any surgical intervention. For instance, So et al found that relief of atypical symptoms attributed to GORD by anti-reflux surgery is less satisfactory and more difficult to predict than relief of heartburn and regurgitation [52]. In this study, laparoscopic fundoplication associated with 93 % success rate in controlling typical symptoms compared to only 56 % of patients had relief of atypical symptoms [52]

Proper diagnostic work-up should include oesophagogastroduodenoscopic examination (OGD). OGD should be offered for patients over 55 years with persistent dyspepsia or any patient with dyspeptic symptoms with one or more of the following: bleeding, iron deficiency anaemia, unexplained weight loss, abnormal looking mass on a swallow test, persistent vomiting or dysphagia. It allows direct visualisation of the mucosa and obtains tissue for histological examination.

Investigations like 24-h pH monitoring, oesophageal manometry, and oesophageal impedance monitoring may have additional diagnostic value in patients with GORD symptoms. It is also vital to have a documented evidence of reflux before considering anti-reflux surgery. For instance, in patients with typical reflux symptoms and negative OGD, 24-h pH manometry may confirm the diagnosis. Oesophageal manometry will aid to exclude oesophageal motility disorders like achalasia where anti-reflux surgery will be disastrous. Oesophageal impedance monitoring allows detection of the reflux and differentiation between gas and liquid reflux irrespective of pH. The combination of oesophageal impedance and pH monitoring is now considered as the most sensitive investigation for GORD [53].

Treatment of Gord in Obese Patients

The Weight Loss

The main objectives of treating reflux disease are to control reflux symptoms, to improve quality of life, and most importantly to decrease the risk of developing associated complications like Barrett oesophagus and oesophageal adenocarcinoma. The initial challenge for an obese patient with reflux symptoms is to reduce weight. Weight loss is proven to associate with significant improvement of reflux symptoms and the quality of life [52]. the Nurses' Health Study has clearly demonstrated that weight loss over a period of time decreased the risk of frequent reflux symptoms by nearly 40 % [22]. In a large prospective population-based cohort study, weight loss was dose-dependently associated with reduction of reflux symptoms and increased chance of treatment success with anti-reflux medication. This study also suggested that patients with GERD using regular anti-reflux medication might benefit from weight reduction [54].

Conservative Treatment Versus Surgical Management

The management of GORD in the context of obesity has always been a matter of debate among physician and surgeons. Initial management includes lifestyle modification, weight reduction, and acid suppressive medication. However, it is well known that surgical management of GORD has better long term outcome compared to medicinal treatment [55, 56]. In patients if symptoms are intractable or they refuse to stay on long term antacid medication, anti-reflux surgery is usually considered as a long term solution. Undoubtedly, successful outcome of any surgical intervention is mainly determined by proper medical assessment, preoperative work up and the selection of the right procedure. Several factors should be considered when it comes to offer a surgical intervention for treatment of GORD such as what are patient's choice and expectations? Does patient need a bariatric procedure or anti-reflux surgery? What is the best approach for surgical repair of any concomitant hiatus hernia? Which bariatric procedure if any to be considered?

Antireflux Surgery and Obesity

Anti-reflux surgery has been an evolving process for over half a century. Changes in technique were aimed at improving patient outcome and satisfaction. Surgical management of GORD has increased in popularity since the introduction of laparoscopic approach in 1991 [57]. In none obese patients, laparoscopic fundoplication is considered as a gold-standard procedure for treatment of refractory GORD. However, available evidence is rather scarce and controversial about long term outcome of anti-reflux surgery in obese patients [58]. Moreover, there is a lack of a well-designed randomised controlled trial which addresses the best surgical approach for treatment of GORD in obese patients [58]. While few reports suggested that obesity is not a predictor of postoperative outcome of laparoscopic anti-reflux surgery [57, 59–61], others have suggested that BMI of >30 is associated with increased complication rates and poor operative outcome [62, 63]. In a recent survey of 92 members of Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), surgeons were less likely to offer fundoplication at a higher BMI and the majority of respondents felt that laparoscopic Roux en-Y gastric bypass (LRYGB) was the best option to treat medically refractory GERD in morbidly obese patients (91 %), followed by laparoscopic sleeve gastrectomy (LSG) (6 %). This indicates that the issue of obesity will continue to be a necessary consideration in the evaluation and appropriate selection due to the increasing incidence of obesity in patients presenting for treatment of GORD [58].

The Role Bariatric Surgery

Patients with GORD and obesity should certainly be approached as patients with obesity and GORD [64]. Marco Fisichella of Brigham and Women's Hospital in Boston stated in an editorial that "this distinction is important as the surgical treatment of GORD independent from the primary achievement of weight loss does not act on the distinct pathophysiologic mechanism of GORD in this patient population as (i) it may result in an increased failure rate of anti-reflux surgery in the long term (ii) may cause a conversion to a bariatric operation more difficult and more morbid in those who will eventually elect to a gastric bypass (iii) may have detrimental effects on the overall well-being of obese patients, as their comorbidities will certainly not improve over time if a gastric bypass is not performed" [65].

Bariatric surgery has been shown to be the most effective and efficient means of achieving significant and sustainable weight loss in severely obese individuals. It is important to understand the underlying anatomical and physiological alternations in each bariatric procedure when it comes to offer a weight-reducing procedure in the context of GORD (see also chap. 23 in this book). The most commonly performed bariatric procedures are LRYGB, LSG, and laparoscopic adjusted gastric band (LAGB). LSG and LAGB are both restrictive procedures while

LRYGB is a mal-absorptive as well as restrictive procedure.

The majority of obese patients with significant GORD exhibit other significant weight related comorbidities. Hence, the consideration of bariatric surgery in this group seems a viable option to help patients to achieve weight loss as well as resolution of comorbidities including GORD. Moreover, many of the current bariatric procedures, which are designed primarily for weight reduction, also have an inherent anti-reflux mechanism.

LRYGB has been shown to provide consistent and effective relief of reflux symptoms, with several authors reporting greater than 95 % success in resolution of reflux symptoms after this bypass surgery. The possible underlying results are the near abolishment of acid secretion by the creation of a small gastric pouch and prevention of alkaline reflux by complete diversion of duodenal contents [64]. Hence, many surgeons advocate that LRYGB is an effective primary procedure for treatment of GORD in morbidly obese patients and as a secondary procedure for those patients who have a refractory GORD with prior failed other anti-reflux surgery [66, 67].

The role of LAGB in the treatment of GORD in obese patients is still unclear. In a recently published systematic review of 20 studies and including 3307 patients, De Jong et al found that a decrease in the prevalence of reflux symptoms from 32.9 % (16–57) preoperatively to 7.7 % (0–26.9) postoperatively, and a decrease in the use of anti-reflux medication from 27.5 % (16–38.5) preoperatively to 9.5 % (3.1–19.2) postoperatively. In addition, the prevalence of erosive oesophagitis decreased postoperatively from 33.3 % (19.4–61.6) to 27 % (2.3–60.8). However, 15 % (6.1–20) of the patients developed new reflux symptoms following gastric banding. Moreover, newly developed oesophagitis was observed in 22.9 % (0–38.4) of patients. In those patients, documented pathological GORD was demonstrated in 55.8 % (34.9–77.4) preoperatively and in 29.4 % (0–41.7) postoperatively [68].

There is increasing trend in using LSG as a standalone procedure for treatment of morbid obesity. Yet, its implication in the context of severe GORD is rather questionable as it may associate with worsening of reflux symptoms as well as the development of *de novo* GORD. Moreover, consensus among bariatric surgeons is to avoid, wherever it is possible, offering LSG to patients with morbid obesity and coexisting hiatus hernia. It has been suggested that LGS results in a high pressure tube which increase the risk of reflux of gastric contents. Moreover, technical steps in LSG include the abolishment of the angle of HIS (an acute angle between the abdominal oesophagus and fundus of the stomach) as well as destruction of the sling fibres component of the GOJ which are important anti-reflux mechanisms. The loss of these factors may also predispose to development of GORD in morbidly obese patients undergoing LSG [69].

Selection of Right Procedure

Surgical management of refractory GORD in obese patients should consider patient's BMI as well as the constellation of obesity related comorbidities. It seems that anti-reflux surgery is still a practical option for treatment of refractory GORD in patients with overweight (BMI 25–29.9) or class I obesity (BMI 30–34.9) without comorbidities as there is no enough evidence to support the use of bariatric surgery over fundoplication as anti-reflux procedure. Patients with class I obesity and comorbidities should be evaluated selectively as there is a lack of well-defined randomised controlled trial evaluating the effectiveness of bariatric surgery in those borderline patients [58]. In contrast, primary anti-reflux surgery offers no weight loss or resolution of associated comorbidities in patients with class II (BMI 35–39.9) or class III obesity (BMI ≥40). Moreover, it may also render any future bariatric procedure in those potential candidates to be difficult. Therefore, those patients should be evaluated in a bariatric service to assess the suitability of bariatric surgery as treatment option for GORD as well as obesity-related comorbidity [58].

Conclusion

Overweight and obesity are important risk factors for GORD. In addition to the increased transient

lower oesophageal relaxation periods and hypotensive lower oesophageal sphincter, visceral obesity leads to increase intra-abdominal pressure. Preoperative evaluation and demonstration of an objective reflux disease are essential prerequisite before planning any surgical management of GORD. Weight loss is associated with improvement of symptoms. Yet, surgery has better long-term outcome over conservative management of GORD. The selection of any surgical approach for management of GORD in obese patients should be based on patient's BMI and associated comorbidities as well as patient's choice.

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Obesity and Gastrointestinal Disorders in Children

12

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Introduction

Obesity in childhood is a major problem facing pediatricians all over the world. In the United States, the prevalence of obesity {defined as body mass index (BMI) at or above 95th percentile for age and gender} increased from 5 % before 1980 to 17 % in 2012 among 2-to19-years-old children [1]. Similar to the United States, the prevalence of obesity is rising throughout the world [2]. It is now a global health issue and affects children in both developed and developing countries [3–5]. As in adults, obesity in children can lead to many health-related complications. Obesity in children is associated with several co-morbidities including diabetes, hepatic steatosis, hypertension, dyslipidemia, and metabolic syndrome. In addition to these diseases, obesity adversely affects the psychosocial well-being and the quality of life of children [6–9].

Recent studies in adults and children have reported an association between obesity and a wide range of gastrointestinal disorders [10]. The common gastrointestinal disorders in children include gastroesophageal reflux (GER), functional gastrointestinal disorders (FGID) such as constipation and irritable bowel syndrome, and organic gastrointestinal disorders such as celiac disease and inflammatory bowel disease (IBD). In this chapter, we discuss association of obesity and these disorders in children. We describe prevalence, possible mechanisms, and treatment implications of this association for the practicing physician.

Obesity and GER

Gastroesophageal reflux is a very prevalent problem in adults and children. There is convincing evidence in adults that obesity is a risk factor for GER [11], erosive esophagitis, Barrett's esophagus and esophageal adenocarcinoma [12, 13] (See also Chap. 11).

In contrast to the abundant literature for adults, the data in pediatrics are limited (Table 12.1). Stordal et al. in a study from pediatric clinics in Norway compared GER symptoms in 872 children with asthma and 264 controls [14]. They found that being overweight was associated with a higher prevalence of GER symptoms in children of 7–16 years of age with and without asthma (OR 1.8, 95 % CI 1.2–2.6). Following this report, Malaty et al. assessed children presenting with diagnosis or symptoms of gastroesophageal reflux disease (GERD) to a pediatric gastroenterology clinic at Texas [15]. The authors

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Table 12.1 Pediatric studies on the relationship between obesity and GER

	References	Sample size	Design	Results
1.	Stordal et al. [14]	Study group = 872 (asthmatics) Controls = 264	Cross-sectional Questionnaire to assess GERD symptom score	Higher prevalence of GER symptoms in overweight than in normal-weight children (OR 1.8, 95 % CI 1.2–2.6)
2.	Malaty et al. [15]	N = 627 No control group	Retrospective study. Chart review	21.4 % of children with GERD are obese
3.	Pashankar et al. [16]	Study group = 236 (obese children) Control group = 101 (non-obese)	Cross-sectional. Questionnaire to assess GERD symptom score	Higher prevalence of GER symptoms in obese children (13.1 %) than controls (2 %)
4.	Teitelbaum et al. [17]	Study group = 757 children Controls = 255 + 1436 children	Diagnosis based on clinical history. Less commonly on endoscopic/histologic finding Cross-sectional	Higher prevalence of obesity in children with GERD compared to control group

reported that children with GERD were more likely to be obese with a BMI higher than the BMI reported by the National Health and Nutrition examination survey data.

We compared the prevalence of GER symptoms between 236 obese children attending obesity clinics and 101 children with normal BMI from the general pediatric clinics from Connecticut, USA [16]. In this study, each subject was interviewed using a questionnaire for reflux symptoms and a reflux score was calculated. Obesity remained as the only significant predictor for a high reflux symptom score after controlling for variables such as age, sex, race and caffeine exposure. Also, the reflux symptom score increased in a linear fashion with their increasing BMI. In a group of severely obese children (BMI z-score >2.7), 20 % of children had a positive reflux symptom score [16]. Similarly, Teitelbaum et al. also found a higher prevalence of obesity amongst children with GER referred to a gastroenterology practice as compared to healthy controls in local and New Jersey control populations [17].

Mechanism of Association with Obesity and GER

A possible mechanism of obesity inducing GER includes extrinsic gastric compression by surrounding adipose tissue leading to an increase in intra-gastric pressures and subsequent relaxation of the lower esophageal sphincter [18]. Another potential theory is that excess fat in diet could result in a delay in gastric emptying with resultant gastroesophageal reflux.

Clinical Significance

It is well known that obesity in childhood often persists up to adulthood. In addition, gastroesophageal reflux in childhood is also likely to continue in adulthood. Therefore obese children with acid reflux are likely to grow into obese adults with acid reflux and may develop reflux related complications including esophagitis, Barrett's esophagus and even malignancy. Hence early diagnosis and prompt therapy in obese children with GER is crucial to prevent long term morbidity and complications of this condition. In adults, decrease in BMI has been shown to improve symptoms of acid reflux. While pediatric literature is limited on this topic, weight reduction should be an integral part of management of obese children with gastroesophageal reflux.

Obesity and Functional Gastrointestinal Disorders (FGIDS)

Obesity and Functional Constipation

Functional constipation is a common gastrointestinal disorder in adults and children [19]. In

Table 12.2 Pediatric studies on the relationship between obesity and constipation

	References	Sample size	Design	Results
1.	Fishman et al. [22]	Study group = 80 (obese children) No control group	Cross-sectional study. Questionnaire to assess constipation	Higher prevalence of constipation in obese children (23 %)
2.	Pashankar et al. [23]	Study group = 719 (constipation) Control group = 930	Retrospective chart review	Higher prevalence of obesity in children with constipation (22.4 %) than control group (11.7 %)
3.	Misra et al. [24]	Study group = 101 (constipation) Control group = 100	Retrospective chart review	Higher prevalence of overweight in children with constipation than control group (43 % vs 30 %)
4.	Teitelbaum et al. [17]	Study group = 757 (children seen at GI practice) Control group = 255 + 1436	Cross-sectional study	Higher prevalence of obesity in children with constipation than control group
5.	Phatak et al. [25]	Study group = 450 healthy children	Cross-sectional study. Questionnaire to assess constipation per ROME III criteria	Higher prevalence of constipation in obese/overweight children (23 %) than normal-weight children (14 %)

adults, large population based studies by Talley et al., and Delgado-Aros et al. could not demonstrated any significant association between obesity and constipation [20, 21]. In addition, a meta-analysis of ten adult studies also could not find any significant association between increasing BMI and constipation [11].

In contrast to the studies on adult subjects, the pediatric literatures suggest a positive relationship between obesity and constipation (Table 12.2). Fishman et al. in 2004 administered questionnaires to 80 consecutive children who presented to an obesity clinic in Boston about their bowel movements [22]. The authors reported that 23 % of obese children met the criteria for constipation and 15 % reported fecal soiling in this cross-sectional study. This prevalence of constipation and encopresis in the obese children was noted to be higher than the historical prevalence reported in the general pediatric population [22].

Following these studies, we performed a large retrospective chart review in 2005 comparing 719 children with chronic functional constipation with 930 age- and gender- matched controls from pediatric clinics in Iowa, USA [23]. We found that the overall prevalence of obesity in both boys and girls was significantly higher in the constipated group (22.4 %) compared with the control group (11.7 %). Another retrospective chart review by Misra et al. reported a similar finding that children with constipation were more likely to be overweight when compared with controls [24]. The authors also noted that among the children with chronic constipation, the group of overweight children was male predominant (70.45 % vs 47.36 %), had increased incidence of psychological/behavioral disorders (45.45 % vs 22.8 %) and was more likely to fail treatment (40.9 % vs 21.05 %).

More recently two large cross sectional studies by Teitelbaum et al. and our's have found a positive association between obesity and constipation [17, 25]. We interviewed 450 children who presented for routine annual physical examinations and immunizations to pediatric clinics in Connecticut. A diagnosis of functional constipation was made using a questionnaire based on the Rome III criteria. We found that healthy obese/overweight children had a significantly higher prevalence of constipation than their healthy normal-weight counterparts (23 % vs. 14 %) [25]. Hence, all pediatric data thus far report a significant association between obesity and constipation.

Obesity and Irritable Bowel Syndrome

In adults, the available data on the association between obesity and irritable bowel syndrome (IBS) are conflicting. A study of 43 morbidly obese adults referred for surgical consultation for gastric bypass surgery were found to have increased prevalence of symptoms of IBS as compared to normal weight controls [26]. Similarly, a large epidemiologic study in USA found a positive relationship between diarrhea and BMI [21]. In contrast, a large cohort study in New Zealand did not find a statistically significant relationship between obesity and IBS in adults [20].

In children, there are two studies that have explored this association. Teitelbaum et al. found a significantly higher prevalence of obesity in children with IBS as compared to local and statewide controls in New Jersey, USA [17]. In our study from Connecticut, we found an increased prevalence of IBS in obese/overweight children (16.1 %) as compared with normal-weight children (6.9 %) [25]. We also found that the statistical significance was maintained when obese and overweight children were compared independently with normal-weight children; thus both pediatric studies have noted a positive relationship between obesity and IBS.

Mechanism Behind Association of Obesity and FGIDS

Overall, the exact mechanism of association between obesity and FGIDs remains unclear. Based on the present data, it remains to be elucidated whether the association between obesity and FGIDs is spurious or whether there is a mechanistic link between the two. Several different theories including the role of an unhealthy diet, alterations in the levels of neuropeptides and psychosocial factors have been implicated as potential mechanisms for the association between obesity and FGIDs.

Obese and overweight children often have a diet low in natural fiber and high in sugar and fat. One potential theory for this association is that a diet low in natural fiber (fruits and vegetables) could result in increased prevalence of constipation in obese children. Some obese children often consume diet containing excess sugars such as fructose corn syrup present in fruit juices and carbonated beverages. It is thought that a diet high in such sugars may result in an osmotic effect with resultant pain, bloating and diarrhea.

Alterations in psychosocial functioning with resultant depression, anxiety, and poor self-esteem are often present in obese children [6–9]. There is also an association between these factors and FGIDs [27]. It is however unclear at present whether these factors are causes or effects of association between obesity and gastrointestinal disorders.

Another area that is of great interest in obesity is the role of brain-gut neuropeptides such as leptin, ghrelin, cholecystokinin, and glucagon-like peptide-1 [28]. Even minor alterations in the levels of these neuropeptides have been implicated in altered eating behaviors, hunger, satiety and changes in gastrointestinal motility. One potential explanation is that these neuropeptides may be the missing link between obesity and FGIDs. It has been shown that normal-weight individuals have higher levels of ghrelin than obese-individuals [28]. In addition, GI neuropeptides such as ghrelin accelerate colonic and small intestinal transit and have strong pro-kinetic actions. Benninga et al. in a cross-sectional study evaluated the role of delayed colonic motility in 19 obese children with constipation [29]. The authors reported a high frequency of constipation in obese children but were unable to find a significant relationship between delayed colonic transit time and constipation in these obese children. Although the authors found that the colonic motility was delayed only in a minority of obese children, this possible mechanism needs to be further explored in larger groups of children [29].

Clinical Significance

The recently reported association of obesity with FGIDs in children has clinical implications.

In our study, 47 % of the obese/overweight children had at least one FGID as compared with 27 % of the normal-weight children. Interestingly, only 36 % of the children with a FGID sought medical attention for their symptoms [25]. These results underscore the need for better awareness of this association amongst health care providers and the need to explore for gastrointestinal symptoms in obese/overweight children.

In a prospective cohort study, Bonilla et al. evaluated the possible effect of obesity on the outcome of 188 treated children with abdominal-pain related FGIDs. The authors found that obese children were more likely to have significantly higher intensity and frequency of pain, school absenteeism and disruption of daily activities at 12–15 months follow-up than non-obese children [30]. This study first highlighted the poor long-term prognosis of obese children with abdominal-pain related FGIDs and the need for prompt diagnosis and aggressive management. Similarly, obese children with constipation were more likely to fail therapy compared to non-obese children with constipation in another study by Misra et al. [24]. In addition, the authors also found that the obese children with constipation were more likely to have psychological and behavioral problems as compared to the control group. Therefore, awareness of this association and prompt therapy may prevent both physical and psychological morbidity in this group of children. In addition to standard therapy, dietary intervention in form of high fiber diet is strongly recommended in these children as it is beneficial to both obesity and constipation.

Obesity and Organic Gastrointestinal Disorders

Obesity and Celiac Disease

Celiac disease is an autoimmune disease triggered by exposure to gluten-containing foods in genetically predisposed individuals. The classic manifestations of celiac disease include symptoms of malabsorption including diarrhea, malnutrition and failure to thrive. However, more recently, obesity is being increasingly recognized at diagnosis of celiac disease. Tucker et al. in their study cohort of 187 adults diagnosed with celiac disease between 1999 and 2009, found that 44 % were overweight, 13 % were obese and only 3 % of subjects were underweight at the time of diagnosis of celiac disease [31]. Recent pediatric studies report prevalence rates of overweight/obesity ranging from 5 to 19 % at the time of diagnosis of celiac disease (Table 12.3) [32–37]. It is interesting that these prevalence rates are higher than the prevalence rates of being underweight in most of these studies. As obesity is increasing in the general population, it is not surprising that certain patients with celiac disease are obese at the time of their diagnosis.

The treatment for celiac disease is implementation of a strict gluten-free diet. Typically, a gluten-free diet leads to symptomatic improvement in patients including improvement in growth parameters. Recent studies have reported a trend towards obesity on a gluten-free diet. In a study of 679 adults with celiac disease from Boston, 15.8 % of patients with normal to low BMI became overweight on a gluten-free diet [35]. In children the effects of a gluten-free diet on the BMI z-scores are mixed. Some studies have noted an increase in BMI z-scores [32, 34] whereas others have reported a decrease in BMI z-scores [33, 36, 37] on a gluten-free diet. In their cohort of 142 children with celiac disease, Reilly et al. noted that compliance to a gluten free diet was an important factor to prevent obesity on a gluten-free diet [33]. Thus recent studies show that children with celiac disease can be obese at presentation and also have a risk of developing obesity on a gluten-free diet.

Obesity and Inflammatory Bowel Disease

Inflammatory bowel disease includes chronic conditions such as Crohn's disease, and Ulcerative colitis. Traditionally, weight loss and poor growth were common presenting symptoms at the time of diagnosis of IBD. Contrary to these classic presenting symptoms, recent studies in adults and children have suggested a rise in

Table 12.3 Prevalence of obesity at diagnosis of celiac disease and inflammatory bowel disease (IBD)

References	Sample size	Disorder	Overweight/obese at presentation
Norsa et al. [32]	114	Celiac	14.1 %
Reilly et al. [33]	142	Celiac	19 %
Valletta et al. [34]	149	Celiac	14 %
Brambilla et al. [36]	150	Celiac	12 %
Venkatasubramani et al. [37]	143	Celiac	5 %
Kugathasan et al. [39]	783	IBD	10 % Crohn's disease, up to 30 % Ulcerative colitis
Long et al. [40]	1598	IBD	20 % children with Crohn's disease and 30 % children with ulcerative colitis were overweight or obese

prevalence of obesity at the time of diagnosis of IBD. Moran et al. conducted a time-trend analysis of 40 randomized controlled adult trials from 1991 to 2008 to include a total of 10,282 patients with Crohn's disease [38]. They found a significant increase in weight and BMI at the time of diagnosis over this time period.

In a multicenter pediatric study, Kugathasan et al. evaluated 783 children with newly diagnosed IBD from USA [39]. Although majority of these children were normal weight, 10 % of children with Crohn's disease and up to 30 % of children with ulcerative colitis had a BMI diagnosis consistent with overweight. Long et al., in a cross-sectional study design of 1598 children, found that the prevalence of overweight/obesity in their cohort of children was 20.0 % for Crohn's disease and 30.1 % for ulcerative colitis and indeterminate colitis [40]. African American race and Medicaid insurance were positively associated with overweight/obese status in their study cohort. Hence presence of obesity is not an uncommon finding at the time of diagnosis of IBD in children.

Mechanisms of Association of Obesity and Organic Gastrointestinal Disorders

It may be that this increase in prevalence of obesity at the time of diagnosis of organic diseases such as celiac disease and IBD is merely mirroring the increasing prevalence of obesity in the general population. Increased awareness and prompt work-up have helped in diagnosing these children early before growth failure sets in. It appears that children with celiac disease are likely to be overweight or obese if their diagnostic work up was initiated based on positive screening tests rather than clinical features [41].

It is unclear at present whether there is a cause-effect relationship between obesity and IBD. The current adult data are mixed and no pediatric studies have been conducted to date to explore the nature of this association. Chan et al. reported a lack of association between obesity and development of incident IBD [42], however, Khalili et al. reported that adiposity was associated with an increased risk of Crohn's disease in a large cohort of US women [43]. Obesity has been linked to elevated levels of pro-inflammatory cytokines such as TNF-alpha and IL-6 [44]. Obese individuals have also been shown to have high levels of inflammation in the gastrointestinal tract as measured by fecal calprotectin [45]. It is possible that the elevations in the pro-inflammatory cytokines may be a link between obesity and IBD. Hence, it appears that the association between obesity and IBD is evolving and larger studies are needed to explore this association further.

Clinical Significance

Celiac disease and inflammatory bowel disease are organic gastrointestinal disorders in children and historically were associated with failure to thrive at presentation. Recent reports indicate

rising prevalence of obesity in children with these disorders at presentation. Interestingly, more children with celiac disease diagnosed at present are likely to be overweight or obese than being underweight [32–37]. So practitioners should consider these diagnoses in appropriate settings despite presence of obesity. In children with celiac disease, gluten-free diet can lead to rapid increase in weight and put children at increased health risks associated with obesity. Close nutritional monitoring of children on gluten-free diet is recommended to avoid this problem.

Obesity can adversely affect the course of IBD in adults and children. In a large retrospective analysis of 2065 adult patients with Crohn's disease from a gastroenterology clinic in Paris, Blain et al. reported that obese patients had increased morbidity, worse disease activity and more frequent perianal complications [46]. Two studies in adults report dose escalation of biologic therapy due to severity of disease in obese adults with IBD [47, 48]. Krane et al. found that operative time and blood loss were significantly longer in the overweight and obese adults undergoing surgery for IBD as compared to normal-weight adults [49]. In children, Long et al. found that high BMI was associated with previous IBD related surgery suggesting that these children may have a more severe disease course [40]. This finding is in contrast to the pediatric study by Zwintscher et al. who reviewed the 2009 inpatient database from Washington State for all IBD admissions [50]. No significant association was noted between obesity and IBD disease severity and the rate of surgical intervention after review of 12,465 inpatient pediatric admissions. As obesity may adversely affect the course of IBD, nutritional counseling and weight management should be an integral part of the management strategy in these patients.

Conclusion

In summary, recent pediatric studies show that there is an association between obesity and gastrointestinal disorders such as gastroesophageal reflux, constipation and irritable bowel syndrome in children. Obesity is also being identified at diagnosis of conditions such as celiac disease and inflammatory bowel disease which used to be associated with growth failure in the past. Obesity can adversely affect outcome of these gastrointestinal disorders. It is important for practicing physicians to be aware of this association and its significance so that they can provide appropriate care to children such as weight reduction measures which can improve the symptoms of gastrointestinal disorders.

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Non-alcoholic Fatty Liver Disease in Obesity

13

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of excessive lipid accumulation in the liver (at least in 5 % of the hepatocytes) of individuals without significant alcohol consumption and/or other known causes of steatosis, such as use of steatogenic medications and prior gastric or jejunoileal bypass. NAFLD encompasses a spectrum of clinicopathological conditions that ranges from simple hepatic steatosis (nonalcoholic fatty liver [NAFL]) to hepatic steatosis associated with necroinflammatory lesions (nonalcoholic steatohepatitis [NASH]), which may progress to hepatic fibrosis and cirrhosis and even to hepatocellular carcinoma (HCC) [1].

NAFL and NASH have different histological features, natural history and clinical evolution. NAFL is characterized by the presence of hepatic steatosis without any evidence of hepatocellular injury. Otherwise, NASH is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury associated or not with fibrosis [1]. Patients with NAFL have very slow if any histological progression, while NASH can exhibit histological progression to cirrhotic-stage disease [2]. In a long-term follow-up study, 10 % of the patients with NASH developed end-stage liver disease in a period of 13 years. Progression of liver fibrosis was associated with more pronounced insulin resistance (IR) and significant weight gain. Survival of patients with NASH was reduced; they often died from cardiovascular or liver-related causes [3].

The differences in the natural history of NAFLD are believed to be related to host characteristics, and associated risk factors. NAFLD is usually associated with the metabolic syndrome (MS) [4], which is characterized by numerous interrelated risk factors for cardiovascular disease such as obesity, IR, type-2 diabetes and arterial hypertension. Obesity and diabetes are predictors of advanced liver fibrosis and cirrhosis in NAFLD patients [5].

The global incidence of NAFLD is unknown since it depends on the population studied and on the methods used to diagnose this condition (e.g., liver biopsy, magnetic resonance spectroscopy and/or ultrasound). In spite of these limitations, the prevalence of NAFLD and NASH in the general population in the Western Countries is estimated to reach 20–30 % and 1–3 %, respectively [3, 6–8]. Furthermore, some data indicate that NAFLD has become the most common cause of chronic liver disease in young adults and children [9]. Evidence suggests that obesity and IR are the major factors that lead to the development of NAFLD [10]. Because the prevalence of MS and

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obesity has increased in most countries, the burden of NAFLD is also expected to rise [11]. In this context, unhealthy dietary patterns and physical inactivity, which represent the current lifestyle, probably have contributed significantly to this pandemic.

Obesity represented either by excessive body mass index (BMI) or by visceral obesity is a well-documented risk factor for NAFLD [1]. Most patients with NAFLD are obese or morbidly obese and have accompanying IR. However, even subjects with normal BMI can develop NAFLD particularly in the presence of high waist circumference or IR [12, 13]. In patients with severe obesity undergoing bariatric surgery, the prevalence of NAFLD can exceed 90 % and up to 5 % of the patients may have unsuspected cirrhosis [14–16].

In this chapter we discuss the different aspects of NAFLD.

Etiology and Pathophysiology

Although the pathogenesis of NAFLD is not fully elucidated, according to the most accepted theory, IR is the key factor that initiates hepatic fat accumulation and, potentially, NASH [17].

It is not yet understood which factors could be the driving forces toward the more progressive and inflammatory disease phenotype. Earlier Day and James proposed the "two hit" model to explain NAFLD pathogenesis [18]. According to this model the first hit was represented by fat accumulation in the liver, which could be followed by the development of oxidative stress, necroinflammation and fibrosis (second hit). However, more recently, a new model has been introduced. According to this model, many hits, such as gut- and adipose tissue-derived factors may act concomitantly to cause hepatic inflammation [19].

Several metabolic pathways are believed to be involved in the development of NAFLD: (i) excessive importation of free fatty acids (FFA) from adipose tissue to the liver due to enhanced lipolysis in both visceral and subcutaneous adipose tissue; (ii) increased FFA supply to the liver as a result of a high-fat diet; (iii) impaired of the hepatic β-oxidation of FFA; (iv) increased *de novo* lipogenesis (DNL) in the liver; and (v) decreased hepatic export of FFA due to reduced synthesis or secretion of very low density lipoprotein (VLDL) [19–21] (Fig. 13.1).

In the interesting study by Donelly et al. the biological sources of hepatic and plasma lipoprotein triglyceride (TAG) in obese patients with NAFLD were quantified (by gas chromatography/mass spectrometry). About 59.0 ± 9.9 % of the hepatic TAG arose from plasma nonesterified fatty acid (NEFA); 26.1 ± 6.7 %, from DNL; and 14.9 ± 7 %, from the diet [22].

To compensate the excessive hepatic fat storage, the mitochondrial β-oxidation of fatty acids in obese individuals is stimulated and maintained until mitochondrial respiration becomes severely impaired [23]. Accelerated β-oxidation causes excessive electron flux in the electron transport chain and rises the production of reactive oxygen species (ROS), leading to mitochondrial dysfunction [24] due to damage to the mitochondrial membrane and DNA, and due to impairment of the mitochondrial metabolic functions [25]. Additionally, FFAs induce several cytochrome p-450 microsomal lipoxygenases capable of producing hepatotoxic ROS [26]. The consequent increased generation of ROS and reactive aldehydic derivatives leads to oxidative stress and cell death, via ATP, NAD and glutathione depletion, and DNA, lipid and protein damage. Oxidative stress also triggers the secretion of inflammatory cytokines, migration of polymorphonuclear leukocytes, formation of hyaline corpuscles, collagen synthesis in the hepatic parenchyma and fibrosis. Those alterations culminate in the liver damage that characterizes NASH, which may progress to cirrhosis and also HCC [23, 27].

The increased production of proinflammatory cytokines, especially tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1 and IL-6, contributes to the onset of peripheral and hepatic IR, which increases fatty infiltration into the hepatic parenchyma resulting in a vicious cycle that promotes more tissue damage [28].

In addition to the increased IR, inflammatory mediators derived from various tissues as gut- and adipose tissue-derived factors may also play a role in the evolution of NASH [19, 28]. Below,

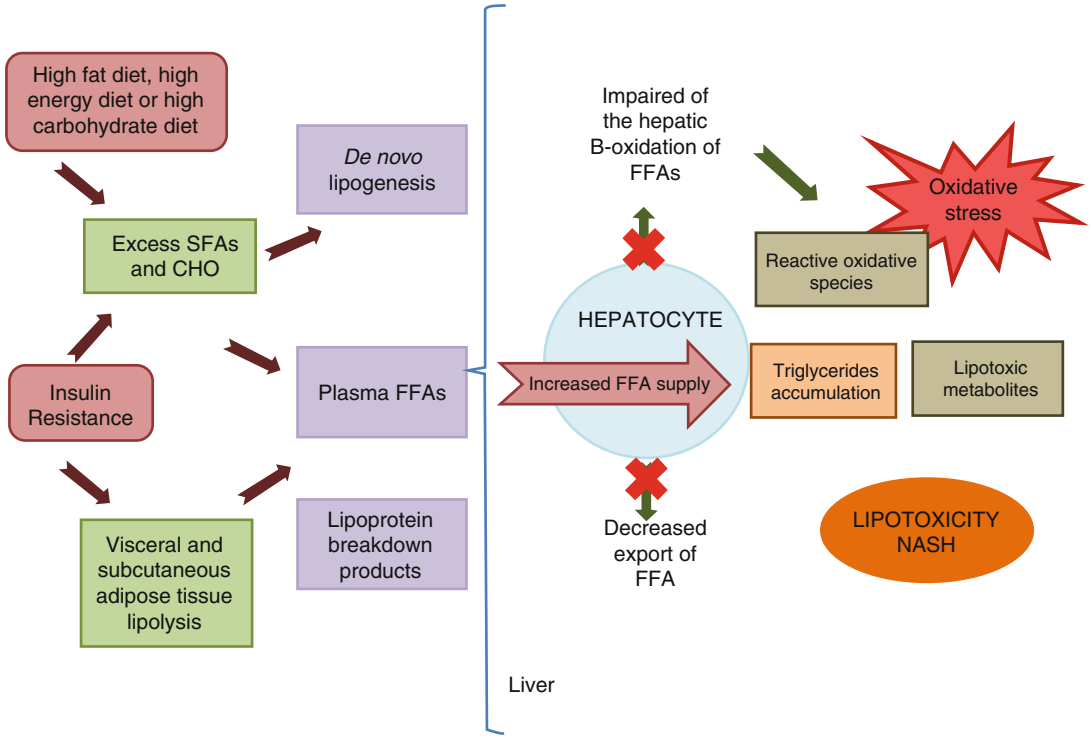

Fig. 13.1 Metabolic pathways involved in the development of NAFLD (Adapted from Peverill et al. [21])

we briefly discuss the role of IR, adipokines and gut microbiota in NAFLD pathogenesis.

Insulin Resistance

Obesity, especially high visceral fat content is associated with both peripheral and hepatic IR [29]. IR in the adipose tissue and skeletal muscle increases lipid oxidation in the adipose tissue and, therefore, enhances the influx of NEFAs to the liver [30]. Once diacylglycerol is increased in the hepatocytes, the tyrosine phosphorylation of insulin receptor substrate 2 (IRS-2) diminishes. The impaired activity of both IRS-2 and phosphatidylinositol 3-kinase (PI3K) leads to increased glucose synthesis in the liver [31]. Increased secretion of insulin also develops in response to IR in the adipose tissue; and, hyperinsulinemia is another factor related to the hepatic downregulation of IRS-2. Hyperinsulinemia increases the levels of sterol regulator element-binding protein-1c (SREBP-1c), which up-regulates lipogenic gene expression, increases fatty acid synthesis and accelerates hepatic fat accumulation [32]. Like SREBP-1c, the carbohydrate responsive element-binding protein (ChREBP) stimulates lipogenesis by inducing lipogenic gene expression in response to the consumption of a high-carbohydrate diet [24, 33].

IR occurs when the insulin receptors are not phosphorylated properly or there is an impairment or inhibition of the signal transduction. Some proinflammatory cytokines as TNF causes inhibition of Janus kinase (JAK) pathway, which results in the inability of insulin to stimulate pathways for the synthesis and translocation of glucose transporters (GLUT) [34].

Obesity leads to endoplasmic reticulum (ER) stress causing suppression of insulin signaling through the serine phosphorylation of IRS-1 and activation of the c-Jun N-terminal kinase (JNK) pathway, which contributes to the inflammatory response [35]. Patients with NASH showed

higher levels phosphorylated JNK protein compared to subjects with NAFL. Indeed, NASH individuals did not generate spliced manipulation of X-box-binding protein-1 (sXBP-1), which is an important regulator in ER stress related to insulin action [35]. Obese subjects who lost weight show improvement in ER stress via suppression of phosphorylated JNK and suppression of the α-subunit of translation initiation factor 2 (eIF2α, a well-known ER stress marker) in the adipose tissue and liver [36].

Adipokines, Proinflammatory Cytokines and Peroxisome Proliferator-Activated Receptors

The adipose tissue, in addition to be a major organ of TAG deposition, is also a highly active endocrine organ that secretes several hormones and adipocytokines such as adiponectin, leptin, retinol-binding protein, IL-6, TNF-α and plasminogen activator inhibitor (PAI)-1 [37]. Imbalance in the secretion of the adipokines may affect the adipose tissue and important target organs as the liver [38]. Adiponectin is an anti-inflammatory adipocytokine [24]. Adiponectin increases glucose utilization and fatty-acid oxidation by stimulating phosphorylation of AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) in the liver and muscles [24, 39]. Obesity is related to hypoadiponectinemia and in the individuals who lose weight, the levels of adiponectin increase [40, 41]. Some experimental data suggest that adiponectin may be protective against the progression of NASH [38].

Leptin is a peptide hormone synthesized chiefly by the adipocytes, and is regulated by food intake, energy status, hormones and the overall inflammatory state [42]. Leptin acts on the hypothalamus to reduce appetite; stimulates pathways that augments fatty acid oxidation; decreases lipogenesis; and diminishes the ectopic deposition of fat in the liver and muscle. Leptin contributes to glucose homeostasis regulating insulin and glucagon secretion and in abundant energy states such as obesity hyperleptinemia has been observed. This finding was associated with downregulation or inactivation of the leptin receptor in the hypothalamus and in the liver of obese rats [43, 44].

The levels of leptin are enhanced by proinflammatory cytokines (e.g. IL-1, TNF-α) and by infectious stimuli (lipopolysaccharides [LPS]); and this adiponectin contributes to perpetuate the loop of chronic inflammation in obesity [45]. IR seems to be related to high leptin concentrations in plasma, independent of its levels in the adipose tissue [46]. Therefore, leptin may be involved in NASH development and progression by contributing to IR, development of steatosis, and also by its action on the hepatic stellate cells due to its proinflammatory role [47]. Although there is no consensus, some studies demonstrated increased levels of leptin in NASH patients; furthermore, they were correlated with the grade of hepatic steatosis [47–50]. Some authors believe that leptin synthesis and resistance may have a crucial role in the pathogenesis of NASH; however, the mechanisms are unclear [51].

Leptin and adiponectin can increase the hepatic oxidation of fatty acid by activating the nuclear receptor super-family of transcription factors, namely peroxisome proliferator-activated receptor (PPAR) [7]. PPARs remain the key element in the process of lipogenesis and lipolysis in adipose and non-adipose tissues.

Three types of PPARs have been identified: PPAR-α (expressed in the liver, kidney, heart, muscle and adipose tissue), PPAR-γ (expressed namely in adipose tissue), and PPARs- β/δ (expressed markedly in the brain, adipose tissue and skin) [52]. PPAR-α and PPAR-γ acts in coordination in order to maintain the balance between oxidation and synthesis of fatty acids. PPAR-α regulates the expression of genes involved in peroxisomal and mitochondrial β-oxidation in the liver and skeletal muscle. PPAR-γ is an important regulator of adipogenesis, determining the deposition of excess calories in adipocytes and is also involved in the anti-inflammatory effects in the adipose tissue [53, 54]. Adiponectin increases PPAR-γ in the adipose tissue, enhances its anti-inflammatory effects and insulin sensitivity in the adipose tissue [7].

Recent studies have suggested that in the presence of NAFLD obesity-related, there is a downregulation of PPAR-α [55] and an upregulation of PPAR-γ promoting overall lipogenesis over oxidation of fatty acids. It is likely that PPAR-α downregulation may facilitate the activity of hepatic pro-inflammatory cytokines, favoring the progression from steatosis to NASH [56]. Certain antidiabetic drugs such as rosiglitazone and pioglitazone act as a PPAR-γ agonist in the adipose tissue, diminishing the release of NEFAs and improving hepatic insulin sensitivity [57].

In obese subjects, the adipose tissue stimulates secretion by the macrophages of several inflammatory cytokines [58]. Thus, TNF-α promotes high expression in the liver and adipose tissue of these patients. This cytokine shows metabolic, inflammatory, proliferative and necrotic effects, making it an important agent in NAFLD pathogenesis. It is believed that TNF-α participates in every stage of NAFLD: development of IR, liver steatosis, hepatocelular necrosis, apoptosis and fibrosis [59]. This cytokine impairs insulin-dependent peripheral uptake of glucose by enhancing serine phosphorylation of IRS-1, which causes inhibition of the translocation of the glucose transporter type 4 (GLUT4) to the plasma membrane [60]. It also stimulates hormone sensitive lipase determining increase in the hepatic influx of FFA. Lipid accumulation in the liver activates several pathways involving transcription factors as nuclear factor kappa-B Kinase (IKK-B) and nuclear factor-kappaB (NF-κB) that upregulates gene expression of proinflammatory cytokines including TNF-α and IL-6 [61].

TNF-α is also produced by the Kupffer cells in response to bacterial endotoxins, which stimulates the toll-like receptors (TLR) in the liver. In the hepatocytes, TNF-α induces suppressors of cytokine signaling (SOCS) that diminishes insulin signaling and also induces SREBP-1c, which is involved in the genesis of hepatic steatosis. TNF-α intensifies ROS synthesis that further increases TNF-α production, enhances mitochondria permeability and the release of mitochondria cytochrome c, and causes more ROS formation determining hepatocyte death [28].

TNF-α seems to up-regulates IL-6 synthesis from adipocytes and macrophages infiltrated in the adipose tissue. As mentioned above, FFAs accumulated in the hepatocytes lead to the expression of various proinflammatory cytokines, including IL-6 [28]. IL-6 levels were significantly higher in NAFLD patients, particularly in those with advanced histopathological findings, when compared to the subjects with other chronic liver disease [62]. The development of NAFLD may be associated with polymorphisms of the IL-6 gene [63].

Although numerous human studies have shown a correlation between IL-6 levels and NAFLD, data concerning its relationship with the stages of the disease are contradictory [64–70]. IL-6 should not be used as a single noninvasive marker for predicting the presence of NASH [28].

IL-1α and IL-1β were also demonstrated to have a role in the progression of steatosis to steatohepatitis and liver fibrosis in NAFLD patients [71]. Kupffer cells and macrophages generate IL-1β via NF-κB [72]. LPS and saturated fatty acids also induce production of pro-IL-1β, via TLR in the Kupffer cells, which is cleaved by caspase-1 to a mature biologically active form [73, 74]. IL-1 serum concentrations were also higher in NAFLD patients than in subjects with other chronic liver disease. The highest levels were found in the NAFLD patients with advanced stage of fibrosis [62].

Gut-Microbial Alternation and TLRs Stimulation

The liver is constantly exposed to gut microbiota-derived products that activate hepatic TLR4, which has been related to liver inflammation, fibrosis and HCC [75]. Obese subjects present alterations in their microbiota composition with predominance of Firmicutes over Bacteroidetes, which has been associated with fasting hyperglycemia, hyperinsulinemia, hepatic steatosis, increased expression of genes involved in DNL and in higher efficiency in harvesting energy from the diet [76–78]. The same modification of microbiota composition was seen in patients with NASH independently of BMI and fat intake [78].

Different mechanisms have been proposed to explain the relationship between microbiota and increased hepatic fat storage. The liver contains macrophages, dendritic cells and natural killer T cells, which consist in the first-line defense against microorganisms and endotoxin. TLRs present on liver cells recognize pathogen-associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) present on endogenous ligands, and initiates an adaptive immune response signaling cascade resulting in activation of proinflammatory genes (i.e. TNF-α IL-6, etc.) [79]. In addition to the innate immune cells, all types of liver cells (hepatocytes, Kupffer cells, sinusoid endothelial cells, hepatic stellate cells and biliary epithelial cells) present a wide expression of TLRs [80]. The most well-known PAMP is LPS, which consists in a component of the gram-negative bacteria cell membrane and the active component of endotoxin. The liver is exposed to LPS due to bacterial translocation from the gut microbiota that reaches the portal vein. LPS binds to LPS-binding protein, which in turn, binds to CD14 and activates TLR4 in the Kupffer cells activating essential inflammatory cascade involving stress-activated and mitogen-activated protein kinases, JNK, p38, interferon regulatory factor 3, and the NF-κB pathway [81]. The production of proinflammatory cytokines results in prolonged inflammation and liver damage [82]. Indeed, the activation of proinflammatory pathways leads to impairment of the insulin signaling by diminishing the phosphorylation of the insulin receptor [83] as discussed above.

Different dietary patterns can determine alterations in the gut microbiota enhancing liver steatosis and inflammation. In an experimental study, LPS concentrations rise after high-fat diet during 4 weeks, and this alteration was followed by increase in fasting glycaemia, insulinemia, markers of inflammation, liver TAG content and liver IR [84] Another study demonstrated that mice fed with fructose presented elevated endotoxin concentrations in the portal blood, higher intrahepatic lipid accumulation, lipid peroxidation and TNF-α expression [85].

Fukunishi et al. verified that the administration of LPS in rats increased TNF-α and SREBP-1c expressions in the liver, indicating that LPS may play a role in the evolution of steatosis. Furthermore these animals exhibited higher expression of enzymes involved in the lipogenetic pathway, suggesting that LPS is involved in mitochondrial fatty acid β-oxidation. The animals also presented low levels of adiponectin contributing to liver damage [86].

Clinical and Laboratory Investigations in NAFLD

The diagnosis of NAFLD is based on the presence hepatic steatosis on imaging methods or histology; absence of significant alcohol consumption (ongoing or recent alcohol consumption >21 drinks on average per week in men and >14 drinks on average per week in women); no other etiologies of hepatic steatosis (namely, significant alcohol consumption, hepatitis C, some medications, parenteral nutrition, Wilson's disease and severe malnutrition); and no coexisting cause of chronic liver disease (such as hemochromatosis, autoimmune liver disease, chronic viral hepatitis and α-1 antitrypsin deficiency) [1, 87].

Patients with NAFLD may present mildly elevated serum ferritin and it does not represent elevated iron stores [87, 88]. In the presence of high serum ferritin and transferrin saturation, it is advisable testing for genetic hemochromatosis. Although the significance of mutations in the HFE gene in NAFLD patients is unknown, they are relatively common in this condition [88]. Thus, liver biopsy to evaluate iron deposits should be considered in patients with suspected NAFLD and concomitant increased serum ferritin levels and a homozygote or compound heterozygote C282Y mutation in the HFE gene [1, 89]. Elevated serum autoantibodies are frequent in NAFLD patients and may be considered an epiphenomenon; however, in the presence of high serum titers of autoantibodies associated with other features suggestive of autoimmune liver disease (very high aminotransferases, high serum globulins) it is recommended investigating for autoimmune liver disease [1].

The most common laboratory presentation of NAFLD patients is mild or moderate elevation in serum aminotransferase concentrations. The aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ratio (AST/ALT) is generally lower than 1, but the ratio increases as the liver fibrosis progresses [13, 15].

The gold standard to diagnose NAFLD is liver biopsy – a costly, invasive and morbimortality associated diagnostic approach [90]. Thus, it should be performed only in the patients who will benefit from diagnostic, therapeutic or prognostic perspectives. According to the American Association for the Study of Liver Diseases (AASLD) practice guidelines, liver biopsy should be considered: (i) in patients with NAFLD who are at increased risk of having NASH and advanced fibrosis, i.e. patients with the MS and those in which the NAFLD Fibrosis Score indicates advanced fibrosis (see below); (ii) in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and coexisting chronic liver diseases cannot be excluded without a liver biopsy [1].

Ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) are non-invasive methods that can detect NAFLD; however, they do not identify inflammation and initial fibrosis [91]. US is widely used in the diagnosis and follow-up of NAFLD patients because it is a simple, non-invasive, easily applicable and safely repeatable method. It detects hepatic steatosis with a sensitivity of 60–94 % and a specificity of 66–97 % [92]. The major disadvantages of US are its low accuracy in mild steatosis, and the fact that it is an operator dependent method, which is of major importance as the evaluation of fatty liver depends on subjective evaluation of hepatic echogenicity [92–95].

Transient elastography (Fibroscan, Echosens) is an ultrasound based technique for measuring liver stiffness that seems to have a strong correlation with increasing degrees of fibrosis [96–98]. Its main limitation in NAFLD patients is the high failure rate in individuals with a increased BMI [1].

There are several MRI techniques to evaluate hepatic fibrosis such as diffusion weighted imaging (DWI), perfusion MRI, magnetic resonance spectroscopy (MRS), and magnetic resonance elastography (MRE) [98–102]. In the presence of liver fibrosis there is an increased stiffness of the hepatic parenchyma which may be measured by MRI techniques [103–108]. The MRE presents some advantages over transient elastography as it provides quantitative maps of tissue stiffness over large regions of the liver instead of providing localized spot measurements of limited depth in the liver in areas where there is an acoustic window; it is less operator dependent; the sequence usually require less than a minute of acquisition time; and it has a low rate of technical failure [98]. Hepatic iron overload can decrease hepatic signal intensity in gradient echo based MRE sequences to unacceptably low levels. However, at the present, MRE is the only non-invasive technique that has been able to stage liver fibrosis or diagnose mild fibrosis with reasonable accuracy [109].

MS is a strong predictor of NASH in patients with NAFLD [87, 110–112]. Because of the relationship between the MS and the risk of NASH, the AASLD recommends that patients with MS may be target for a liver biopsy [1].

NAFLD Fibrosis Score is a non-invasive method to identify advanced fibrosis in patients with NAFLD and it is based on six readily available variables (age, BMI, hyperglycemia, platelet count, albumin, AST/ALT ratio) and is calculated using the published formula [1, 113].

Circulating levels of cytokeratin-18 (CK18) fragments have been investigated as a biomarker of steatohepatitis in patients with NAFLD. Plasma CK18 fragments have been demonstrated to be higher in patients with NASH compared to those with NAFL or healthy controls. CK18 may independently predicted NASH. According to the findings of a recent meta-analysis, plasma CK18 concentrations have a sensitivity of 78 %, specificity of 87 %, and an area under the receiver operating curve (AUROC) of 0.82 (95 % CI: 0.78–0.88) for the diagnosis of steatohepatitis in patients with NAFLD [2]. However, currently, this assay is not commercially available and there is no established cut-off value for identifying NASH [1].

Treatment

Life Style Modification – Diet and Physical Exercise

Intervention focusing on life style modification (calorie-restricted diet and/or physical exercise) leads to significant reduction in the aminotransferases levels and in hepatic steatosis, when measured by either US or MRS [114–132]. Life style modification associated with cognitive behavioral therapy improves the results [133].

Some authors have also demonstrated hepatic histological improvement with physical exercise and weight loss [132, 134, 135]. Physical exercise diminishes IR in skeletal muscle via GLUT4 expression, and improves glucose utilization which can result in decreased liver fat mass, since hyperinsulinemia could stimulates hepatic steatosis via the SREBP-1c pathway [136].

Moderate-to-intense aerobic exercise should be performed during 30 min at least three to five times per week, taking the necessary precautions with the individuals at high cardiovascular risk [137]. Until present, there is no optimal exercise prescription established. Aerobic exercise seems to be superior to resistance training [138, 139]. For the patients who do not have a satisfactory adherence to a hypocaloric diet, more intense physical exercise should be recommended, while patients that have adhered to a dietary prescription, moderate exercise is sufficient to improve NAFLD [119, 140, 141]. A cross-sectional study, which enrolled 72,359 healthy adults, demonstrated that regular exercise (at least three times/week, minimum duration of 30 min each time) was associated with decreased risk of NAFLD (for all BMI categories >19.6 kg/m^2), and reduction of the liver enzymes levels in individuals with recognized NAFLD independently of BMI [142]. Physical activity is associated with improvement in cardiovascular condition, IR and lipid metabolism, and reduces hepatic fat, regardless of weight loss [138, 143–146]. However, the benefit of exercise with minimal or no weight loss on alanine aminotransferase levels is uncertain [147].

Currently, there is consensus in advising physical exercises at least of moderate intensity for all NAFLD patients to improve IR and reduce fat liver accumulation, regardless its effects on the liver enzymes. A randomized clinical trial comparing obese subjects with NASH in an intensive lifestyle changes (diet, behaviour modification and a 200-min/week moderate physical activity for 48 weeks) versus obese subjects with NASH that received dietary counseling alone demonstrated that the intervention group had 9.3 % weight loss while the control group lost only 0.2 % [148]. The participants who lost ≥7 % of the initial weight had significant improvement in steatosis, lobular inflammation, ballooning and NAFLD Activity Score (NAS). Harrison et al. observed that subjects who lost >5 % of body weight improved steatosis, whereas individuals who lost ≥9 % body weight had significant improvement in steatosis, lobular inflammation, ballooning, and NAS [149]. Loss of weight also ameliorates IR [57].

Weight loss should be gradual since the lost of >1.6 kg/week may be associated with portal inflammation and progressive fibrosis [114]. The AASLD guidelines recommend loss of at least 3–5 % of body weight to improve steatosis; and a higher weight loss (up to 10 % of body weight) could be needed to improve necroinflammation [1]. Loss of body weight by means of life style modifications has optimal cost-benefit ratio, no contraindications or side effects and all the additional medical benefits [57].

For the treatment of NAFLD, it has been recommended reducing 600–800 calories in the usual daily oral intake or setting caloric restriction at 25–30 kcal/kg/day of the ideal body weight [115, 117, 150]. Carbohydrate consumption should not exceed 40–45 % of the total energy intake and all NAFLD patients should be advised to consume fruits and vegetables instead of sugar-rich food [151]. Low-carbohydrate diets are associated with decreasing in hepatic TAG and levels of aminotransferases [151–154]. Protein ingestion should be 1–1.5 g/kg per daily [151]. Daily consumption of fat should not exceed 30 % of the total energy intake wherein <10 % of caloric intake should come from saturated fat [118, 120, 155]. High-fat and high-cholesterol diets, as well as diets poor in polyunsaturated fat, fiber and antioxidants vitamins such as vitamins C and E are related to NASH [118, 150, 156].

Weight Loss Medications

Sibutramine is a serotonin-norepinephrine reuptake inhibitor that increases postprandial satiety and energy expenditure, and has been found to be temporarily useful for weight loss. There is only a small study demonstrating reduction in IR, some improvements in the hepatic enzyme concentrations and fat accumulation in the liver measured by US, following the administration of this drug [157]. On the other hand, the use of this agent showed a significant risk of cardiovascular adverse events which led the Committee of Medicinal Products for Human Use of the European Medicines Agency and the United States Food and Drug Administration (FDA) to recommend against its continued use [158, 159].

Orlistat is commonly indicated to achieve weight loss. This drug consists in an enteric lipase inhibitor leading to fat malabsorption. Its effects associated with lifestyle modification were investigated in two randomized controlled trials. In the study by Ziegler-Sagi et al., orlistat caused an average weight loss of 10.3 kg in obese patients with NAFLD, decreased ALT concentrations and steatosis measured using US [160]. Contrary to these findings, Harrison et al. did not found any improvement in body weight or liver histology using orlistat in NAFLD patients [149]. This agent has not shown any significant benefit on the liver independently of weight loss [57].

Rimonabant is a cannabinoid 1 receptor antagonist and although has effect on the reduction of calorie intake, it is not recommended for the treatment of NAFLD because it has potential psychiatric adverse effects related to anxiety and depression [161]. All prospective studies on this medication were halted, and the product was recalled [57].

Bariatric Surgery

Bariatric surgery is a therapeutic option for weight loss in cases of morbidly obesity if lifestyle modification and pharmacological therapy have not yielded long-term success [162]. Bariatric surgery may be associated with long-term improvements in MS and cardiovascular risk factors, such as diabetes mellitus, hypertriglyceridemia and hypertension, compared with conventional methods for weight loss [163]. Bariatric surgery is also associated with regression of inflammation and fatty infiltration of the liver [164] However, randomized clinical trials assessing the effects of bariatric surgery on NASH are lacking, and its long-term effects have not been studied. Bariatric surgery may also have complications with an average mortality of 0.3 % and morbidity of 10 % [57]. According to the AASLD, bariatric surgery is not contraindicated in otherwise eligible obese individuals with NAFLD or NASH without established cirrhosis [1]. A recent review in the Cochrane Database does not recommend to perform bariatric surgery specifically to treat NASH [165].

Insulin-Sensitizing Medications

Oral hypoglycemic and insulin-sensitizing medications have been used to treat NAFLD [166–170]. Metformin and the thiazolidinediones (pioglitazone and rosiglitazone) seem to improve NAFLD by ameliorating liver function: normalization of the aminotransferases in 50 % of the cases, decrease in steatosis measured by US or MRS, partial improvement of liver necrosis and inflammation, and less evident partial improvement in hepatic fibrosis after 1 year of follow-up [171–173]. Metformin is a biguanide that reduces hepatic glucose synthesis, increases peripheral uptake of glucose by the muscles, and decreases IR induced by TNF-α. Metformin improves IR and hyperinsulinemia [174]. Initially, metformin could lead to improvement in the aminotransferases levels [175]; however, after 1 year of treatment, no improvements were demonstrated [176].

Studies on the use of metformin to treat NAFLD whose results were assessed by hepatic biopsy are lacking. An investigation in which metformin was prescribed to 173 pediatric patients with NAFLD during 96 weeks demonstrated no effects on hepatic histology [177, 178]. A systematic review including eight randomized controlled trials, also, did not disclose any beneficial effects of the use of metformin on hepatic histology [179]. Until nowadays,

metformin has not been recommended specifically for the treatment of NAFLD, but it can be used in insulin-resistant patients (without renal insufficiency or heart failure) [1, 57].

The thiazolidinediones activate the nuclear transcription factor PPAR-γ improving insulin sensitivity in the adipose tissue [7]. Studies using rosiglitazone (4 mg twice daily for 48 weeks) [180] or pioglitazone (30 mg/daily during 48 weeks or 45 mg/daily during 6 months) [173, 181] demonstrated improvement in IR and normalization of the biochemical and histological parameters. Nevertheless, after the end of the treatment with the thiazolidinediones, the patients showed weight gain and the biochemical and histological parameters worsened.

The PIVENS study was a multicenter investigation comparing the use of pioglitazone with vitamin E or placebo, during 96 weeks, in a population of 247 non-diabetic patients with NAFLD [182]. Histological assessment was performed at the beginning and at the end of the treatment. The pioglitazone group showed a reduction in the serum aminotransferase levels ($p<0.001$), hepatic steatosis ($p<0.001$) and lobular inflammation ($p=0.004$) compared with the placebo group, but there were no improvements in the fibrosis scores ($p=0.12$). The pioglitazone patients gained more weight in comparison with the patients that received vitamin E or placebo. After treatment discontinuation, serum aminotransferase abnormalities reappeared.

The long-term safety of the thiazolidinediones has been questioned due to its cardiovascular adverse effects, namely congestive heart failure and increased rates of coronary events [183], and also increased rates of bladder cancer and bone loss [57]. The use of pioglitazone in nondiabetic patients with biopsy-proven steatohepatitis is supported by AASLD guidelines, but it is highlighted that the long-term safety of pioglitazone has not been established [1].

Hypolipidemic Medications

Several studies have suggested that cardiovascular disease is the major cause of death in subjects with NAFLD. Considering this fact, the treatment of dyslipidemia should be considered in the overall framework to treat NAFLD patients [184]. Hypolipidemic medications are also suggested as a potential treatment option for NAFLD because they can ameliorate hypertriglyceridemia and low HDL-cholesterol levels [185, 186].

Fibrates could affect the metabolism of hepatic TAG and the intrahepatic TAG content by stimulating PPAR-α, which regulates the expression of genes involved in mitochondrial fatty acid oxidation [187]. In experimental studies, fibrate therapy increases hepatic fatty acid oxidation and resolves steatosis [188, 189]. NAFLD patients treated with gemfibrozil (600 mg/daily for 4 weeks) presented moderate improvement in the biochemical parameters in a controlled trial [190]. However, in another study, the use of clofibrate in NAFLD patients resulted in no changes in the mean values of ALT, AST, gamma-glutamyltransferase, bilirubin, TAG and cholesterol, or in the histological grades of steatosis, inflammation, or fibrosis after 12 months of treatment as compared with the beginning of the study [191]. More recently, the effect of fenofibrate was investigated in obese subjects with NAFLD and was followed by a reduction in plasma TAG concentratios without alterations in the hepatic TAG content [187]. There are no data from large multicenter studies to support the use of fibrates to treat NAFLD [186, 192].

Statins are an important class of agents to treat dyslipidemia. Elevated aminotransferases are common in patients receiving statins, but serious liver injury from these drugs is seldom observed in the clinical practice. Several studies [193–197] have established that statins are safe in patients with liver disease including NAFLD. There is no current evidence of increased risk of hepatotoxicity when statins are administered in standard doses to patients with NAFLD or other liver diseases. Indeed, in some small limited studies, statins seem to improve liver biochemistry and histology in patients with NASH; however, until nowadays there is no randomized clinical trial with histological endpoints which investigated statins to treat NASH [192, 197–203]. So the recommendation of the AASLD practical guidelines

is that given the lack of evidence that NAFLD subjects are at high risk for serious drug-induced liver injury from statins, these agents may be used to treat dyslipidemia in those patients [1].

Antioxidants

Due to the role of oxidative stress and inflammation in NAFLD, some studies have investigated the use of antioxidants to protect cellular structures from the damage caused by the ROS and reactive products of lipid peroxidation. However, the results are contradictory [57, 88, 118, 204, 205]. In a Cochrane Review, available data about the use of antioxidants in NAFLD were analyzed and the authors concluded that the use of these agents is associated with improvement in aminotransferase levels, but there is insufficient evidence either to support or to refute the utility of antioxidants in NAFLD [206].

Studies evaluating vitamin C in NAFLD patients have not shown clear beneficial effects. It is noteworthy that in most of them, vitamin C was used in association with vitamin E [88, 168, 171, 207–209].

The use of vitamin E in patients with NAFLD has been assessed in several investigations [205, 207–214]. According to the results from the PIVENS study, the use of vitamin E resulted in histological improvement (reduction in steatosis and lobular inflammation with no changes in fibrosis), and normalization of the serum aminotransferases concentrations in non-diabetics patients with NAFLD. After discontinued treatment, the aminotransferases values returned to the basal levels. No significant adverse effects have been observed with the use of vitamin E after 2 years of treatment [182]. In another study, the authors assessed the histological parameters after the use of vitamin E in a pediatric population during 96 weeks. Although this study did not find any significant benefit of this vitamin in serum aminotransferases concentrations, it showed improvement in the histological characteristics (ballooning and NAFLD activity score) in the patients with initial hepatocellular ballooning degeneration [177, 178].

Several concerns have been raised due to an increase in all-cause mortality with the long-term use of vitamin E; however, this issue is controversial [215, 216]. Currently, the use of Vitamin E (α-tocopherol) in a dose of 800 IU/day is recommended for non-diabetic adults with biopsy-proven NASH. This vitamin should be considered as a first-line pharmacotherapy for this patient population since it improves liver histology. Until nowadays, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis [1, 57].

Omega-3 Polyunsaturated Fatty Acid Supplementation

Several studies have been conducted to evaluate the effects of omega-3 polyunsaturated fatty acid (PUFA) supplementation in the treatment of NAFLD in humans. A recently meta-analysis, involving 355 individuals given omega-3 PUFA or an alternative intervention (medications such as artovastatin and orlistat, or calorie restricted as recommended by the American Heart Association, or placebo, or no intervention), demonstrated reduction in liver fat and in the AST levels with the use of omega-3 [217]. However, the authors highlighted that there was significant heterogeneity among the studies. Indeed, the optimal dose is currently not known. Therefore, it is premature to prescribe omega-3 fatty acids for the treatment of NAFLD, but they might be considered in the treatment of hypertriglyceridemia in patients with NAFLD [1, 57].

Probiotics

Evidence suggests that the gut-liver axis could be a point of attack in the treatment of NAFLD [218–224]. The liver is constantly exposed to LPS, lipopeptides, unmethylated DNA and double-stranded RNA derived from the gut microbiota which might evoke intense inflammatory reaction contributing for the progression from steatosis to NASH [75]. Probiotics are defined as live microorganisms that when consumed in

adequate amounts confer a healthy benefit to the host [75]. They are able to modulate gut microbiota, modify the gut barrier function, and have immunomodulatory, anti-inflammatory and metabolic effects [75]. Several interventional studies assessed the use of oral probiotics in modifying gut microbiota in NAFLD patients. Their results demonstrated improvement in the oxidative stress markers, inflammatory parameters, and liver biochemistry [218, 219, 221–225]. The authors of a recent meta-analyses concluded that probiotic therapy reduces liver aminotransferases levels, total-cholesterol, TNF-α levels and IR in individuals with NAFLD suggesting that modulation of the gut microbiota could represents a new complementary therapeutic approach in NAFLD [226]. Additionally, probiotics are low cost, present good tolerability, and are safe. However, it is important to emphasize that the studies differ regarding the probiotic doses, strains of bacteria and duration of treatment, and in most of them the response to probiotic use was not evaluated by liver biopsy, which hamper the establishment of the best intervention [227].

Ursodeoxycholic Acid (UDCA)

The clinical trials that assessed the use of UDCA, a hydrophilic cytoprotective bile acid, in patients with NAFLD demonstrated contradictory results. A systematic Cochrane Review analyzed four studies on UDCA in NAFLD treatment and just only one had adequate methodological quality. Its results suggested that UDCA did not present any benefit in NAFLD patients [228, 229]. Currently, there is no robust evidence recommending the use of UDCA in the treatment of NAFLD [1, 57, 191, 228–231].

Conclusion

NAFLD is currently recognized as one of the most common chronic liver diseases. Its pathogenesis is unclear, but available evidence suggests a complex process involving multiple parallel metabolic hits as IR, lipotoxicity and oxidative stress that result in hepatocyte damage, inflammation and fibrosis/cirrhosis. Obesity and type 2 diabetes are predictors of advanced liver fibrosis and cirrhosis. Currently, lifestyle interventions, including dietary changes and increase in physical activity, are the first-line treatment for this disorder, but different therapeutic approaches are under intense investigation.

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Obesity, Cardiometabolic Risk, and Chronic Kidney Disease

14

Samuel Snyder and Natassja Gangeri

Introduction

According to the World Health Organization (WHO), obesity has more than doubled since 1980 worldwide. In 2014, there were more than almost 2 billion (39 %) adults over the age of 17 who were overweight and 600 million of these were obese (13 %). Of these 600 million adults that were deemed obese, 11 % were men and 15 % were women. In 2013, there were about 42 million children under the age of five who were deemed overweight or obese [1]. Overweight is defined by body mass index (BMI). Overweight is divided into four categories: these include pre-obesity (BMI between 25 and 29.99), obesity class I (BMI between 30 and 34.99), obesity class II (BMI between 35 and 39.99), and obesity class III (BMI greater than or equal to 40) [2]. A meta-analysis and systematic review reported hazard ratios of all-cause mortality for overweight and obese patients compared to normal weight patients in the population. They showed that when compared to patients with normal weight, patients that were obese class II and III had a significantly higher all-cause mortality [3].

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What Defines Metabolically Healthy Verses Abnormal Obesity?

Not all obese patients have metabolic and cardiovascular risk factors. On the flip side of this, not all lean patients have a healthy metabolic profile. Therefore, the distinction between metabolically healthy obesity (MHO) vs. metabolically abnormal obesity (MAO) becomes important clinically and epidemiologically [4, 5].

In a review by Phillips in 2013, she references four sets of criteria for what defines MHO (Table 14.1) [4]. In 2014 Perez-Martinez et al. used Wildman et al.'s criteria for what they defined as MHO and further broke down body size into six phenotypes: normal weight, metabolically healthy (NWMH), normal weight, metabolically abnormal (NWMA), overweight, metabolically healthy (OWMH), overweight, metabolically abnormal (OWMA), obese, metabolically healthy (OMH), and obese, metabolically abnormal (OMA) [4, 6]. Perez-Martinez et al. may have chosen to use Wildman's criteria for defining MHO, but he also included, the homeostasis model assessment of insulin resistance (HOMA-IR) as a criteria as well as c-reactive protein (CRP) levels, which the other authors did not use (Table 14.1) [5–10].

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Table 14.1 Criteria used to define metabolically healthy individuals according to five authors

	Wildman et al. [6]	Aguilar-Salinas et al. [7]	Karelis et al. [8]	Meigs et al. [9]	NCEP ATPIII [10]
Blood pressure (*mmHg*)	SBP ≥ 130 or DBP ≥ 85 or Treatment	SBP < 140 and DBP < 90 or No treatment		SBP ≥ 130 or DBP ≥ 85 or Treatment	SBP > 130 and/or DBP > 85
Triglycerides (*mmol/L*)	≥1.70		≤1.70	≥1.70	≥1.70
HDL- cholesterol (*mmol/L*)	<1.04 (male) <1.30 (female) or Treatment	≥1.04	≥1.30 and No treatment	<1.04 (male) <1.30 (female)	<1.03 (male) <1.20 (female)
LDL-cholesterol (*mmol/L*)			≤2.60 and No treatment		
Total cholesterol (*mmol/L*)			≥5.20		
Fasting plasma glucose (*mmol/L*)	≥5.55 or Treatment	<7.00 and No treatment		≥5.60 or Treatment	≥5.6
HOMA	>90th percentile		≤1.95		
C reactive protein	>90th percentile				
Waist circumference (*cm*)				>102 (male) >88 (female)	>102 (male) >88 (female)
Metabolic health criteria	<2 of the above	All of the above	≥4 of the above	<3 of the above	<3 of the above

ATPII Adult Treatment Panel III, *DBP* diastolic blood pressure, *HDL* high density lipoprotein, *HOMA* homeostasis model assessment, *LDL* low density lipoprotein, *NCEP* the National Cholesterol Education Program, *SBP* systolic blood pressure

Wildman et al. describes six metabolic components that can be measured including (i) elevated blood pressure, (ii) elevated triglycerides, (iii) elevated fasting glucose, (iv) elevated CRP, (v) elevated HOMA-IR and (vi) reduced high-density lipoprotein cholesterol (HDL) [6]. They provide cut-off values for the six cardiometabolic components which include: systolic blood pressure greater than or equal to 130 or a diastolic blood pressure greater than or equal to 85 or on anti-hypertensive medications; fasting triglyceride level greater than or equal to 150; HDL of less than 40 in males or less than 50 in females or on lipid-lowering medications; fasting glucose level of greater than or equal to 100 or on anti-diabetic medications; HOMA-IR greater than 5.13; and a high-sensitivity CRP greater than 0.1 [6]. They also define criteria for body size phenotypes, which include: NWMH have a BMI less than 25.0 and have less than two cardiometabolic abnormalities; NWMA have a BMI less than 25.0 but have two or more cardiometabolic abnormalities; OWMH have a BMI between 25.0 and 29.9 and have less than two cardiometabolic abnormalities; OWMA have a BMI between 25.0 and 29.9 but have two or more cardiometabolic abnormalities; OMH have a BMI greater than or equal to 30 and have less than two cardiometabolic abnormalities; and OMA have a BMI greater than or equal to 30 but have two or more cardiometabolic abnormalities [4, 6].

Because of studies conducted by several authors including Wildman et al., there is more focus now on cardiometabolic abnormalities than just having a high BMI and being considered overweight or obese. Wildman et al. showed that there were quite a large proportion of patients that were normal weight individuals but metabolically abnormal, whereas many individuals were overweight/obese but metabolically healthy. There were close to 30 % obese males and 35 % obese females that exhibited metabolically healthy profiles vs. 30 % of normal-weight males and 21 % of normal-weight females that had two or more cardiometabolic abnormalities [6]. These findings suggest that perhaps in addition to looking at obesity as a mat-

ter of weight alone, we should also be focusing on cardiometabolic health as well. More research is needed to properly define MHO and MAO. Obesity is defined with BMI and/or waist circumferences, but both of these measures have their limitations and can lead to incorrect classification of patients [5]. For example, BMI does not differentiate between lean and fat body mass and waist circumference is only a measure of visceral fat but does not take other areas of body fat into account, such as perinephric fat or non-alcoholic fatty liver (NAFL), which has been shown to have an impact on the adverse outcomes of obesity [11–14]. The focus of this chapter will be the relationship between MAO patients and the development of chronic kidney disease (CKD).

Risk Factors for Developing CKD in the Obese Patient

It is well known that the two most common risk factors for developing CKD are hypertension (HTN) and diabetes mellitus (DM). However, recent studies demonstrate that metabolic syndrome (MetS) is a major risk factor for developing obesity related glomerulopathy (ORG), and the risk factors for developing CKD include metabolic syndrome as well as obesity [15–17].

In one particular study, the authors were the first to study MHO and MAO populations and the incidence of CKD development. They used the International Diabetes Federation criteria to define MHO vs. MAO. The parameters for this criteria were as follows: systolic blood pressure greater or equal to 130 or a diastolic blood pressure greater or equal to 85 or treatment; triglyceride levels greater than or equal to 150 or treatment; HDL less than 40 in males and less than 50 in females; and a fasting plasma glucose of greater than or equal to 100. They defined metabolically healthy as having one or none of the criteria above, and they defined metabolic abnormal as having two or more of the criteria. They found that MHO phenotype was not associated with increased risk of developing CKD, however they did see an increase in risk of developing kidney disease in patients with an MAO phenotype. They also showed that the MAO phenotype had higher incident proteinuria. This suggests that individuals with an MHO phenotype may have protection from the metabolic complications of obesity [15]. One can infer from these findings that the association between obesity and CKD is likely mediated more by biological mechanisms such as inflammation, endothelial dysfunction, oxidative stress, and hormonal factors, rather than obesity itself [15]. This study also paves the way for a better understanding of how obesity leads to chronic kidney disease, and how being obese alone may not be the only problem. Instead, MAO phenotype individuals have a higher risk of developing CKD than their MHO counterparts. However, because this study did not take into account other parameters for MAO such as waist circumference and insulin resistance to name just two, patients may have been misclassified [15].

Song et al. investigated whether reduced glomerular filtration rate (GFR) was associated with MetS as defined by ATPIII criteria (Table 14.1). Their study suggests that MetS may be an independent risk factor for decreased GFR, regardless of age or gender [16]. Prior to Panwar et al., numerous studies found an incidence of CKD in obese patients, but obesity was not differentiated into "healthy" vs. "abnormal" (in other words, if the patient had metabolic syndrome or not). Panwar et al. found that patients that were overweight or obese but without metabolic syndrome had a lower risk of end-stage renal disease (ESRD). Conversely, normal weight patients with metabolic syndrome had a two-fold greater risk of developing ESRD as compared to normal-weight patients without metabolic syndrome. These findings support the idea that developing ESRD depends on a patient's concurrent metabolic health, and not just on their BMI [17]. Therefore, more studies are needed to continue to evaluate the development of CKD in patients with metabolic syndrome regardless of their BMI.

MHO patients do not have an increased risk of developing cardiovascular disease (CVD) compared to metabolically healthy non-obese control group [18, 19]. This proposes that overall metabolic health is a better predictor of cardiovascular disease (CVD) than overall adiposity [18]. MHO phenotype was associated with a lower risk for type II diabetes mellitus (DMT2) than MAO phenotype;

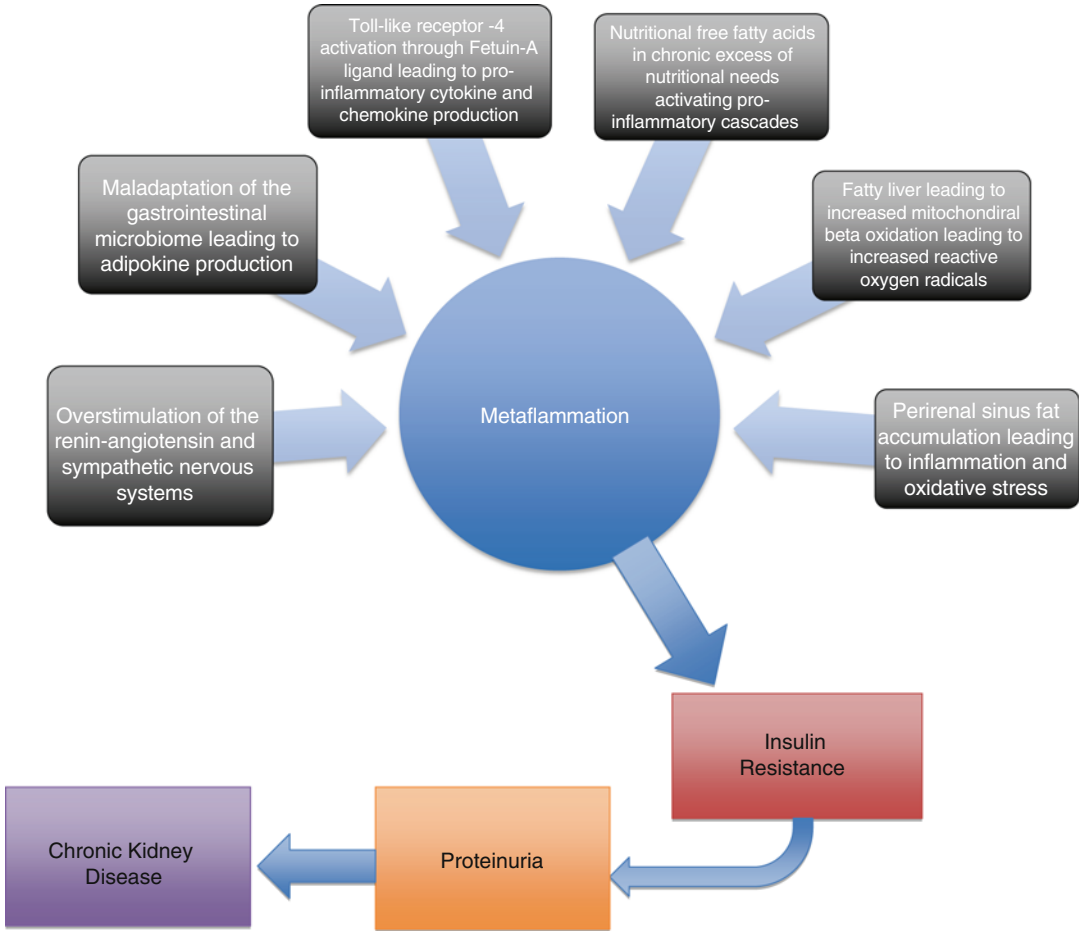

Fig. 14.1 Various causes of Metaflammation and its link to CKD

however, the risk of CVD was high in both MHO and MAO groups [20]. CVD and DMT2 are both also thought to have similar pathogenic mechanisms as CKD with their common pathway being inflammation-mediated. Thus, one can link the fact that obesity is related to increased inflammatory states causing CVD and likely CKD as well.

Pathophysiology of Obesity Related Kidney Disease

Obesity Leads to Metaflammation

Obesity related glomerulopathy (ORG) is a recently described disease entity that has gained a lot of interest in the past few years. ORG is a secondary form of glomerular disease that occurs in patients that are obese [21]. ORG is defined pathologically as a variant of focal segmental glomerulosclerosis (FSGS) with concomitant glomerulomegaly [22].

ORG is thought to be a consequence of inflammation, specifically by what has been termed metaflammation, a low-level chronic inflammatory state caused by obesity and chronic overnutrition. The exact mechanisms are still being investigated, but here we describe a few possible pathways that lead to metaflammation and, as a consequence, insulin resistance, which has been implicated in the development of renal disease and microalbuminuria [23–25]. Likely these mechanisms are all involved and conspiring together instead of

acting individually in the unfolding of this pathological state.

The possible mechanisms by which metaflammation arises include: (i) nutritional free fatty acids (FFA) in chronic excess of nutritional needs activating pro-inflammatory cascades, (ii) toll-like receptor-4 (TLR-4) activation through Fetuin-A ligand leading to pro-inflammatory cytokine and chemokine production, (iii) fatty liver accumulation through a two-hit hypothesis leading to oxidative stress and inflammation, (iv) maladaptation of the gastrointestinal (GI) microbiome leading to adipokine production and inflammation, (v) perirenal sinus fat accumulation leading to oxidative stress and inflammation, and (vi) overstimulation of the renin-angiotensin aldosterone system (RAAS) through various mechanisms (Fig. 14.1) [13, 22, 26–32]. These individual mechanisms have not yet been shown to directly lead to insulin resistance, but many researchers have shown how "inflammation" leads to insulin resistance and how it is the basis for MetS. Therefore, we propose here that mechanisms a-f above may all contribute to "metaflammation" which results in insulin resistance and thereby leading to CKD and proteinuria.

Nutritional Free Fatty Acids: Their Link to Metaflammation

Obesity-induced increases in free fatty acids in adipose tissue as well as increased nutritional free fatty acids lead to activation of TLR-4; this in turn results in stimulation of JNK and NF-κB inflammatory cascades, producing increased levels of TNF-α and IL-6 [26]. It was shown that in mice with a TLR-4 knockout gene, free fatty acid infusions did not lead to release of TNF-α or IL-6, and these knockout mice did not develop insulin resistance. They were able to conclude that mice with a knockout gene for TLR-4, when given a high-fat diet did not become insulin resistant, but instead they showed improved insulin sensitivity. Therefore, TLR-4 is a necessary step for high-fat diets to induce inflammatory mediators in peripheral tissues [26]. This may have implications for possible treatment strategies, to be discussed later.

FFA, FETUIN-A, and TLR-4 Leading to Metaflammation

Fetuin-A (alpha2-Heremans-Schmid glycoprotein) is a hepatokine, which is a type of protein with signaling properties. It is thought that the expression of Fetuin-A is increased in non-alcoholic fatty liver disease (NAFLD) because of fat accumulation in the liver. It is well known to inhibit insulin signaling and more recently has been linked to induce cytokine expression in monocytes and adipose tissue [28, 33]. Fetuin-A has also been shown possibly to exert other functions, such as inhibiting the insulin receptor tyrosine kinase in the liver and skeletal muscle. Mathews et al. showed that mice that had a Fetuin-A knockout gene had improved insulin sensitivity and were resistant to weight gain when fed a high-fat diet [34]. This has implications for possible therapeutic efforts against Fetuin-A. Increased levels of Fetuin-A were associated with insulin resistance in humans and that they were also increased in patients with fat accumulation in the liver [35]. Nutritional fatty acids have also been linked to activate TLR-4, which activates an inflammatory cascade [26]. Fetuin-A is thought to be involved in this cascade as a ligand to TLR-4 by presenting free fatty acids, which leads to the subsequent activation of the cytokines and inflammatory mechanisms described above [36].

Fetuin-A may thus be the mediator between free fatty acids and TLR-4 activation. As free fatty acids are present in excess, they get presented to TLR-4 receptors by the hepatokine Fetuin-A. This then initiates the protein kinases JNK and IKK complex pathways that lead to transcription of pro-inflammatory genes that encode cytokines, chemokines, and other effectors of the innate immune system. Furthermore, activation of IKK complex leads to stimulation of NF-κB, which results in downstream activation and secretion of IL-6 and monocyte chemoattractant protein 1

(MCP-1) [26, 37]. It has been shown that MCP-1 is secreted by adipose tissue macrophages as well as by adipocytes themselves. Adipose tissue MCP-1 has been recognized as a main chemokine that leads to adipose tissue infiltration by monocytes and macrophages leading to increased inflammation and therefore resulting in insulin resistance [29].

Fatty Liver Accumulation: Its Connection to Metaflammation

NAFLD is one of the most frequently diagnosed causes of chronic liver disease in Western countries. The spectrum of liver disease ranges from hepatic steatosis to cirrhosis. It has been shown that MetS increases with increased severity of liver disease [30].

Excess adipose tissue, more so visceral adipose, is recognized as an endocrine organ because of its association with cytokine production. It produces leptin, adiponectin, resistin and TNF-α. Leptin, resistin and TNF-α are the hormones that cause increase in insulin resistance, whereas adiponectin has been shown to have opposite effects and decreases insulin resistance [38]. Free fatty acids, or increased alimentation, stimulate TNF-α as previously described above through our proposed mechanism involving Fetuin-A activation of JNK, NF-κB, and IKK complex pathways [26, 36–38]. It has been observed in several studies that adiponectin is suppressed in disease states such as insulin resistance, obesity, and diabetes [39–41]. The question that arises is what is the intermediate step that links increased inflammatory states to insulin resistance? It has been recently found that IL-6, TNF-α, and other cytokines are negative regulators of adiponectin [28, 38–40, 42, 43]. It has been observed in mice injected with recombinant IL-6 that their glucose and insulin levels increase [39]. Adiponectin increases the ability of insulin to suppress glucose production in the liver [44]. Therefore, it has been proposed that IL-6 downregulates adiponectin and subsequently inhibits its ability to suppress insulin, thereby causing hyperglycemia and eventual insulin resistance [39, 40, 42, 44]. Thus, it has been suggested that this is a paracrine system in which there is negative feedback affecting adiponectin production in obesity [40, 42, 45]. It was discovered that adiponectin reduces TNF-α levels; therefore it is thought that it possibly enhances insulin sensitivity through its inhibitory effects on TNF-α. More research is needed to better characterize this relationship and investigate causality [45]. Targeting this interaction between these paracrine modulators may be a great topic for investigation for treatment options directed at restoring insulin sensitivity.

Healthy subjects with low adiponectin levels had higher alanine transaminase and γ-glutamyl transpeptidase, which may mean that adiponectin, is needed for maintenance of liver integrity [46, 47]. Regardless of the subjects' BMI, there were lower adiponectin concentrations in NAFLD patients when compared to controls [30]. A two-hit hypothesis has been proposed in which the first hit is secondary to an accumulation of lipids that leads to steatosis. Then the second hit consists of oxidative stressors and cytokine production. The second hit is thought to be due to lipid peroxidation and abnormal cytokine production observed in NAFLD [11]. It is thought that increased activity of cytokines in NAFLD may also be due to oxidative stress or bacterial overgrowth [11, 12, 48, 49].

Therefore, fatty liver disease leads to insulin resistance through its association with decreased levels of adiponectin, secondary to paracrine negative feedback effects, and increased levels of cytokines and oxidative stress. This in turn results in the development of proteinuria and CKD.

Gastrointestinal Microbiome Associated with Metaflammation Through Increased Adipokines Causing a Leaky Gut

Normal intestinal microbiota in adults consists of *Firmicutes*, *Bacteriodetes*, *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, *Spirochaetae* and

Verrucomicrobia, as well as many other genera. Ninety percent of all intestinal flora consists of *Firmicutes* and *Bacteriodetes*. Any change in this composition leads to what is termed "dysbiosis." Dysbiosis has been related to several conditions such as obesity, fatty liver disease, and diabetes to name a few [50, 51].

Many studies have shown that dysbiosis in obesity consists of a microbiome with low amounts of *Bacteriodetes* and high amounts of *Firmicutes*. Aside from this distinction, these obese patients also have less diversity of their GI microbiome [50, 52, 53]. *Bifidobacteria* levels, although not a major part of the normal intestinal flora, are reduced in mice fed high-fat diets. These bacteria are what are thought to be responsible for the microinflammatory conditions produced during disease states such as obesity [50, 54, 55].

Germ-free mice were protected from high-fat diet induced obesity by two independent mechanisms, in contrast to mice with a normal gut microbiota [53, 56]. Furthermore, intestinal microbiota taken from an obese individual and transplanted into lean germ-free mice led to more fat deposition as compared to transplantation from lean donor mice [53, 57]. These findings lead to questions about the differences between obese mice and lean mice in relation to their gut microbiota composition. The answer seems to be *Bifidobacteria* [54]. It has been shown that mice fed high-fat diets have an increase in intestinal permeability thought to be due to reduced expression of genes encoding tight junctions of the intestinal barrier. It has been proposed that the interruption of the intestinal barrier is secondary to dysbiosis of gut bacteria. This conclusion was made when it was observed that there was recovery of intestinal epithelial integrity after administration of antibiotic treatment [53, 58, 59]. It was shown that high-fat diets in mice induced a low-grade inflammation that resulted in low levels of *bifidobacteria*. This group of bacteria is known to reduce lipopolysaccharide (LPS) in the intestines and to improve the mucosal barrier function [53–55, 58]. Therefore, it is thought that low levels of this particular bacteria leads to unopposed increases in LPS, in turn, stimulating TLR-4 and CD14 receptors which then initiate the inflammatory cascade described above. These changes in the gut with low levels of *bifidobacteria* are reversible with weight loss and a low-calorie diet, another area of research for discovery of possible treatment options [50, 60–62].

In high-fat fed mice with low levels of *bifidobacteria*, the animals were found to have high plasma level of endotoxin, LPS, concentrations; this has been defined as metabolic endotoxemia [54, 55]. A study was conducted in which researchers found that metabolic endotoxemia in mice increased as the fat food content was higher. This low-grade endotoxemia was also shown to increase adipose TNF-α and IL-6 feeding into the vicious cycle causing metaflammation [54, 63]. Studies have shown that TLR-2 regulates tight junctions in the intestinal epithelial barrier and that a deficiency can lead to alterations in this barrier and loss of integrity of the intestinal mucosa [31, 64, 65]. There is also a close interaction between TLR-4 and TLR-2 in the activation of the innate immune response. They showed that mice with a TLR-2 knockout gene developed insulin resistance likely from gut microbiota alteration [31].

TLR-4 and CD14 are known to be a key LPS-sensing receptors [63]. CD14 knockout mice were shown to lack the innate immune response to bacterial LPS and macrophages did not secrete proinflammatory cytokines when stimulated with LPS [55]. Mice with knockout genes for TLR-4 were shown to be immune to diet-induced obesity. This mutation prevents high-fat diet induced activation of proinflammatory pathways (IKK and JNK) as well as prevention of insulin resistance [63, 66]. They showed that hepatic steatosis did not occur in CD14 mutant mice after consuming a high-fat diet or infusion with LPS. Additionally, the LPS-CD14 interaction sets a threshold at which insulin resistance and its associated diseases such as diabetes, obesity, and NAFLD occur [55]. These findings can help with therapeutic targets to the TLR-4 and CD14 receptors as a treatment for obesity and insulin resistance.

Activation of the RAAS Through Various Mechanisms, Specifically Perirenal Sinus Fat Accumulation Leading to Metaflammation and Oxidative Stress

Obesity and inactivity leads to fat accumulation at the arteriolar level, allowing adipocytokines like TNF-α to accumulate and inhibit signaling of endothelial nitric oxide (NO) synthesis as well as inhibiting native capillary recruitment, thus, leading to vasoconstriction [67, 68]. Yudkin et al. coined the term vasocrine signaling, in which cytokine production leads to inhibition of insulin-mediated capillary recruitment. They showed that arterioles from rats are under regulation by insulin in two manners: first through activation of endothelin-1 mediated vasoconstriction and second through NO mediated vasodilation. They show that the arterioles of obese rats have impaired insulin-stimulated NO synthesis which results in unopposed vasoconstriction through endolethin-1 activity. It has been proposed that obesity, in which there are states of excess calorie intake and inactivity, leads to fat deposition at the level of the arterioles [67, 68]. This leads to increased TNF- α production along with other adipocytokines, promoting inhibition of insulin-induced vasodilation and nutritive capillary recruitment [69, 70]. Hence, increased vasoconstriction occurs. The authors term this action vasocrine signaling because it occurs downstream from the fat pad deposition; there is no fat within the arterioles themselves. They believe that the high concentration of cytokines produced leads to arteriolar permeability and affects the entire vascular tree including precapillary arterioles [68]. It is thought that these findings can likely be applied to renal vessels as well, which may be another explanation for microalbuminuria seen in obesity, or for the phenomenon of glomerular hyperfiltration.

The normal pathway of the renin-angiotensin-aldosterone system (RAAS) starts with the synthesis of renin by the juxtaglomerular cells (JG) that line mainly the afferent arteriole of the renal glomerulus. Mature active renin, which is formed after proteolytic cleavage, is stored in the granules of the JG cells and is released by an exocytic process. Active renin is secreted when a renal baroreceptor in the afferent arteriole senses a decrease in renal perfusion pressure, or a decrease in sodium chloride delivery detected by the macula densa, or an increase in sympathetic nerve stimulation via beta-1 adrenergic receptors, or lastly when a negative feedback occurs through direct action of angiotensin II. The activity of the RAAS is determined by renin secretion; it is the rate-limiting step. Renin when activated, will allow for cleavage of angiotensinogen to form angiotensin I.

Angiotensinogen is mainly made in the liver constitutively; however it is also made in other tissues such as renal and cardiac tissues. Angiotensinogen levels have been shown to rise in response to several other substances, for example, glucocorticoids and inflammatory cytokines. Then inactive angiotensin I is hydrolyzed by angiotensin converting enzyme (ACE), which forms angiotensin II, a known potent vasoconstrictor. ACE is also known to metabolize bradykinin and kallidin, which are vasodilators, into inactive forms; thus, the overall action of ACE is to cause vasoconstriction.

Angiotensin II is the primary effector of the RAAS. There are four angiotensin receptors all conveying different activities, two of which will be described here. The type I receptor mediates actions on the cardiovascular system leading to vasoconstriction and hypertension, as well as the renal system leading to renal tubular sodium reabsorption and inhibition of renin release, as well as the sympathetic nervous system and adrenal cortex leading to aldosterone production and release. This receptor also mediates the effects on the inflammatory response. The type II receptor when activated in the kidney, has been proposed to influence proximal tubule sodium reabsorption and stimulation of the conversion of renal prostaglandin E2 to F2α, however, these actions still remain unclear. Angiotensin II production can also be initiated by adrenocorticotrophic hormone (ACTH) and endothelin. On the other hand, it can be inhibited by NO. Aldosterone is a major regulator of sodium and potassium balance. It regulates extracellular volume. It

enhances the reabsorption of sodium and water in the distal tubules and collecting ducts while promoting potassium excretion [71].

However in the setting of obesity, it has been shown that plasma renin and angiotensin II concentrations are elevated [72, 73]. This helps explain how obesity is related to MetS and hypertension. According to various studies, there are several mechanisms thought to help explain the activation of the RAAS in obesity and metabolic syndrome. These include sympathetic stimulation, adipokine production secondary to perivascular fat, hemodynamic alterations, which lead to interference with renal blood flow, and visceral and perirenal fat causing mechanical compressive changes to the glomeruli [22, 74–76]. Despite sodium retention, extracellular volume increase, and hypertension, the RAAS is still overtly activated, inappropriately, in metabolic disorders including obesity. Some potential mechanisms thought to be the cause of increased renin and angiotensin II include activation of the renal sympathetic nerves and increased sodium reabsorption at the loop of Henle with subsequent decrease in sodium chloride delivery to the macula densa. There has also been shown that adipose tissue secretes angiotensinogen, which can elevate angiotensin II levels [77, 78]. Regardless of the precise mechanisms involved, RAAS activation appears to contribute to elevation of blood pressure in obese subjects [78].

The exact pathway of how angiotensin II leads to hypertension in obesity remains a subject of much research. However, it is known that angiotensin II is increased in obesity. Therefore, it has been proposed that possibly through angiotensin II's direct action on the kidneys, and stimulation of aldosterone secretion, and activation of the sympathetic nervous system may all be plausible causes of hypertension mediated by angiotensin II [78, 79]. When there are systemic elevations in plasma angiotensin II, there is a positive-feedback endocrine loop that results in increased angiotensinogen production. This occurs through the interaction of angiotensin II with AT1a receptors found directly on adipose tissue [80].

Sympathetic stimulation occurs secondary to increased renal tubular reabsorption of sodium, leading to impaired pressure-natriuresis. The increase in aldosterone that occurs in obesity has been attributed to stimulation of the sympathetic nervous system as well as RAAS [74, 78, 81–83]. Leptin is an amino acid peptide that reduces appetite and promotes weight loss. It is thought to do this through stimulation of the sympathetic nervous system causing increased energy expenditure, and consequently increasing arterial blood pressure. Circulating levels of leptin in the plasma correlate to fat cell mass and adiposity [78, 81, 84–87]. Leptin activates the sympathetic nervous system though centrally mediated effect on the hypothalamic pro-opiomelancortin (POMC) pathway. A mutation in the leptin gene or in the receptors mediating leptin activity confers the individual with morbid obesity and metabolic disorders. Thus, chronic blockade of such receptors in rats showed rapid weight gain, insulin resistance, an increase in plasma leptin levels but no increase in blood pressure [78, 81, 88]. Also when NO synthesis is inhibited, the hypertensive effect of leptin are augmented [78, 79]. Therefore, it has been proposed that a functional receptor is the link between excess weight gain and increased sympathetic nervous system stimulation leading to hypertension [78, 89]. When NO synthesis is inhibited, the hypertensive effects of leptin are augmented [68, 78, 90].

It appears that cytokines produced in obesity through the mechanisms already described previously induce insulin resistance and stimulate production and secretion of aldosterone [73, 91]. Increased salt intake and cytokine excess are the causes of increased aldosterone production seen in obese individuals. Excess aldosterone levels lead to increased oxidative stress and are associated with dysfunctional insulin metabolic signaling [73]. Aldosterone is responsible for reabsorption of sodium and excretion of potassium, but also visceral fat compression, which will be described shortly, leads to increased sodium reabsorption [78, 79]. Excess renal tubular sodium reabsorption has been implicated as a major cause of increases in arterial blood pressure and has been associated with weight gain. Obese patients have an impaired renal pressure-natriuresis because these patients require a higher

baseline arterial blood pressure for proper maintenance of sodium balance [74, 81–84]. It is proposed that with chronic obesity, eventually there will be increased arterial blood pressures, increased glomerular filtration, neurohumoral activation, and metabolic changes that may ultimately lead to renal injury [78].

Obesity has been shown to increase renal blood flow, increasing GFR and glomerular pressure, which concomitantly lead to afferent arteriolar dilatation [92, 93]. This results in increased albuminuria and glomerulosclerotic changes referred to as ORG as described above [73]. The pathology features of a renal biopsy taken from obese individuals with normal renal function are characterized by increased mesangial matrix, podocyte hypertrophy, and glomerulomegaly when compared to their normal weight counterparts [73, 94]. This demonstrates how obesity can lead to eventual decline in renal function and ultimately ESRD if not discovered early.

It is thought that abdominal visceral fat can lead to renal medullary compression, increased intrarenal pressures, impaired pressure-natriuresis, and hypertension. There is increased formation of renal medullary extracellular matrix, also known as hyalinosis, in which intrarenal compression and sodium retention occurs. It is unclear what causes the increase in hyalinosis but it is known that its accumulation leads to increased interstitial fluid pressure and inflammation. This increase in pressure would lead to compression of the loop of Henle and vasa recta [32, 78, 79, 84, 95, 96].

Perirenal fat is thought to affect the renal sinus and compress the renal vessels by causing mechanical pressure, which eventually leads to increased renal vein resistance, decreased renal blood flow and ultimately kidney dysfunction and disease, mediated at least in part by RAAS activation [13, 97–99]. It is thought that renal sinus fat can cause compression of the renal vein and cause increases in interstitial pressures and sodium retention, which further activates the RAAS. Previous studies have shown that endothelial dysfunction as a result of high FFA levels and metaflammation can lead to increased oxidative stress [13, 14]. Obese rats were found to have a high level of reactive oxygen radical production in their glomeruli and that perirenal fat was strongly related to increased microalbuminuria and may be a good predictor of early kidney dysfunction in obese individuals [13]. It has also been hypothesized that renal sinus adiposity can decrease medullary blood flow leading to exacerbation of renal hypoxia, which then increases renal sympathetic nervous system activity. This leads to a positive feedback on blood pressure control [95, 100]. Therefore, obesity leads to eventual accumulation of fat around the renal sinus and activation of the RAAS through mechanisms described above, which ultimately results in metaflammation, hypertension, and kidney disease.

CKD as a Result of Metaflammation and Insulin Resistance

Increased levels of Fetuin-A have been shown to have a direct correlation with several parameters of MetS, including most importantly insulin resistance. After adjusting for CRP and adipokine levels, one study showed that there was significant association between serum Fetuin-A levels and increased insulin resistance [101–103]. Several studies have shown that Fetuin-A levels in serum have an inverse relationship to adiponectin levels in serum [27, 101, 104].

The link between Fetuin-A and adiponectin is metaflammation. Adiponectin is an adipose tissue secreting hormone that accounts for about 0.01 % of total plasma protein. It is known to be involved in inflammation and vascular homeostasis. It is thought that Fetuin-A and adiponectin work together to regulate insulin resistance. Adiponectin levels and obesity related diseases have been linked. It is an insulin-sensitive adipokine, and thus, has anti-diabetic and anti-inflammatory properties [104–106].

Insulin resistance is associated with elevated triglycerides in the liver which leads to fatty liver disease and thus there is an increase in fatty acids and decrease in output of triglycerides [30]. There is more insulin resistance with increased hepatic fibrosis [107]. Adiponectin is secreted by adipose cells and is known to modulate insulin

effects. Low levels in the serum of adiponectin have been implicated and associated with increased insulin resistance, MetS, and hepatic fat [29, 43, 48, 108, 109]. Usually free fatty acids from peripheral adipose tissue are delivered to the liver, but if there is an increase in protein or carbohydrate intake, then there will be local synthesis of free fatty acids by the liver. Therefore, liver accumulation of fat occurs when intake exceeds the metabolic capability to process them. This accumulation of fat in the liver is what leads to insulin resistance secondary to increased lipolysis which then leads to increased mitochondrial β oxidation which produces reactive oxygen radicals (ROS) through the two-hit hypothesis previously described [47, 110].

Therefore, when there is an increase in fatty acids and Fetuin-A, there is increased production of IL-6 and TNF-α, which has a negative regulatory effect on adiponectin, decreasing its concentration in serum. In many studies, adiponectin levels have been shown to be low in obese patients, which leads to possible foot process effacement of podocytes and eventually leads to proteinuria [104, 111]. Panduru et al. investigated the possibility of using urine adiponectin concentrations as a predictor of diabetic nephropathy to ESRD. They were able to show that it is a strong independent predictor for progression to ESRD and may be able to be used as a marker for diabetic patients to monitor progression of worsening kidney function [112]. Albuminuria that was induced by increased levels of Fetuin-A was reversible if hepatic steatosis improved. Therefore, the link between obesity and NAFLD may be vital to possibly preventing progression of proteinuria to ESRD by treating and reversing hepatic steatosis [113]. The concept is that liver adipose leads to increased secretion of Fetuin-A and decreased secretion of adiponectin, together initiating an inflammatory cascade that leads to insulin resistance and ultimately proteinuria that develops into CKD. There is an association between NAFLD and increased incidence of CKD further suggesting that our proposed link between the two through metaflammation and insulin resistance is a possibility that needs more research and confirmation [114].

It has been shown that there is significant increase in intestinal permeability in patients with NAFLD. Along these same lines, there is also an increase in small intestinal bacterial overgrowth (SIBO) in patients with NAFLD. Both, the extent of gut permeability and SIBO present, correlate with degree of hepatic steatosis. Additionally, the frequency of SIBO was twice as high in NAFLD patients with increased gut permeability when compared to those with normal intestinal permeability [115]. Gut bacteria seem to contribute to the development of NAFLD just like in CKD through LPS and cytokine production [50, 115]. Intestinal gut microbiota composition may be the link between whether an individual develops NAFLD. It has been shown that depending on the gut microbiota composition, mice respond differently to high-fat diets and some mice develop NAFLD while others do not [116]. There is an abundance of research in this field investigating which bacteria are more prone to lead to NAFLD and which are not. This may pave the way for possible treatment options with fecal transplantation and probiotics [117].

There has been an increasing amount of research in the field of obesity causing inflammation leading to low inflammatory states that can lead to CKD through several mechanisms as discussed in detail in this chapter. The link between leaky gut and ESRD has also been studied. Gut microbiota translocation occurs in ESRD and is associated with microinflammation. It was shown that the total amount of intestinal bacteria detected in the plasma increased in the ESRD group versus control [118]. Bacteria in the GI tract release D-lactate normally; therefore, when the integrity of the intestinal barrier is compromised, D-lactate is released into plasma. Thus, D-lactate can be an early marker for detection of gut mucosal barrier disruption. ESRD patients were shown to have increased levels of D-lactate as well as hs-CRP, linking inflammation with gut bacterial translocation to ESRD [118, 119]. The inflammatory state induced by leaky gut leads to insulin resistance, which may also be a mechanism that can explain CKD in individuals with increased gut permeability [120, 121]. As previously described, TLR4 activation occurs when

bound to LPS that has been released from a leaky gut, which induces upregulation of inflammatory pathways that are known to cause insulin resistance. LPS can also promote expression of inducible nitric oxide synthase (iNOS), causing oxidative stress, which also interferes with insulin signaling pathways, all leading to insulin resistance through a complex mechanism involving S-nitrosation of insulin receptors [121, 122].

Oxidative stress refers to an intracellular accumulation of ROS due to an imbalance between production of oxygen-free radicals and their removal through uncoupling mechanisms. It occurs in situations of increased oxidation of substrates such as glucose and FFA. Therefore, it has been proposed that oxidative stress may also play a role in leading to insulin resistance, and contribute to the deleterious effects of metaflammation [123].

Insulin resistance has been shown to be an independent predictor of cardiovascular mortality in patients with ESRD [124]. Obesity is associated with insulin resistance, activation of the RAAS and sympathetic nervous systems, and endothelial dysfunction to name a few all influencing the development of ESRD. As described above, when the RAAS is over stimulated and there is an increase in sympathetic stimulation, fluid and sodium retention leads to arterial hypertension. Persistence of compensatory mechanisms leads to increased glomerular wall stress, which leads to gradual loss of nephrons and eventual ESRD [125].

In better understanding these pathways and the pathophysiology of obesity, we hope to better understand the path to effective treatment plans for these patients that develop CKD secondary to obesity.

Treatment

Although we have learned much about the pathophysiology of obesity and obesity related kidney disease, and have discovered numerous possible targets for therapeutic intervention, for the most part, these have not yet translated into effective treatments. We reviewed this aspect of care recently [82]. It would be nice to report that significant progress has been made since then, but we cannot. Instead, we can report on a few interesting prospects, and emphasize the most important aspects of what we know so far.

Putative avenues of treatment for obesity related kidney disease that might fall under the general rubric of "good renal care" include good blood pressure control, particularly with drugs that block the RAAS system, good glycemic control, lipid management with statins, and weight loss.

What good blood pressure control means at this time is less clear since the publication of JNC8, rather than more so [126]. There is no specific data on blood pressure goals for obesity related kidney disease in particular, and in fact, the lower goals supported by KDIGO [127] are expert opinion based, rather than evidence based, as pointed out in JNC8. Expert opinion has not yet weighed in on consideration of obesity related kidney disease as a special case, as is diabetic nephropathy, for a lower blood pressure target. And the use of RAAS blockade, though supported in many sources for renal protection in a general way, and sensible based on our understanding of the pathophysiology of obesity related kidney disease, is not specifically supported by clinical evidence.

Regarding glycemic control, there are two pharmacologic bases for intervention that might prove especially beneficial. The thiazolidinedione pioglitazone has been found to reduce oxidative stress and to down regulate PPAR-γ [128], in addition to its glycemic effect. Furthermore, thiazolidinedione has been shown to possibly increase adiponectin levels and antagonize the effects of TNF-α [129]. Adipocyte complement-related protein has been shown to increase in concentration when a PPAR-γ agonist is given and its increase leads to insulin sensitization [130]. In addition, metformin decreases obesity-induced renal injury in mice by mitigating systemic inflammation and insulin resistance, and upregulating the renal AMPK/ACC pathway, theoretically enhancing renal response to stress; [131] however, this has yet to be demonstrated in humans. For neither of these drugs are the beneficial effects mediated by or dependent upon simply their hypoglycemic properties.

There is interesting animal data on the inhibition of lipid accumulation within renal tubules of obese mice by statins, suggesting yet another pleiotropic effect of these drugs that would be of particular benefit in the current context [132]. The suggestion of this study is that hydrophilic statins have potential benefit for obesity related kidney disease through a direct tubular effect, in addition to the systemic benefit of lowering low-density lipoprotein (LDL) cholesterol. This hypothesis is currently under exploration in a prospective human trial in Japan [133].

Some of the agents under investigation and previously reviewed for their potential in disrupting oxidative or inflammatory pathways include pentoxyfilline [134], trigonelline [135, 136], pimagedine [137], and alagebrium [138, 139], among others. An important target for such interventions remains the receptors for advanced glycation end products [140]. One of the more recent pathways targeted for intervention is the DPP4 pathway, activating the immune system when stimulated by high fructose and high fat intake; and the DPP4 inhibitor MK0626 has been shown in mice to suppress inflammation, glomerular and tubular injury in the mouse kidney [141].

The new knowledge about the Fetuin-A pathway and the IKK and JNK pathways of metaflammation create speculation about new targets for intervention. But as the disappointing experience with bardoxolone, which was investigated for diabetic nephropathy in Stage 4 CKD, has demonstrated [142], it can be difficult to intervene in intermediate pathways without creating ripples elsewhere throughout the system that might disallow the use of such an agent.

Perhaps more interesting because of their novelty and their seemingly organic nature are interventions aimed at restoring natural homeostasis, such as restoring balance in the microbiome. The use of probiotics has crossed out of the confines of pure GI disease, and now is being investigated for their global connections to health, including obesity related kidney disease [143, 144]. There is even speculation that fecal transplantation might be of benefit in normalizing the metabolic abnormalities underlying obesity related kidney disease [145, 146].

We and others have reviewed the potential benefit of bariatric surgery [147]. This remains an option for those individuals with morbid obesity; but in terms of public health mandates, this must be considered a niche population, and will not be the main thrust of effort on the part of the medical community [148].

But the most likely interventions that will prove to be useful in this condition are those aimed at lifestyle, especially weight loss and prevention of obesity. There is little specific information regarding particular lifestyle interventions that will be of specific renal benefit. One particular dietary intervention under investigation is a diet high in amylose cornstarch [149]. Although this data is still being studied in animals, the nutritional principles it suggests—preservation of intestinal mucosal barriers, preservation of a healthy microbiome, and mitigation of metaflammation/inflammation by a diet high in fermentable fiber—is interesting in its implications for human application.

Prospective controlled data on treatment and prevention of obesity related kidney disease are hard to come by, but short-term results are beginning to appear [150]. There is widespread acknowledgement that the real answer to the rising epidemic of obesity related kidney disease is less likely to be new specific pharmacologic or surgical interventions, or even specific single-agent dietary manipulations. Rather, it is becoming an issue of public health importance, and the most appropriate interventions will probably be broad based dietary practices that impact populations, not just patients [148, 151, 152]. As clinicians, it does not behoove us to wait for such results before we take appropriate actions with our patients.

Conclusion

Overweight and obesity have been linked to more deaths throughout the world than underweight. Obesity is preventable [1]. We propose that through mechanisms a-f shown schematically in Fig. 14.1, metaflammation develops in the setting of obesity and leads to insulin resistance. Obesity itself, metaflammation, and insulin resistance all have been implicated in

the development of proteinuria and eventual ESRD. The area in which research is needed is in therapeutic options. It has been well established that weight loss is the primary treatment, but it is a difficult task for individuals to accomplish. Therefore, more research is needed in pharmacological agents as well as possible mechanisms for prevention, and greater efforts at the public health level for control and prevention of obesity are needed.

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Polycystic Ovary Syndrome and Obesity

15

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Introduction

The importance of obesity rests in its clinico-pathological sequelae, which are far-reaching, and affect virtually every tissue of the body. It is these sequelae that contribute towards the ever-burgeoning obesity epidemic, through effects on morbidity, premature mortality, psycho-social functioning, work productivity and healthcare expenditure. Polycystic Ovary Syndrome (PCOS) is commonly associated with obesity in reproductive-age women [1–4].

PCOS is the commonest endocrine condition to affect reproductive-age women. Its prevalence varies between studies, but has been estimated at 6–10 % of pre-menopausal women [5–7], a figure that is likely to increase in the future as the global obesity epidemic ensues. The cardinal characteristics of PCOS, and those that form its diagnostic criteria include oligo-amenorrhoea (irregular and infrequent or absent menses) and hyperandrogenic features (hirsutism, acne, androgenic alopecia, or biochemical evidence of raised androgens such as testosterone) [4]. Although not a diagnostic feature, an important aspect of PCOS is its association with metabolic aberrations that include insulin resistance, dyslipidemia, non-alcoholic fatty liver disease [8] and a higher risk for developing Type 2 Diabetes Mellitus (T2DM) [9]. Obese women with PCOS generally manifest a metabolic 'double-whammy', resulting from effects of PCOS *per se* (that is associated with insulin resistance, independent of co-existent obesity) and obesity [4, 10]. Insulin resistance is implicated in the aetiology of PCOS, and this may explain why development of obesity (with associated insulin resistance) is usually required to unmask the clinical and biochemical features of PCOS [4, 11], and why PCOS often becomes manifest during adolescence [4]. It is also apparent that Obstructive Sleep Apnoea (OSA) (see also chapter 10 to be filled later), a condition that is associated with insulin resistance independent of fat mass, is common in women with PCOS, with risk of OSA being five- to tenfold higher in PCOS than in BMI-matched control women [12]. Furthermore, the increased risk of early-onset impaired glucose tolerance (30–40 %) and T2DM (10 %) in women with PCOS, may be further heightened through concurrence with OSA

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[12, 13]: PCOS, obesity and OSA representing a metabolic 'triple-whammy'.

In this chapter, the complex links between obesity and PCOS will be explored. This will include: analysis of evidence to support a link between obesity and PCOS; discussion of the role of fat in the manifestation of PCOS through effects on insulin resistance, steroid metabolism and adipokines; exploration of the heterogeneity of cardio-metabolic risk factors in PCOS; outline of fat distribution in PCOS, and review of the treatment strategies for obese women with PCOS.

Linking PCOS with Obesity Through Epidemiology and Genetics

There is clear evidence in the literature to support a link between PCOS and obesity. Epidemiological data reveal that the majority of women (between 38 and 88 %, depending on the study) with PCOS are either overweight or obese [4, 6, 7]. The link between PCOS and obesity is further strengthened from an aetiological perspective, with observations that even modest weight-loss of just 5 % in obese women with PCOS can result in improvements in the clinical and biochemical features of PCOS, including menstrual cyclicity, fertility, hirsutism and, of course insulin resistance and other cardio-metabolic risk factors [1, 2]. More recent evidence to corroborate the epidemiological and aetiological links between PCOS and obesity comes from genetic studies.

Following a genome-wide association study (GWAS) on obese subjects with T2DM versus controls, *FTO* (fat mass and obesity-associated gene) was the first gene demonstrated to have a robust effect on susceptibility for development of common polygenic obesity [14, 15]. Variants within *FTO* are known to influence fat mass, with a per-allele difference in BMI of approximately 0.36 kgm^{-2} [14]. Given that development of T2DM is influenced by fat mass, it was hypothesized that *FTO* variants contribute to susceptibility for development of T2DM (Odds Ratio [OR] 1.27) via effects on fat mass [14]. Given that PCOS development is also influenced by fat mass, our own group conducted a study on 463 UK PCOS cases compared with >1300 UK female controls, with genotyping of the rs9939609 single nucleotide polymorphism within *FTO* [11]. We demonstrated a significant association between this *FTO* variant and PCOS-status (OR per minor allele copy 1.30), attenuated by adjustment for BMI between cases and controls. In this study, we demonstrated the first genetic evidence to corroborate a mechanistic link between PCOS and obesity [11]. Association between variants in *FTO* and PCOS have since been confirmed in other studies from diverse populations [16–18]. As demonstrated in our study [11], it would appear that the association of *FTO* variants with PCOS is influenced by the disparity of BMI between cases and controls, further supporting mediation of effects of *FTO* through fat mass.

As outlined in the introduction, obesity is neither necessary for PCOS to develop (a minority of women with PCOS are lean), nor is PCOS an inevitable consequence of obesity (indeed, most obese women do not develop PCOS). Our current understanding, based on the known heritability of PCOS [19–21] and the epidemiological studies outlined above, is that two factors are usually required for manifestation of PCOS: (i) an underlying genetic susceptibility (likely oligogenic), and (ii) weight gain and obesity. This dual perspective would explain why not all obese women develop PCOS, this condition only manifesting in those women who are genetically predisposed to its development. In this sense, PCOS is analogous to the development of T2DM, which typically manifests following development of weight gain-related insulin resistance in those who are genetically predisposed.

Fat as a Contributor to Development of PCOS

Weight-gain and obesity are important prerequisites for manifestation of PCOS in most women who are genetically predisposed to its development. The mechanisms implicated warrant further discussion. In this section, we explore two important consequences of increasing

adiposity: enhanced insulin resistance and its effects on steroid metabolism and adipokines. For each, we discuss current evidence to support mediating roles in the development of PCOS.

Fat and Insulin Resistance in PCOS

PCOS is associated with insulin resistance [22] and between 50 and 90 % of women with PCOS are insulin resistant beyond that what would be expected in age- and BMI-matched control women without PCOS [23–25]. Insulin resistance results in compensatory hyperinsulinemia, which in turn has pleiotropic effects on peripheral tissues including ovary. Insulin has co-gonadotrophic effects within ovarian theca cells, interacting synergistically with luteinising hormone (LH) [26–28]. The synergy of insulin and LH (through activation of CYP17 [P450c17α], a key enzyme in ovarian androgen biosynthesis), results in enhanced generation and release of androgens [29]. Insulin also causes arrest of pre-antral follicle development [30, 31]. Through these mechanisms, insulin promotes hyperandrogenemia and menstrual disturbance respectively. Conversely, improvement in insulin sensitivity in PCOS (with a resulting fall in serum insulin levels) either through drug therapy or weight-loss results in improved metabolic profile, ovulatory function, menstrual cyclicity and fertility [2, 4, 32]. Thus, as with metabolic syndrome [33], insulin resistance (which is worsened by weight-gain) is believed to underlie aetiology of PCOS [4].

In addition to ovarian effects, insulin has been shown to enhance LH pulse amplitude in pituitary tissue in rodent models [24, 34]. There is also evidence in PCOS to implicate insulin in stimulation of adrenal P450c17α activity [29], and suppression of hepatic sex hormone binding globulin (SHBG) production [35, 36]. Such peripheral non-ovarian effects of insulin in PCOS would be expected to further exacerbate hyperandrogenemia through enhanced LH-stimulation of ovarian androgen production, enhanced adrenal androgen production, and an increase in free (biologically available) testosterone. Such ovarian and non-ovarian insulin-related mechanisms explain how hyperandrogenic features in PCOS become manifest with weight-gain and associated worsening of insulin resistance and serum insulin levels.

The adverse effects of raised serum insulin in PCOS, as outlined above, of course are dependent upon functioning insulin receptors and pathways. This raises an apparent paradox given that PCOS is an inherently insulin resistant condition. Understanding the molecular mechanisms involved provides resolution of this apparent paradox. Following stimulation of its receptor, insulin mediates its cellular functions via two key pathways, each having specific and disparate functions. These are the phosphatidylinositol 3-kinase (PI3-kinase) and mitogen-activated protein kinase (MAP kinase) pathways. The PI3-kinase pathway mediates metabolic effects of insulin within the cell (including glucose disposal into skeletal muscle). Conversely, the MAP kinase pathway mediates cell growth and steroidogenic effects [37]. In women with PCOS (analogous to T2DM), aberrant PI3-kinase pathway functioning pertains, whereas the MAP kinase pathway remains relatively intact [4]. Therefore, although resistance to the metabolic effects of insulin exist in PCOS, the compensatory hyperinsulinemia that ensues stimulates concurrently the intact steroidogenic post-insulin-receptor pathway [38]. A more accurate depiction of PCOS is that: this is a condition associated with concurrent but divergent responses to insulin, with resistance to its metabolic effects and sensitivity to its steroidogenic effects. What ensue are metabolic aberrations in the context of hyperandrogenemia and reproductive dysfunction: the quiddity of PCOS.

Fat, Steroids and Adipokines in PCOS

Enhanced steroidogenesis is a key component of pathogenesis of PCOS. Steroidogenic pathways in PCOS appear to be influenced by adiposity. In the largest study to date on urinary steroid profiles in women with PCOS (n = 178) compared with 100 BMI-matched control women, our own group demonstrated a clear association of PCOS with enhanced

5-alpha reductase activity [39]. We also demonstrated, in both the PCOS and control group, that 5-alpha reductase activity associates with increasing adiposity [39]. Enhanced 5-alpha reductase activity (expressed predominantly within the skin and the liver) has two main effects: (i) conversion of testosterone into a more androgenic product (5-dihydroxytestosterone), thereby contributing towards the association between weight gain and androgenicity in PCOS, and (ii) conversion of cortisol into its breakdown products. This second effect results in diminished negative feedback at the level of the pituitary, and enhanced hypothalamo-pituitary adrenal (HPA) activity. This over-drive of the HPA axis results in enhanced adrenal steroid (including androgenic steroid) production, thereby further contributing towards association between adiposity and androgenicity in PCOS [39].

A further mechanism whereby adiposity contributes towards development of PCOS is through effects on adipokine release [40]. One of the most studied adipokines in PCOS is adiponectin, with >30 (mostly observational) studies published to date. In a meta-analysis on >3400 subjects, serum adiponectin levels were shown to be lower in PCOS than in control women, following adjustment for BMI [41]. As adiponectin is known to inhibit androgen production from ovarian theca cells [42], suppressed adiponectin levels in PCOS may allow enhanced ovarian androgen production [40]. Consistent with this hypothesis, linking adiponectin with the androgenicity of PCOS, are data from a study on 56 pubertal girls with Type 1 Diabetes Mellitus, in which reduced levels of adiponectin correlated with increased levels of testosterone and ovarian volume [43]. In addition to effects on androgenicity, reduced levels of adiponectin may also contribute towards insulin resistance in this condition [41]. It should be noted, however that there is controversy regarding the role of total adiponectin versus high molecular weight (HMW) adiponectin in influencing insulin sensitivity, and that HMW adiponectin (a component of total adiponectin) may be more closely associated with insulin sensitivity in humans [44, 45]. In a study on 50 women with PCOS versus 28 control women, our own group showed equivalent levels of HMW adiponectin between the two groups, following adjustment for fat mass and age [46]. The androgenic and metabolic effects of lowered adiponectin levels in PCOS, the mechanisms implicated and how these relate to the components of adiponectin (specifically HMW-adiponectin) should be areas for further better-focused studies.

Visfatin is another adipokine that may be implicated in development of PCOS [40]. Visfatin is a multifunctional protein implicated in metabolism, inflammation and development of insulin resistance [40, 47]. In a study on lean PCOS versus controls, higher levels of visfatin were demonstrated in the women with PCOS [47]. Other studies have confirmed higher levels of visfatin in PCOS than in control women matched for age and BMI [48, 49] and in studies on an Asian population [50]. There is therefore ample evidence from clinical studies for an association between PCOS and elevated visfatin levels. There is also evidence for association between PCOS and elevated levels of resistin [51]. Evidence for a potential role of resistin in promotion of hyperandrogenemia in PCOS comes from demonstration of enhanced activity of 17 α-hydroxylase (an enzyme implicated in ovarian steroidogenesis) activity in cultured human theca cells from women with PCOS, in the presence of resistin and forskolin or a combination of resistin, forskolin and insulin [51].

Weight gain, adiposity and development of PCOS are inextricably linked. The epidemiology of this association and evidence for involvement of genetic factors has been outlined earlier. In this section, some of the mechanisms that mediate effects of weight gain and obesity on development of the cardinal metabolic, hyperandrogenic and reproductive components of PCOS have been explored. These mechanisms implicate insulin resistance, steroidogenesis and adipokines.

Cardio-Metabolic Risk Factors Across Phenotypic Subgroups of PCOS

Compared with BMI-comparable control women, metabolic syndrome is commoner in women with PCOS, and has been estimated at 34–46 %

of US-based white women with PCOS using National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) criteria [9]. The risk of developing T2DM is also greater in PCOS [10]. Although PCOS is clearly associated with cardio-metabolic risk, it is unclear whether this actually translates into future increased risk of cardiovascular events (which would require a long-term prospective study) [4]. It would seem reasonable though, given the translation of cardio-metabolic risk into future cardiovascular events in the general population that the same correlation would pertain in PCOS [4]. Given this reasonable assumption, it is important to ascertain any heterogeneity of cardio-metabolic risk across the Rotterdam-defined [52] phenotypic subgroups of PCOS, so that appropriate screening and management of such risk is apportioned appropriately, and based on best evidence.

Application of the 'Rotterdam' diagnostic criteria for PCOS [52] leads to emergence of four distinct phenotypic subgroups: 'HO', 'PHO', 'PH' and 'PO' H = hyperandrogenism; P = polycystic ovarian [PCO] morphology; O = oligoamenorrhoea. It is important to explore and compare cardio-metabolic risk between these subgroups, particularly with regard to the controversial 'PO' subgroup, given that by definition this subgroup displays normal androgens. We reported data on 309 UK-based Europid women with Rotterdam-defined PCOS [52, 53]. Subgroups included 'PHO' (n=191), 'PH' (n=76) and 'PO' (n=42) and data were compared with those from control women (n=76) [53]. We demonstrated clearly that insulin resistance is confined to women in the 'PHO' subgroup, even following adjustments for BMI and age [53]. Conversely, women in the 'PH' and 'PO' subgroups were metabolically-equivalent to women in the control group, with comparable insulin sensitivity [53]. There was also a preponderance of metabolic syndrome in women from the 'PHO' subgroup [53]. Many other reported studies on women with PCOS from diverse populations have demonstrated consistent results, both in terms of metabolic normality (including insulin sensitivity) of the 'PO' subgroup [54–57] and insulin resistance of the 'PHO' subgroup [58, 59]. A large study in a Chinese population of PCOS cases (n=719) and control women (n=85) also showed consistent patterns of metabolic profile across the phenotypic subgroups [60]. It would seem reasonable to conclude on the basis of current evidence that insulin resistance and metabolic dysfunction in PCOS is heterogeneous and predictable based on Rotterdam-defined phenotypic subgroup [52]. Insulin resistance and metabolic aberrations in PCOS are more prevalent in the majority subgroup of women who manifest the cardinal dual clinico-biochemical reproductive and hyperandrogenic features with PCO morphology ('PHO'). Conversely, those women who display either reproductive or hyperandrogenic features (without the other) are more likely to be metabolically normal and insulin-sensitive.

A limitation of the studies outlined above is their retrospective and 'snap-shot' approaches. Although the literature is clear regarding the heterogeneity of cardio-metabolic risk factors amongst women with PCOS within specific phenotypic subgroups at any one time, what is unclear is the translation of such heterogeneity into differences in cardiovascular outcomes over the longer-term. This will require longitudinal studies, where women with PCOS in each phenotypic subgroup are followed-up prospectively over many years. Such a study would also enable tracking of women over time, to explore migration between phenotypic subgroups, in which predictors and metabolic implications of such migrations would emerge.

To summarise this section, we have learnt that insulin resistance and other metabolic aberrations are heterogeneous across the phenotypic subgroups of PCOS. We have also learnt that insulin resistance is an inherent feature of 'PHO'-PCOS compared with BMI-adjusted control women.

Fat Distribution in PCOS

Visceral adipose tissue is known to be associated with metabolic aberrations including insulin resistance, through hepatic and peripheral effects of adipokines and fatty acid release [61–63]. It is important to explore the possibility that differences in visceral fat quantity and fat

distribution between PCOS and control women contribute towards disparity in insulin resistance between these groups [40]. Such a hypothesis, promoted by some researchers [64], is based on studies using imaging techniques such as lipometer [65], ultrasound [66], and dual-energy X-ray absorptiometry (DEXA) [67, 68]. Limitations of these studies though include operator-dependence (especially ultrasound), lack of ability to discern between abdominal fat depots, and problems with image resolution [40]. Some of the studies also failed to include PCOS and controls with similar BMI [40].

To explore further the fat distribution in PCOS, our own group employed Magnetic Resonance (MR), with the advantage of highly-resolved images and clear delineation of fat depots [69]. In this study, we compared 22 obese BMI- and fat mass-matched pairs of PCOS and their controls. Measurements were taken from cross-sectional areas of fat depots based on axial MR images at anatomically pre-defined sites [69]. Fat depot areas (including visceral and abdominal and gluteal subcutaneous depots) were equivalent between women with PCOS and control women [69], despite the PCOS group being significantly more insulin resistant than controls. Data from our study [69] were corroborated by data from a subsequent MR-based study on abdominal fat depots in 31 age- and BMI-matched pairs of PCOS cases and controls (BMI range: 19–41 kgm^{-2}). Volumes and distributions of abdominal fat depots were equivalent between groups [70]. In a further smaller MR-based study on ten lean BMI-matched pairs of PCOS and control women, there was a tendency for women with PCOS to have less visceral fat than control women [71].

It would appear therefore that women with PCOS appear to manifest global adiposity, with similar distribution to BMI-matched control women. Data from our own study [40, 69], corroborated by a large DEXA-based study on women with PCOS (n = 110) and weight-matched control women (n = 112) [72], demonstrate a similar relationship between increased fat mass and abdominal fat in women regardless of whether or not they have PCOS. Although differences in eutopic fat distribution between PCOS and control women do not appear to explain why PCOS is an inherently insulin resistant condition, it remains possible that differences in ectopic fat pertain in PCOS, and this should be a focus for further MR-based studies.

Treatment Strategies for Obese Women with PCOS

Unfortunately, many of our current therapies for PCOS provide little more than a 'medical sticking plaster'. Menstrual cyclicity can be improved through use of combined oral contraceptive pill (cOCP), and there are various therapies for hyperandrogenism [4]. However, there are serious concerns regarding use of cOCP in obese women with PCOS that include heightened risk of thromboembolism [73]. Furthermore, anti-androgenic drugs (such as spironolactone and finasteride) generally confer risk of teratogenicity [74]. As a result of our incomplete understanding of pathogenesis of PCOS, and our lack of armamentarium in this clinical arena, we do seem limited in our treatment options for PCOS, with current therapies informed and directed generally by patient-specific priorities (including fertility, menstrual cyclicity and hyperandrogenic features).

There is a clear need for development of novel therapies for PCOS that can target underlying pathogenic mechanisms, and accordingly would address the triple problems of hyperandrogenism, reproductive, and metabolic features that characterize this condition. In this chapter, the evidence linking weight-gain and obesity with development of PCOS has been explored. However, there is also good evidence that weight loss (even as little as 5 %) can translate into significant improvements in menstrual cyclicity, fertility, insulin resistance and hyperandrogenic features in those women who already manifest established PCOS [4]. This scenario is similar to the clinical improvements with weight-loss of other obesity-related conditions, including T2DM and OSA [75]. Given the close association between weight gain and obesity with development of PCOS, it should not be a surprise that the reverse is also

true. It should also not be a surprise that weight-loss remains the most important and key therapeutic strategy for obese women with PCOS. Losing weight is, however, not easy. Weight-loss through lifestyle implementation is largely focused on dietary modification [76, 77]. Unfortunately, to maintain any weight loss, activity levels necessarily need to increase and this can be difficult to implement on a regular basis [78]. Women with PCOS often suffer from low self-esteem and other mental health problems such as depression that conspire to cause loss of interest in exercise and other forms of outdoor activities [79]. Although therapies such as metformin can be considered for management of metabolic dysfunction in PCOS [80], there are very few therapies currently licensed for weight-loss, with little evidence for use in context of PCOS [81]. Although currently unlicensed for use in obese women with PCOS (at the time this chapter was written), there is some evidence to support effective weight-loss with Glucagon Like Peptide-1 (GLP-1) agents in this group [82]. Future therapeutic innovations for women with PCOS should focus on novel strategies for establishment, and maintenance of weight-loss.

An interesting future target for weight-loss therapeutics in PCOS and one that holds great potential is human brown adipose tissue (BAT). Physiologically, BAT functions in an antithetical way to white adipose tissue (WAT). Instead of storing energy as fat, BAT burns energy through uncoupling oxidative phosphorylation, thereby releasing heat in the process [83]. The discovery of active BAT in human adults a few years ago resulted in a re-awakening of interest in this field [84]. From a metabolic perspective, BAT activation confers favorable effects on glycaemia, lipid profile and fat mass through burning off calories. It has been estimated that a sugar-cube volume of BAT, if activated for a year would burn its way through between 3 and 4 kg of WAT [85]. Therapeutic strategies implicating BAT might include augmentation of BAT mass through stem cells or trans-differentiation from WAT into 'beige' cells (with functionality similar to BAT), or alternatively activation of existing BAT depots. The study of human BAT is in its infancy, and there are many important questions that need to be addressed as a priority. One such question relates to how many of us have any BAT. Our own group is tackling this through use of a type of MR to image human BAT: we recently published the first proof of concept paper using MR to image BAT in a living human adult using histological and immunohistochemical verification [86]. We hope to develop this technique as a radio-quantifier for BAT content in humans.

In the context of obese women with PCOS (and obesity *per se*), a therapy that facilitates enhanced energy expenditure through BAT augmentation and activation would represent a novel weight-loss, anti-glycemic and anti-lipidemic therapy to complement other lifestyle measures such as dietary modification. Such a therapy, through enhancement of energy expenditure, could provide a 'metabolic panacea' in obese women with PCOS and would also facilitate maintenance of weight-loss. A BAT-enhancing therapy would act independently from reproductive and steroidogenic pathways thereby facilitating complementarity with other therapies, and would represent a significant breakthrough in the effective management of PCOS and other weight-related conditions. Until such a therapy is developed, we will have to persist with traditional weight-loss strategies that include lifestyle (including dietary) measures and of course the option of bariatric surgery.

Concluding Remarks

Obesity and PCOS are inextricably linked. A major challenge for the future is to disentangle the complex mechanisms that weave together these two clinical entities of obesity and PCOS. Our current understanding of PCOS is that its clinico-biochemical manifestation usually depends upon a diverse aetiology. It is clear that genetics plays an important role [87]. The first pathogenic pre-requisite scenario is therefore a genetic (likely oligogenic) predisposition towards future development of PCOS. The second pre-requisite scenario for development of PCOS is subsequent weight-gain (often resulting in

obesity) occurring against this genetic backdrop of predisposition to PCOS [4]. Of course, this view is necessarily over-simplified in that exceptions exist: not all women with PCOS are obese. Therefore, in a lean subgroup of PCOS the presumption is that genetic predisposition is such that PCOS will become manifest regardless of future weight gain. This hypothesis is further complicated by recent emergence of potential role of epigenetics in the pathogenesis of PCOS [88]. It is apparent however, given the strong links between obesity and PCOS outlined in this chapter, that weight-gain is necessary for the manifestation of PCOS in the majority of women with this condition. We will perhaps never know how many genetically-predisposed women 'escape' development of PCOS through avoidance of weight gain during their reproductive years. It is clear, however that weight gain *per se* in women is not sufficient for features of PCOS to become manifest in that not all obese women develop PCOS: some women are presumably genetically protected from developing PCOS regardless of how much weight they gain (much in the same way that a subgroup of people seem protected from development of T2DM following weight gain). The situation becomes even more complex when one considers that BMI itself is also heritable. Given that PCOS is associated with obesity, and weight gain is on a pathogenic pathway for PCOS, it is possible that at least some of the genetic predisposition for PCOS is mediated via genetic association with a gain in fat mass. The study outlined above on *FTO* variants in PCOS supports this view [11]. Similarly, genetic variants that influence insulin resistance may also be implicated in development of PCOS. Future genome-wide association studies will shed novel insights into pathogenesis of PCOS and also provide direction for future therapeutic targets.

Unfortunately, the name 'Polycystic Ovary Syndrome' belies its strong association with obesity and cardio-metabolic risk. Shakespeare said 'What's in a name?' That which we call PCOS by any other name would maintain intrigue and inner beauty. To the uninitiated though, and even to some healthcare professionals, the term 'PCOS' does what it says on the tin, and may imply to them little more than a few ovarian cysts. It has been suggested that the name 'PCOS' be changed to 'female metabolic syndrome' or 'syndrome XX', to reflect its cardio-metabolic aberrant associations [89]. Whether its name is eventually changed or not, what is important is that all those involved in the management of PCOS, appreciate its importance as a condition with often profound implications and consequences for the patient, their partner, friends and family: a condition comprising multidimensional reproductive, hyperandrogenic and metabolic aberrations, with broader implications for mental health and psycho-social functioning [90]. In a sense, the name 'PCOS' is the door that Alice entered, leading into a world of edificial proportions. Like Alice, we are only just beginning to understand this complex world beyond the door. Given that our genetic constitution is unlikely to change radically over coming years, the ever-burgeoning obesity epidemic will ensure that numbers of women developing PCOS will continue to rise globally. Whilst it is not too late to act, there is a danger of doing too little too late, and that, like Rabbit, we will collectively peer at our waistcoat watches with lateness anxiety in future. Let us avoid this grim scenario by acting NOW, to give PCOS and obesity the respect they deserve, to develop novel and effective therapies that include weight-loss strategies, and to mitigate the potentially devastating impact of an impending tsunami of obesity-associated and PCOS-related sequelae.

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Obesity and Cancer

16

Xiang Zhang, William K.K. Wu, and Jun Yu

Introduction

During the past several decades, the proportion of populations that is overweight (≤25 body mass index (BMI) <30 kg/m^2) or obese (BMI ≥30 kg/m^2) has increased markedly [1]. It is undoubtedly related to changes in lifestyle that affects the diet and physical activity. Nowadays, more than one-third of the adult populations in developed countries are obese [2]. Obesity which is a preventable cause of illnesses if remains uncontrolled contributes to premature mortality and metabolic complications [3]. Obesity and overweight account for 2.8 million adult's death each year, making it the fifth leading risk for overall mortality. In addition to the increased risk of cardiovascular disease and Type 2 diabetes mellitus, morbid obesity seems to be a significant risk factor for several malignancies, including hepatocellular carcinoma (HCC), esophageal adenocarcinoma, endometrial, gallbladder, and renal cancer [1, 4, 5]. The increased BMI has also been identified to be associated with an increased risk of colorectal, breast, pancreatic and thyroid cancers [1]. From National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) data, it has been estimated that about 7 % new cases of cancer in women and 4 % in men were due to obesity in the United States, while the percentage increased to 40 % for endometrial cancer and esophageal adenocarcinoma. Moreover, obesity is linked to poorer treatment outcome, worse prognosis and increased cancer-related mortality. It has been reported that excess body weight leads to 1.52-fold and 1.62-fold increases in the relative risk of cancer-related death in men and women, respectively [5]. High rates of death from HCC, colorectal, esophageal and breast cancer were associated with obesity [5].

How Obesity and Cancer are Linked?

The molecular mechanisms underlying the connection between obesity and cancer are complex. It has been recognized that increased lipid accumulation, inflammatory process, insulin resistance and adipokines could contribute to obesity-associated cancer.

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Lipid Accumulation

Lipid accumulation in obesity may influence cancer pathogenicity and contribute to tumorigenesis. Obesity could induce elevated lipogenesis by upregulating fatty-acid synthase (FAS) gene and activating sterol regulatory element-binding protein (SREBP), thereby promoting cancer development (Fig. 16.1). FAS is an enzyme that produces endogenous fatty acids, which could be modified into structural lipids required for cancer cell proliferation. SREBP, a master transcription factor that controls lipid metabolism, could link oncogenic signaling and tumor metabolism. In addition, the accumulated lipids in adipocytes could be transferred to cancer cells. Cancer cells can then utilize these transferred lipids as an energy source, which in turn promotes cancer cell proliferation [6].

Metaflammation

Obesity may induce metabolic inflammation (metaflammation), which is a chronic, low-grade, metabolically-linked status. This kind of inflammation is associated with cancer initiation, promotion and progression, thereby participating in the link between obesity and carcinogenesis. Macrophages, especially adipose-tissue macrophages (ATMs), are major players in this inflammatory process [7]. Chronically activated ATMs produce a wide range of cytokines, chemokines and growth factors, such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), resulting in increased cell proliferation and enhanced tumor growth. Macrophage-derived TNF-α and IL-6 promote tumor development and stimulate cell proliferation through Janus kinase/signal transducers and activators of transcription (JAK/STAT3) pathway (Fig. 16.1). Mice deficient in TNF-α receptor TNFR1 or IL-6 reduced high-fat diet (HFD)-induced liver lipid accumulation and macrophage and neutrophil infiltration in the livers, leading to ameliorated cancer development [8]. Moreover, as revealed by gene expression profiles, ATMs are similar to human tumor-associated macrophages (TAMs), which can directly affect neoplastic growth, and promote tumor invasion and metastasis [7].

Insulin Resistance

Insulin resistance, and its associated hyperinsulinemia and increased production of insulin-like growth factor 1 (IGF-1), occur in the majority of obese people. They play a pivotal role in the development of malignancy. Hyperinsulinemia in obesity leads to upregulated production of IGF-1 and activation of insulin receptor substrate-1 (IRS-1), which can activate several downstream molecules and signal pathways including mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3 kinase (PI3K)/Akt (Fig. 16.1). These pathways play a significant role in cancer development by the induction of cell proliferation and inhibition of cell apoptosis [3]. Multiple case reports and case reviews have identified a strong association of diabetes with many kinds of malignancies, including breast, endometrial, colorectal, pancreatic, and hepatocellular cancers [9]. Moreover, insulin resistance in obese states can increase the release of free fatty acids (FFAs), leading to the ectopic lipid accumulation, which in turn promotes insulin resistance further.

Adipokines

Adipokines are adipocyte-derived hormones. They have important roles in regulating metabolism and insulin resistance, contributing to chronic inflammation associated metabolic syndrome. Leptin and adiponectin are two major adipokines. In this respect, obesity is associated with increased leptin and decreased adiponectin levels and the increased leptin-to-adiponectin ratio has been implicated in tumor progression [9]. Leptin and its receptor OB-Rb can increase cell proliferation and survival in a number of malignan-

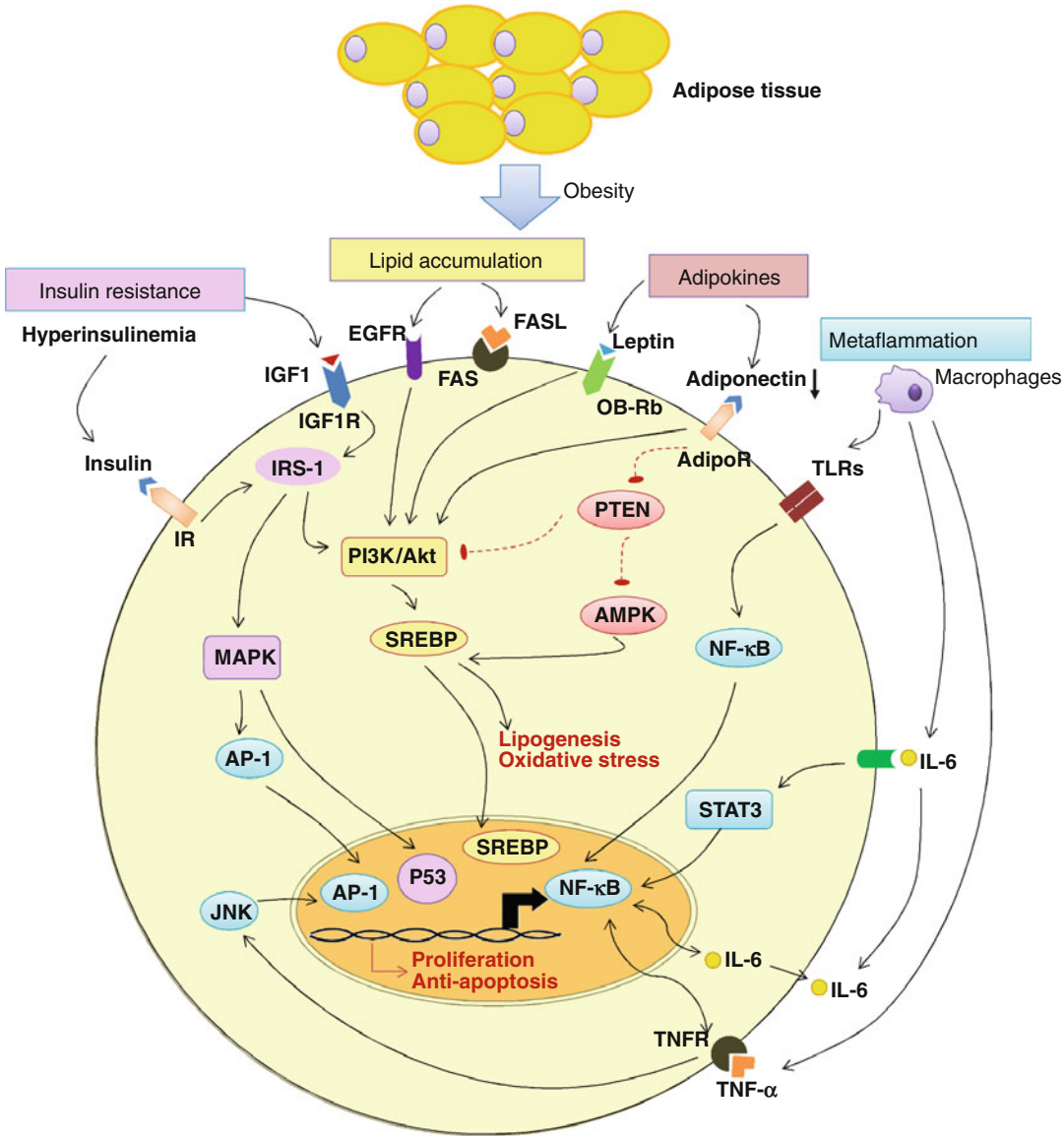

Fig. 16.1 Schematic diagram for the mechanism of obesity-derived carcinogenesis. Obesity and adipose tissue dysfunction could induce lipid accumulation by upregulating fatty-acid synthase (*FAS*) gene and activating sterol regulatory element-binding protein (*SREBP*), and trigger metaflammation through inflammatory pathways including nuclear factor kappa B (*NF-κB*) and toll-like receptors (*TLR*). The production of pro-inflammatory cytokines (*TNF-α* and *IL-6*) activates signaling pathways of JNK/STAT3, which subsequently promotes cell proliferation and anti-apoptosis effects. On the other hand, hyperinsulinemia in obesity also leads to an increased production of insulin and insulin-like growth factor-1 (*IGF-1*). Upon binding to insulin receptor (*IR*) and insulin-like growth factor-1 receptor (*IGF1R*) respectively, insulin and IGF-1 activate insulin receptor substrate-1 (*IRS-1*) and its downstream mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3 kinase (PI3K)/Akt pathways which eventually activate p53, thereby plays key roles in lipogenesis, adipogenesis and oxidative stress. Decreased adipokines in obesity can inhibit PI3K/Akt pathway via suppression of phosphatase and tensin homolog (*PTEN*) and Adenosine 5'-monophosphate-activated protein kinase (*AMPK*), leading to the tumorigenesis. Increased leptin production in obesity can also induce tumor progression through PI3K/Akt activation

cies, including breast, endometrial, ovarian, colon and prostate cancers. Leptin/Ob-Rb binding can induce IRS phosphorylation and PI3K/Akt activation, thereby promoting carcinogenesis [10]. In contrast, adiponectin may inhibit tumorigenesis through inducing apoptosis and G_1 cell cycle arrest in colon, prostate, endometrial and breast cancers. Impaired adiponectin in obesity can also promote tumor development by upregulating PI3K/AKT signaling and downregulating of phosphatase and tensin homolog (PTEN) (Fig. 16.1). Other adipokines, such as resistin, visfatin, and chemerin, are also implicated in tumorigenesis [11–13].

Obesity that Linked to Specific Cancers

Hepatocellular Carcinoma

HCC is the fifth most frequently diagnosed cancer worldwide and the second most frequent cause of cancer death in men [14]. Obesity has been associated with an increased risk of HCC, especially in men, where HCC mortality rates are five times greater than those with a normal BMI. The death rate from liver cancer in subjects with BMI ≥25 is 10.29 with relative risk (RR) 1.13 (0.94–1.34) but increased to 19.22 with RR 1.90 (1.46–2.47) in those with BMI ≥30 (Table 16.1) [5]. It is further supported by another study from Denmark that the relative risk of HCC of 40,000 obese patients increased to 1.9 compared to the general population [4].

Comparative to hepatitis B virus (HBV)- and hepatitis C virus (HCV)-induced HCC, obesity-related liver cancer could develop from non-alcoholic steatohepatitis (NASH). We have identified that obesity-associated cytokine CXCL10 accounts for NASH development [15]. NASH is the liver manifestation of metabolic syndrome, which constellates obesity, insulin resistance and dyslipidemia. It is an advanced stage of non-alcoholic fatty liver disease (NAFLD) at the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis. NAFLD is now considered as the most common cause of chronic liver disease in Western countries and Asia. It is estimated that NAFLD is prevalent in 30–40 % of the adult population in the United States. With the growing economy and lifestyle changes in Asia, the number of people diagnosed with NAFLD in Asian countries has increased from 13 % before 1990 to 30 % by 2008 with an even higher prevalence >50 % in obese children and adolescents [16]. The first stage of NAFLD is hepatic steatosis. Simple steatosis follows a relatively benign clinical course, it may progress to NASH, which can lead to cirrhosis in around one third of affected subjects. About 27 % of NASH-associated hepatic cirrhosis further progresses to HCC. Actually, NASH has been proposed in recent years to be an important causative factor of HCC. Data from

Table 16.1 Obesity increases the incidence and mortality risk of cancers

	Rank of incidence in male	Rank of incidence in female	Rank of mortality rate in male	Rank of mortality rate in female	Cancer risk by per 5 kg/m^2 increase BMI in male (RR)	Cancer risk by per 5 kg/m^2 increase BMI in female (RR)	Mortality from cancer caused by overweight (RR)	Mortality from cancer caused by obese (RR)
Liver cancer	5	9	2	6	1.24	1.07	1.13	1.90
Colorectal cancer	3	2	4	3	1.24	1.09	1.20	1.47
Esophageal cancer	7	–	6	9	1.52	1.51	1.15	1.28
Pancreatic cancer	12	12	7	7	1.07	1.12	1.13	1.41
Breast cancer	–	1	–	1	–	1.12*	1.34*	1.63

Note: RR denotes relative risk; *postmenopausal breast cancer.

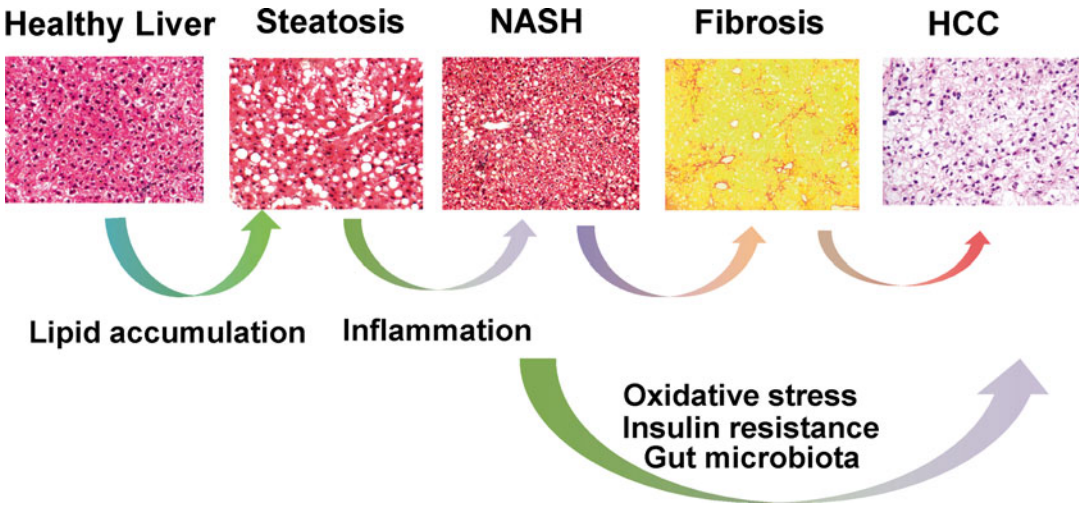

Fig. 16.2 Obesity and hepatocellular carcinoma. Mechanisms by which obesity could contribute to carcinogenesis in the liver are shown. In early stages of obesity, lipid accumulation contributes to the frequency and development of steatosis. Development of NASH was associated with chronic low-grade inflammation. The transition from NASH to tumorigenesis is believed to be mediated by gut microbiota, insulin resistance and oxidative stress

the United States suggested that although only 5–20 % of NAFLD patients progress to NASH, this still translates to nationwide incidences of 2–5 % in the general population, who are at risk of developing HCC. Large population-based cohort studies demonstrate that the prevalence of NASH-related HCC has increased fourfold compared with 2.5-fold for hepatitis, making it the most rapidly growing indication for liver transplantation [17]. Indeed, it is anticipated that with the steadily increasing prevalence of obesity, diabetes coupled with metabolic syndrome, a large proportion of the general population will be at risk of developing NASH and the related cirrhosis, and ultimately HCC (Fig. 16.2).

The underlying mechanisms especially the genomic and metabolic perturbations linking obesity associated-NASH to HCC are complex and still elusive. Despite a strong association of HCC development from NASH-associated cirrhosis, accumulating evidence from clinical cases and experimental models suggest that NAFLD itself could promote HCC in the absence of cirrhosis [18]. NAFLD-related HCC could take place in earlier stages of NAFLD. Indeed, 10–75 % of the NAFLD-related HCC arose from non-cirrhotic livers. Nowadays, NAFLD-induced HCC is thought to be resulted from a series of steps that begin with lipid accumulation in the liver followed by peroxidation of these lipids, thus inducing insulin resistance, inflammatory cell infiltration as well as oxidative stress. Consequentially, this continuous process induces HCC development.

NAFLD and HCC may be regulated by similar signaling molecules and pathways related to inflammation. Lipid accumulation in NAFLD triggers cancer-related pathways including c-Jun N-terminal kinase (JNK), NF-κB and toll-like receptors (TLRs) signaling pathway, and overexpression of oncogenes [19]. JNK, which can regulate cell proliferation and act as oncogenes, is thought to have the most important role in both the development of NASH and HCC. The activation of JNKs and NF-κB can induce tumor progression by instigating the cross-talk between inflammatory cells and neoplastic cells [19]. Moreover, NF-κB and TLRs are critical regulators for the production of the cytokines associated with tumor promotion. Elevated levels of proinflammatory cytokines (TNF-α and IL-6) and decreased anti-inflammatory signals (adiponectin) in NAFLD may also activate oncogenic molecular pathways and promote HCC development [8]. Insulin resistance that is associated with NAFLD is another important mechanism

that may induce hepatic malignancy. In a large Veteran Affairs study, the risk of HCC doubled in patients with diabetes compared with those without [20]. A meta-analysis that pooled 13 cohort studies suggested diabetes could promote HCC before the development of cirrhosis [21]. Moreover, diabetes was still an independent risk factor for HCC in which patients with cirrhosis had been excluded [22]. Oxidative stress has been shown to go hand-in-hand with insulin resistance via a series of cytokine-mediated pathways. It is involved in all stages of carcinogenesis and may contribute to the development of both NASH and HCC. Oxidative nuclear DNA damage, formation of mitochondrial DNA damage and mutation and alternation of mitochondrial genomic functions have been revealed to contribute to the process of HCC. Dysfunction of endoplasmic reticulum (ER) stress induced by fatty acids enhanced reactive oxidative stress (ROS) from microsomal enzymes. ER-stress and ROS further promote inflammation, cell proliferation, or mutation of cancer-related genes. Gut microbial metabolite induced by obesity may also promote liver cancer development. Obesity can induce the alterations of gut microbiota, leading to the increased expression of deoxycholic acid (DCA), a gut bacterial metabolite known to cause DNA damage. The increased DCA provoke senescence-associated secretory phenotype (SASP), which can promote the secretion of tumor-promoting factors, thereby facilitating HCC development [23]. Taken together, besides oncogene and tumor suppressor gene mutations, multiple factors account for the development of HCC in NAFLD, including lipid accumulation, inflammation, insulin resistance, oxidative stress and gut microbiota.

Colorectal Cancer

Colorectal cancer (CRC) is the third most common cancer in males and the second in females worldwide. It's estimated 1.4 million new cases and 693,900 deaths in 2012 [24]. The risk of CRC increases with age and the lifetime risk is approximately 6 %. The relative risk attributable to obesity is 1.09 (1.05–1.13) for colon cancer and 1.02 (1.00–1.05) for rectum cancer, while the risk ratio in men of colon cancer is 1.24 (1.21–1.28) [1]. In a systematic review of eight meta-analyses and studies, obesity is closely associated with an increase of CRC (RR: 1.37–1.95), colon (RR: 1.24–1.71) or rectal cancer (RR: 1.09–1.75) in men, while the association is less in women [25]. Obesity is not only related to increased risk of CRC, but also linked to the CRC death rate. A prospective study of 900,000 adults with 16 years follow-up showed that the relative risk of mortality from colorectal cancer was 1.20 (1.12–1.30) in subjects with BMI ≥25 and 1.47 (1.30–1.66) in subjects with BMI ≥30 (Table 16.1) [5]. Studies assessing CRC incidence and mortality before and after bariatric surgery suggested that weight loss may be associated with decreased CRC incidence [25].

Obesity is not only associated with the incidence of CRC, but also related to the advanced stage and the recurrence of colon cancer. A prospective population-based study from Sweden, which included 28,098 patients, demonstrated an association between obesity and increased risk of more advanced-stage CRC (T3/T4, N1, or M1 disease), especially in men [26]. A multivariate analysis of 940 patients with CRC found that, BMI ≥30 is an independent predictor of CRC recurrence [27]. In line with this, clinical observations suggest a more severe course of CRC in patients with obesity.

Similar to other kinds of cancers, factors that relate obesity and CRC include; (i) Chronic inflammation in obese status induces the secretion of TNF-α, IL-6, thereby inhibiting cell apoptosis and promoting cell survival; (ii) Insulin resistance leads to increased insulin, IGF-1 and glucose, which may promote cell proliferation; (iii) Changes of adipokines secretion from dysfunctional adipose tissues, such as increased leptin and decreased adiponectin, could inhibit cell apoptosis, promote cell proliferation, invasion and metastasis. Apart from these factors, obesity-induced gut microbiota contributes to the pathogenesis of CRC [28]. Obesity is associated with dramatic differences in the composition of gut microbiota when compared with normal-weight individuals. The alterations of gut microbiota (dysbiotic microbiota) induce the changes

of epigenetically active metabolites such as folate. Folate is essential for DNA methylation. In obesity, folate deficiency contribute to colonic DNA hypomethylation, thereby inducing colorectal cancer development [25]. The gut microbiota can also convert the primary bile acids to secondary bile acids, which are associated with cancer development through tumor-promoting activities.

Esophageal Cancer

Esophageal cancer represents the eighth most common cancer worldwide with about 482,300 new esophageal cancer cases and 406,800 deaths occurred in 2008 worldwide. About 50 % of them are adenocarcinoma in the West. Obesity is an independent risk factor for esophageal adenocarcinoma [29]. Several large population-based, case-control studies and prospective cohort studies have showed a strong correlation between obesity and the risk of esophageal adenocarcinoma. A prospective study from United States recruited 480,475 subjects, they found that BMI was closely associated with increased risk of esophageal adenocarcinoma with hazard ratios 2.27 [30]. Another prospective cohort study of 1.2 million women in UK also showed that increased BMI was associated with an increased incidence of adenocarcinoma of the esophagus [31]. Corley et al. performed a nested case-control study of 206,974 members and showed that increased abdominal obesity was closely associated with the risk of esophageal carcinoma [32]. The prospective study of 900,000 adults with 16 years follow-up suggested that the relative risk of mortality from esophageal cancer was 1.15 (0.99–1.32) in subjects with BMI ≥25 and 1.28 (1.00–1.63) in subjects with BMI ≥30 (Table 16.1).

Although the mechanism underlying the association between obesity and esophageal adenocarcinoma are not fully understood, insulin resistance, adipokines, inflammation, sex hormones and gastric acid reflux might contribute to the link between obesity and esophageal cancer. IGF-1 pathway, which plays an important role in obesity, could regulate cell proliferation, differentiation and apoptosis. The polymorphism in the gene encoding the IGF receptor in obese subjects could affect the risk of esophageal adenocarcinoma. Altered circulating adipokines may be another mechanism linking fat and carcinogenesis of esophageal adenocarcinoma. Increased serum leptin and decreased adiponectin levels are independent risk factor for esophageal adenocarcinoma. Visceral fat has impact on tumor biology through leptin and adiponectin receptors. Low-grade systemic inflammation in obesity generates a procarcinogenic environment, which help esophageal cancer progression. Moreover, estrogen, which is inversely associated with visceral fat, is responsible for the incidence of esophageal adenocarcinoma. This can also explain the gender disparity of esophageal carcinoma in some extent.

Gastric acid reflux is another important risk factor for esophageal cancer in obese subjects. The link between obesity, gastro-esophageal flux, Barrett's esophagus and esophageal cancer has been well established. In a meta-analysis of nine studies regarding the association between obesity and the risk for gastroesophageal reflux disease, the pooled adjusted odds ratios for gastro-esophageal flux is 1.43 (95% CI: 1.158–1.774) in overweight subjects (≤ 25 body mass index (BMI) <30 kg/m^2) and 1.94 (CI: 1.468–2.566) in obese patients (BMI ≥30 kg/m^2) [33]. This suggests that the risk of gastro-esophageal flux is progressively increased with increasing weight. The gastro-esophageal flux in obesity may induce the normal esophageal mucosa progression to Barrett's change, dysplasia and eventually carcinoma. Barrett's esophagus is a precursor lesion metaplastic change from squamous epithelium to stratified columnar epithelium with goblet cells. It has the potential for neoplastic change. Positive association between visceral adipose tissue, central obesity and Barrett's esophagus has been reported, particular in younger patients [34].

Pancreatic Cancer

Pancreatic cancer is one of the most lethal cancers worldwide. Although its incidence is not that high, the 5-year survival is estimated to be 6 %. Due to lack of early diagnosis approach, most

patients are diagnosed with advanced stage and 75 % die within 1 year. Identification of the risk factors is of high clinical significance to establish effective prevention methods. Recent studies have identified that obesity is an important risk factor for the incidence of pancreatic cancer [35]. A pooled analysis of 14 cohort studies of 846,340 individuals showed that obese patients have 47 % higher pancreatic cancer risk compared to individuals with normal BMI [36]. Moreover, individuals who had gained BMI >10 kg/m^2 showed 40 % higher risk of the incidence of pancreatic cancer [36]. A meta-analysis study of six case-control and eight cohort studies involving 6391 pancreatic cancer patients showed that the relative risk per unit increase in BMI is 1.19 (95% CI: 1.10–1.29) for obese people compared to people with a normal body weight [37]. Obesity are not only associated with increased incidence of pancreatic cancer, but also related with pancreatic cancer survival. However, the association of obesity and pancreatic cancer survival is controversial. Some studies reported that obesity linked to worse prognosis of pancreatic cancer, while some studies demonstrated no association between obesity and pancreatic cancer survival [38, 39]. One study found an improved long-term survival in obese patients undergoing pancreaticoduodenectomy for pancreatic cancer [40].

The mechanisms that linking obesity to pancreatic cancer include insulin resistance and adipokines (leptin and adiponectins). High insulin levels in obesity may promote the human pancreatic cancer cell proliferation by direct action or by indirectly increasing the substrate availability [41]. Increased IGF also contribute to the progression of pancreatic cancer through cell proliferation and angiogenesis. Altered levels of adipokines are also associated with pancreatic cancer. Increased leptin and decreased adiponectin in obese patients can influence the carcinogenesis of pancreatic cancer [35].

Breast Cancer

Breast cancer remains the most frequently diagnosed cancer and the leading cause of cancer death among females in less developed countries according to Global Cancer Statistics 2012 [24]. It was estimated that 1,676,600 new cases and 521,900 deaths from breast cancer occurred in 2012, which accounted for 25 % of all cancer cases and 15 % of all cancer deaths in females worldwide. Although an inverse association between BMI and breast cancer has been reported in premenopausal women, obesity is an important risk and prognostic factor of breast cancer in postmenopausal women. It has been estimated that the risk of breast cancer increases 3 % with each unit gain in BMI. The breast cancer diagnosed in obese patients is more likely to be at advanced stage, high grade, of large tumor size and exhibiting recurrence, metastasis and mortality. Therefore maintaining a healthy body weight may reduce the risk of breast cancer. In a pooled analysis of prospective cohort studies of 337,819 women, the relative risk of breast cancer was 1.26 (95 % CI: 1.09, 1.46) in postmenopausal women with higher BMI (>28 kg/m^2) [42]. Another population-based case-control study of 6799 women showed that women gained 30 kg body weight had an odds ratio of 2.4 (95 % CI: 1.20–3.48) of breast cancer than those who had unchanged body weight [43].

An important link between obesity and breast cancer is estrogen, which plays a role in the initiation and progression of breast cancer. In obesity, the conversion from androgen precursor androstenedione in the peripheral adipocytes to estrogen is increased, while the bioavailability of estrogen is decreased [43]. Similarly, a long menstrual history, recent use of oral contraceptives, and never having children, which maximize the number of ovulatory cycles and increase the lifetime cumulative exposure of mammary epithelium to estrogen, are also risk factors for breast cancer. Insulin resistance and increased IGF-1 in obesity have synergistic effect with estrogen in promoting mammary carcinogenesis. Chronic inflammation may drive the synthesis of estrogen through the increased macrophage forming crown-like structures (CLS) and elevated aromatase levels in the mammary glands of obese mice, thus leading to the carcinogenesis of breast cancer. CLS of breast exist in 50 % of breast cancer

patients and it's an index for breast inflammation. CLS index could link BMI and breast cancer, and act as a biomarker for the risk or poor prognosis of breast cancer [44]. Recent study has also suggested that obesity was associated with gene methylation in cancer-related genes in estrogen receptor-positive breast tumors, thereby controlling the expression of carcinogenesis-related genes [45]. That means the differences in methylation by obese status can influence breast cancer. Collectively, obesity-related estrogen, insulin resistance, breast inflammation and changes in the breast cancer-related genes are implicated in the complex effects of obesity on breast cancer incidence and outcomes.

Conclusions

Obesity is linked to the increased risk and worse prognosis of several cancers, particularly gastrointestinal cancers. The systemic and local mechanisms involved in the obesity-cancer link are complex. Obesity induced lipid accumulation, inflammation, insulin resistance, adipokines, gut microbiota and estrogen may be involved in the carcinogenesis. Preventing or reversing the obese state (weight reduction and exercise), targeting metabolic derangements associated with adipose tissue dysfunction, targeting metainflammtion and changing microbiota may be potential approaches for the intervention of cancers. Further investigation of underlying mechanisms of obesity-induced cancer is needed to allow early intervention of cancer formation and provide the opportunity of developing anti-cancer therapeutics.

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Obesity and Thyroid Cancer

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Introduction

Although during the last one decade literature has been consistently showing associations between obesity and cancers, since excessive weight is an extremely varied condition with different factors involved and a wide range of molecular factors might be implicated in this associations [1]. In addition, cancers present extremely complex and diverse pathways implicated in their occurrence and progression. Solid evidence has been presented connecting endometrial and postmenopausal breast cancers to obesity by endogenous estrogen levels [2–6]. On the other hand, literatures suggest that gallbladder, esophagus, lymphomas and myelomas might be influenced by inflammation, a very important factor in the obesity [2, 7–10]. Besides, pancreatic and colon cancers have been linked with obesity through insulin-related pathways [2, 11, 12].

Regarding thyroid tumors, the observational studies linking obesity to these neoplasms are quite convincing, showing a clear relationship between excessive weight (i.e. overweight and obesity) and thyroid cancers, especially differentiated thyroid cancers (DTCs) [13, 14]. However, literature has not yet unveiled the mechanisms behind this association and causal factor(s) has not yet been established linking DTCs and obesity.

In order to understand the possible mechanisms linking these two conditions, it is necessary to revisit some epidemiological data and molecular pathways involved in DTC and obesity; thus trying to create a rationale on how these two conditions are linked as well the possible factors that might justify this association.

Introduction of Thyroid Cancer

Obesity and overweight have long been recognized as triggers for many metabolic complications, such as hypertension, hypercholesterolemia, insulin resistance leading to Type 2 diabetes and different types of cancer. Importantly, thyroid cancer has been recoded to be worldwide increasing during the last few decades [15–19].

Thyroid cancer presents different histological types. The vast majority of thyroid carcinomas consist of two types of tumors: Papillary Thyroid

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Carcinomas (PTCs) and Follicular Thyroid Carcinomas (FTCs). These two types are derived from follicular cells and are classified as DTCs. The other types are considered rare and more aggressive. Among these are, undifferentiated or Anaplastic Thyroid Cancers (ATCs) represent approximately 1 % of all thyroid carcinomas, while Medullary Thyroid Cancers (MTCs) are derived from parafollicular cells, represent only 3 % of all thyroid carcinomas [20]. The most common are PTCs representing approximately 85 % of epithelial thyroid malignancies, and these are mostly responsible for the increase in the incidence of thyroid cancers in general [21]. They are indolent cancers and most of them do not have a considerable clinical evolution that would lead patients to death [22]. This is especially noticeable when we look into recent data showing that although the incidence of thyroid cancers has significantly increased in recent years, mortality rates remained stable, suggesting that many of these tumors possibly would not present a clinical evolution [23].

However, the reasons why DTCs' incidence has increased are not fully comprehended and lead to controversies [24]. Several authors suggest that this increased incidence is solely related to the improvement in diagnostic methods and the population's access to them, since tumors that present the highest incidence rates are those with small size, and in the past they could not be detected by the clinical examination then existed involving on neck palpation [17, 25, 26]. However, other clinicians have shown that the increased incidence is not only due to tumors size smaller than 1 cm (favored by a better image scanning) but also includes larger tumors, making it difficult to affirm that changes in DTC incidence were taking place exclusively due to improvements in diagnostic techniques and improvements in health care [27].

Hence, it is necessary to investigate other factors that may be contributing to this remarkable increase in thyroid cancer incidence. Exposure to ionizing radiation, iodine intake, family history of thyroid disease, hormonal and reproductive factors and altered thyroid stimulating hormone (TSH) levels are well-established and recognized risk factors for thyroid cancers. Recent studies moreover suggest that the genetic profile, presence of inflammation in the peritumoral area and also body mass index (BMI) should be considered as potential risk factors for DTCs [13, 19, 28]. It is to be noted that based on BMI, two terminologies have now been globally accepted for differentiating overweight and obesity. Those people with BMI of between 25 and 30 are considered to be overweight and those between 30 and 40 are obese and weight over 40 are morbidly obese. In this chapter terminology "obesity" will be used for both.

Relationship Between Obesity and Thyroid Cancer

The first obesity boom was reported during 1980s, leading the scientific community to conduct deeper investigations on obesity and its association with other diseases, mainly through observational studies. It is important to remember that there are two different types of observational studies concerning the relationship between the two conditions, obesity and thyroid cancer: (a) thyroid cancer prevalence is investigated in obese patients; (b) patients with thyroid cancer are screened for obesity. Although both approaches to give relevant information and pictures about the two conditions, the second studies needs to be evaluated more thoroughly. This is because obesity could be linked as an epiphenomenon of thyroid cancers, albeit there is no evidence that these cancers induce important metabolic syndrome. The second type of study, however, is necessary when the objectives of the study include the investigation of clinic-pathological features and their modification by other factors, such as the presence of obesity. Below the results of the studies will be presented in chronological orders with special attention to the latest findings.

1990–2000

Earliest studies showing a relationship between obesity and thyroid cancer dates back to from 1980 [29]. Then in 1990, Dal Maso et al.

performed a meta-analysis including 12 case-control studies, analyzing a total of 2056 females and 417 males with thyroid cancer and demonstrated that at diagnosis there was a relationship between BMI and thyroid cancer in women [30]. However, more serious studies with large cohorts, inclusion/exclusion factors and well-described statistical analysis appear to have started only after year 2000. During the following years, several authors described the relationship between obesity and thyroid cancer, mainly through observational studies.

2001–2010

The first strong evidences for a link between obesity and thyroid cancer came from large cohort studies of 30 years by Samanic et al. which included a cohort of 3,668,486 white and 832,214 black male US veterans. They found that obese persons presented a higher risk of developing thyroid cancer. These authors also demonstrated that this increased risk was independent of racial factors, since in this study, white men presented a 1.4 relative risk (RR) and black men presented a 1.9 RR for thyroid cancer [31]. Similarly, Engeland et al. carried out another study with a large cohort (2,000,947 individuals) for 23 years. These authors were able to identify 3046 individuals who developed thyroid cancer during this period, out of which 1415 were obese [32]. Also it was concluded that both men and women had equally increased risk for thyroid cancer. However, when these authors stratified thyroid cancer into its histological subtypes, they confirmed that the association between BMI and thyroid cancer was stronger in females, who presented an increased risk for PTC (RR = 1.19) and FTC (RR = 1.63) and a lower risk of MTC (RR = 0.35) [32], suggesting that the association between thyroid cancer and obesity was due to DTCs. All these data regarding an exclusive association between obese women and thyroid cancer need to be carefully re-analyzed, especially considering two factors: (i) hormones and hormone synthesis might be affected by obesity, and they play an important role on thyroid carcinogenesis, justifying these associations; (ii) it is widely known that women are more susceptible to thyroid cancer, therefore the number of male cases included in thyroid cancer studies is commonly low, leading to the absence of any significant statistical analysis [33]. By the year 2010, higher BMI and obesity had been consistently reported as risk factors for thyroid cancer, but literatures were still scarce on providing mechanisms that would possibly link these conditions, except a few studies pointing out to insulin-related pathways as the major factors that would justify the reported associations [1, 34–42].

2011-Present

In this decade, many authors have been investigating factors that would link obesity and thyroid cancer; these include clinical and molecular features which require further studies.

Between 2011 and 2012, Kitahara et al. published three articles addressing the link between obesity and thyroid cancers. These authors studied a very large cohorts, demonstrating that obese individuals presented higher risks {Hazard Ratios (HRs): 1.20 and 1.53, respectively} of developing thyroid cancer when compared with eutrophic individuals [43]. They also described that both men and women with large waist circumference (>102 cm in men and >88 cm in women) presented an increased risk for thyroid cancer (HR = 1.79 and HR = 1.54, respectively) [45]. Kitahara et al. subsequently reported that individuals with excessive weight who were practicing greater amount of physical activity were at higher risk of thyroid cancer. Additionally in 2012, Rinaldi et al. demonstrated an association between high BMI and thyroid cancer in women, when they analyzed a cohort of 343,765 females and 146,824 males, with 566 incident thyroid cancers [44]. In a meta-analysis of five large cohort studies, which included 8,099,411 individuals and 5154 thyroid cancer patients, Zhao et al. described that excessive weight was associated with an increased risk (Odds ratio – OR = 1.18) of thyroid cancers [13]. Our group has also confirmed these results, in that in 2012 we

demonstrated that excessive weight was associated with increased risk of DTCs (OR = 3.787). We also suggested that this association could be linked to excessive caloric ingestion (OR = 5.89), mainly due to the excess ingestion of proteins (OR 4.60) and carbohydrates (OR 4.90) [44].

Later Kim et al. showed that obesity was not only associated with an increased risk of thyroid cancers, but could also exert an influence on tumor presentation. These authors reported that a 5-kg/m^2 increase in BMI was associated with PTCs >1 cm (OR = 1.31), microscopic extrathyroidal invasion (OR = 1.23), and with advanced tumor node metastasis (TNM) stage (OR = 1.30) [45]. In an interesting study, Han et al. demonstrated that out of 15,068 subjects that underwent a routine health checkup and when screened by thyroid ultrasonography, 7472 presented cystic or solid nodules and 267 patients were confirmed with thyroid cancer after further investigation. Among these cases, the authors found that the prevalence of thyroid cancer in women was associated with a high BMI (OR = 1.63). Also during this year, Pellegriti et al. included obesity as a potential risk factor that would justify the remarkable increase in thyroid cancer incidence in the latest years, given the convincing results what literature has been canvasing since year 2000 [21].

The year 2014 was especially fruitful to explore the relationship between thyroid cancer and obesity in that several articles appeared addressing this issue and, even though a considerable part of them focused on mechanisms justifying this relationship, there were also interesting results in observational studies. Kitahara et al. analyzed 321,085 children from the Copenhagen School Health Records Register including measurements of height and weight from 7 to 13 years of age. These children were followed-up for a median of 38 years, and during this period 171 women and 64 men were diagnosed with thyroid cancer. Both height and increased BMI were positively associated with thyroid cancer risk, suggesting that not only obesity is a risk factor for thyroid cancer, but also it may impact thyroid cancer risk in adult life [46]. In a pooled analysis of three case-control studies, including 1917 patients with PTC and 2127 controls, Xu et al. demonstrated an increased risk of PTC when patients presented greater weight/BMI (OR = 1.72 for overweight *vs*. normal weight and OR = 4.17 for obese *vs*. normal weight). This increase was also reported for body fat percentage (OR = for women and OR = for men, considering the lowest quartile *vs*. the highest quartile) [47]. In the same year Arduc et al., using fine-needle aspiration biopsy, suggested that the presence of obesity and large waist circumference can be used as predictors of thyroid carcinoma in patients with Hurtle-cell lesions. These authors studied 224 women with these lesions, who had underwent thyroidectomy and found that malignancy risk was 3.819 higher in the obese group. Besides, large waist circumference was also shown to be linked with increased risk for malignant lesions (OR = 5.593) [48]. Zhang et al. employing a meta-analysis of large cohort studies, including 16 studies with 12,616,154 subjects showed that the link between obesity and thyroid cancer was higher in males (RR = 1.35) than in females (RR = 1.29). This association was maintained when these authors analyzed the other factors such as age (RR = 1.34), smoking (RR = 1.36), alcohol use (RR = 1.40), and history of benign thyroid disease (RR = 1.51), confirming that data presented by literature so far is consistent and points out to obesity as risk factors for thyroid cancer [49].

Molecular Mechanisms of Thyroid Cancers in Obesity

Both obesity and thyroid cancers are multifactorial diseases that lead to many systematic modifications in patients. Although a considerable part of these modifications have been clinically detected by physical and laboratorial examinations, but some of them can only be detected by molecular analysis. The latest findings, based on studies at molecular levels have been making it possible to hypothesize that obesity and thyroid cancers have more in common than it was ever speculated. There are specific points that need to be considered if we look into molecular mechanisms connecting obesity and thyroid cancers:

Factors involved with these studies include thyroid hormones, adipokines and factors inducing inflammation

Thyroid Hormones

The thyroid gland plays a crucial role in the control of energy metabolism through action of thyroid hormones. There is evidence that the abdominal obesity and a tendency to weight gain are associated with small variations of thyroid hormone levels in euthyroid subjects [50, 51]. Also an association has been reported between low thyroxine (T4) levels and fat accumulation [50, 52].

A positive link has also been reported between free triiodothyronine (T3) levels and both, waist circumference and higher BMI in obese subjects [53]. A moderate increased T3 level in obese individuals has been explained as a compensatory higher conversion of T4 to T3 in order to improve energy expenditure and fat accumulation [53]. The TSH, which promotes the secretion of thyroid hormones to regulate energy expenditure, has also been shown to be altered in obese euthyroid subjects, and a positive link between its levels and increased BMI has been observed [51, 54].

To explain the increase of thyroid stimulating hormone (TSH) in obese individuals, hormonal mediators of adipose tissue, especially leptin, has been suggested as potential stimulators of the hypothalamic-pituitary-thyroid axis [55, 56]. Leptin modulates food intake and energy expenditure and acts as a neuroendocrine regulator, regulating thyrotropin releasing hormone (TRH) expression in the paraventricular nucleus; TSH will then stimulate leptin secretion by adipose tissue [57–60]. In addition, leptin may affect deiodinases, activating the T4 to T3 conversion [61, 62].

Interestingly, besides the association between TSH and BMI, there is a clinical evidence that high TSH levels are linked to increased risk of malignancy in human thyroid nodules at advanced stage of the disease [63]. TSH being the major stimulator of thyrocytes proliferation, we hypothesize a direct role of this hormone in thyroid carcinogenesis in obese individuals [64]. In fact, the mitogenic effects of TSH on follicular cells have been demonstrated using in vitro and animal studies [65–67]. The binding of TSH to its receptor, TSHR, increases the intracellular levels of cAMP and activates proliferation pathways, including PI3K–AKT and RAS–BRAF pathways [68, 69]. The interaction of TSH with insulin represents another possible mechanism linking obesity and thyroid cancer [70]. In insulin resistance, a clinical condition frequently present in obesity is insulin stimulates TSH production promoting proliferation of thyroid cancer cells [64, 71].

Although the importance of TSH in thyroid cell proliferation has been clearly demonstrated, the role of serum TSH levels in tumor growth and anaplastic changes have not been found in animal models [72]. The increased risk of thyroid cancer in obese subjects has also shown to be unrelated to serum TSH levels in human subjects [48, 73]. A clinical study nevertheless has also shown that, in spite of the significantly high TSH levels found in morbidly obese women compared with normal weight and/or slightly overweight women, the prevalence of thyroid nodules has shown to be significantly lower in obese women [74].

In conclusion, there is evidence pointing to a possible involvement of TSH as etiopathogenic element linking obesity and thyroid cancer. However, the present studies and the current data do not allow us to confirm or exclude the possibility of this involvement.

Cytokines, Adipokines and Inflammation

Adipose tissue was once considered as a simple aggregation of cells that are able to store fat in our body. However, the advancement of molecular and cell biology gave us an insight that probably a link exist between obesity and inflammation. In fact, fat cells may be considered a component of the immune system, as it expresses receptors for many cytokines and also produce many proteins and hormones that modulate immune response [75–77]. It has been demonstrated that immune cells infiltrate adipose tissue at the onset of weight gain and directly contribute to and perpetuate the inflammatory state of fat,

systemic insulin resistance, and the promotion of obesity [78].

The altered production or dysfunction of adipokines has been implicated in the metabolic syndrome of obesity [79]. In fact, adipose tissue in obese persons produce more proinflammatory substances (such as TNF-alpha, IL-6, iNOS, TGF-β1 and C-reactive protein) than adipose tissue in lean individuals [80–84]. Uysal et al. were able to generate obese mice with a targeted null mutation in the gene encoding TNF-α and those encoding the two receptors for TNF-alpha (Ref). The absence of TNF-α in the null mutant mice resulted in significantly improved insulin sensitivity in both diet-induced obesity and that resulting for the ob^{-}/ob^{-} obese mice. The TNF-α deficient obese mice had lower levels of circulating free fatty acids and were protected from the obesity-related reduction in the insulin receptor signaling in muscle and fat tissues. These results indicate that TNF- α is an important mediator of insulin resistance in obesity through its effects on several important sites of insulin action, suggesting that adipose tissue of obese patients is inflamed [85]. Weisberg et al. studied the transcript profile of adipose tissue of obese animals and found that the expression of 1304 transcripts correlated significantly with body mass. Of the 100 most significantly correlated genes, 30 % encoded proteins that were characteristic of macrophages and are positively correlated with body mass. Immunohistochemical analysis of perigonadal, perirenal, mesenteric, and subcutaneous adipose tissue revealed that the percentage of cells expressing the macrophage marker F4/80 was significantly and positively correlated with both adipocyte size and body mass [79]. Similar relationship was found in human subcutaneous adipose tissue stained for the macrophage antigen CD68 [85]. These results suggests that not only proinflammatory proteins are produced but also there is an enrichment of macrophages in adipose tissue of patients with obesity. How this inflamed state associate with obesity and cancer is the question remains to be asked.

TNF- α is a hormone that is thought to mediate tumor cytotoxicity as well as new blood vessel growth [86]. Liu et al. investigated whether the Wnt pathway, an intracellular signaling cascade that plays a critical role in colorectal carcinogenesis, is activated by obesity-induced elevation of the inflammatory cytokine TNF- α (Ref). The phosphorylation of glycogen synthase kinase 3 β (GSK3β), an important intermediary inhibitor of Wnt signaling and a potential target of TNF- α, was quantitated by immunohistochemistry. The inactivated (phosphorylated) form of glycogen synthase kinase 3 β was elevated in the colonic mucosa of obese mice. Moreover, β-catenin, the key effector of canonical Wnt signaling also was elevated in the colons of obese mice, as was the expression of a downstream target gene, c-myc (Ref). These data demonstrate that diet-induced obesity produces an elevation in colonic TNF- α and instigates a number of alterations of key components within the Wnt signaling pathway that are pro-transformational in nature.

In thyroid cancer a particular mechanism may be elicited. Pang et al. demonstrated that TNF- α has an anti-proliferative action in human papillary thyroid cancer cell line through a receptor-mediated mechanism [87]. However, the exposure of papillary thyroid cancer cell to TNF-α resulted in the development of progressively increasing loss of the TNF- α-induced anti-proliferation, termed resistance [88]. Probably, the high TNF- α exposure provided by obesity may be inducing TNF- α resistance that facilitates thyroid tumor progression [13]. Interestingly, Rotondi et al. recently investigated whether metformin inhibits the secretion of CXCL8, induced by TNF- α in primary cultures of normal and tumor human thyroid cells as well as in thyroid cancer cell lines. They found that metformin significantly and dose-dependently inhibited the TNF- α-induced CXCL8 secretion in both normal thyrocytes and papillary thyroid cancer cells [89]. CXCL8 directly stimulates the proliferation of thyroid tumor cells via autocrine and paracrine mechanisms beside the fact that CXCL8 also plays a crucial role in promoting the invasiveness of thyroid tumor cells [90]. Thus, the inhibitory effect of metformin on TNF- α-induced CXCL8 secretion could be considered as an additional indirect anticancer property of the drug.

Adipokines – Link Between Obesity and Inflammation

Adipokines or adipocytokines are a subset of cytokines produced by the adipose tissue [91]. They are involved in several crucial processes for human metabolic systems including immunity, regulation of appetite and energy balance, insulin sensitivity, angiogenesis, blood pressure regulation and lipid metabolism [92]. It is well known that obesity is intimately linked with inflammation. Obese individuals also run higher risk to develop insulin resistance. Recent research suggests that when both insulin resistance and inflammation are present they alter the inflammatory profile in that it induces the production of anti-inflammatory factors such as adiponectin which leads to the production of pro-inflammatory adipokines, such as leptin and resistin [93]. Also adipokines can promote tumorigenesis as they have already been implicated in the regulation of inflammation and insulin sensitivity, hence representing the link between inflammation, obesity and cancer [49].

Adiponectin is an adipokine with strong anti-inflammatory properties. It is exclusively produced by adipocytes, and promotes the cells' and adipocyte differentiation and increase insulin sensitivity [94, 95]. Pro-inflammatory factors such as TNF-α, IL-6 and ROS which can play a regulatory role in adiponectin expression. However, recent evidence show that there exists a regulatory feedback loop through which adiponectin controls its own production and the expression of its receptor [96]. Adiponectin also acts as an autocrine and paracrine factor to inhibit the secretion by adipocytes of pro-inflammatory factors such as TNF-α, IL-10, macrophages, T-cells, NK-cells, inducing effects on the storage of lipids and insulin sensitivity in adipocytes. Adipokine is also able to influence cell proliferation and regulate the balance of anti-?what? and always aiming to control inflammation [96–99]. In order to develop these functions, adiponectin binds to two different receptors, AdipoR1 and AdipoR2. These receptors have an important role in improving the insulin signaling on target cells, through the increase in AMPK activity, and PPARα and PGC-α. These molecules might also lead to a reflex on AKT/mTOR/PI3K and MAPK pathways, well known for regulation of cell proliferation [100].

In addition, adiponectin also influences the immune system through NF-κB regulation [101]. Due to its complex antiproliferative and inflammation-restraining functions, this hormone has been linked to breast, endometrial, prostate, colorectal, liver, pancreatic and gastric cancers, as well as some hematological types of leukemia, lymphoma, and myeloma [101]. Recently, evidence presented that adiponectin plays role in developing thyroid cancers. Mitsiades et al. demonstrated that adiponectin serum levels are inversely correlated with DTC, exerting a protective effect against the development of this cancer. Furthermore, these authors demonstrated that thyroid tissues express AdipoR1 and AdipoR2, facilitating the entrance and the functioning of adiponectin in the thyroid [102]. Thus, suggesting that not only adiponectin is expressed in thyroid cells, but it is also functional in them. Another recent study has demonstrated that adiponectin receptors might be important for DTCs (Ref). Comparing tissues of primary papillary thyroid carcinomas with metastatic tissues, Cheng et al. reported that 27 % of primary tumors expressed AdipoR1 and 47 % expressed AdipoR2. When tissues were negative for both receptors, tumors were significantly associated with extrathyroidal invasion, multicentricity, and higher TNM stage, suggesting that the expression of adiponectin receptors can be employed for better prognosis [103].

Leptin is structurally similar to cytokines, IL-2, IL-6, and granulocyte-colony stimulating factor (G-CSF), a characteristic that makes leptin capable of participating in similar cellular and organic processes, such as the control of food intake through satiety sensation, regulation of energy expenditure, activation of monocytes and macrophages, stimulation of VEGF, angiogenesis, cell proliferation, and the suppression of anti-inflammatory cytokines [92]. It is predominantly secreted by adipose tissue, although it can also be produced by skeletal muscle, stomach and blood? plasma [104]. Leptin acts as an endogenous sensing factor, providing a critical link between the environment, metabolism, and immune function [105].

The mechanisms of leptin's action involve its binding to leptin receptor b (ObR or LEPR), leading to the activation of intracellular signals through JAK2, STAT3 and AMPK [92]. These factors regulate AKT/mTOR/PI3K and ERK/MAPK pathways, involved in cell growth and survival as well in COX2, IL-1 and NF-κB, induced inflammation and VEGFs, involved in angiogenesis [106]. Thus, leptin interplays with several factors that participate in diverse carcinogenic stages, and its association with breast, prostate, colorectal, hepatocellular, pancreatic and lung cancers, as well as thyroid cancer, has consistently been presented in the literature [107, 108]. Concerning thyroid cancers, and more specifically DTCs, leptin and ObR expression was first demonstrated by Cheng et al., who found them associated with a high risk of lymph node metastases [109]. In a recent study, our group demonstrated that patients with AA genotype of rs7799039 in *LEP* (the gene that codes for leptin) had higher serum levels of leptin (9.22 ± 0.98 ng/mL) than those with AG genotype (10.07 ± 0.60 ng/mL).

We have also shown that the AG genotype of rs2167270 in *LEP* also produce higher serum leptin (10.05 ± 0.59 ng/mL) than the subjects with GG genotype (9.52 ± 0.79 ng/mL). The AG genotype of rs7799039 in *LEP* was an independent risk factor for DTC (OR = 11.689). Similarly, AG and GG genotypes of rs1137101 in *LEPR* (the gene that codes for leptin receptor) increased the susceptibility to DTC (OR = 3.747 and OR = 5.437, respectively). In this study, we did not find any association between polymorphisms and clinic-pathological features of DTC [110]. Other groups reported leptin's involvement in the clinical phenotype of DTC, and suggested that leptin may affect the migration of thyroid cells, proposing for a worse prognosis and metastasis formation [111–115].

Resistin is an adipokine produced by human monocytes and macrophages, as well as adipocytes [92]. This adipokine was first linked with insulin resistance by the suppression of insulin-mediated signaling in rat adipocytes, but in humans this association is not always found [116]. In fact, resistin presents diverse functions in humans, such as proliferative, antiapoptotic, pro-inflammatory and pro-angiogenicity [104, 117]. Inflammatory cytokines such as IL-1β, IL-6, TNF-α, and LPS can induce resistin expression, but conversely resistin has been demonstrated to stimulate the production of IL-6 and TNF-α through the NF-κB signaling pathway [118]. In addition to its action on the immune system, resistin can also bind to TLR4, activating JNK and p38 MAPK to induce insulin resistance [119]. Due to its ability to regulate immune factors production and its indirect regulation of MAPK pathway and other proliferative events, resistin has been investigated in human cancers. Its expression has been linked to the increased proliferation of prostate cancer by AKT/mTOR pathway stimulation [72]. Resistin has also been linked to breast, endometrial, colorectal, hepatocellular, pancreatic and lung cancers [117, 120–124].

Our group has studied serum concentrations of leptin, adiponectin, resistin and ghrelin, showing that these adipokines may represent excellent markers for malignancy in thyroid nodules. We further showed that DTC patients presented lower adiponectin serum levels when compared with patients with benign nodules. Leptin, on the other hand was higher in DTC than in benign cases. Similarly, resistin levels were higher in DTC than in patients with benign nodules. When we created ROC curves to investigate the accuracy of using these cytokines levels as diagnostic test, we showed that the concentrations of serum adiponectin, leptin and resistin distinguished benign and malignant nodules with 76 %, 100 % and 100 % accuracy, respectively. These cytokines serum levels also helped to discriminate follicular patterned lesions. The follicular variant of papillary thyroid cancer (FVPTC) could be distinguished from follicular adenomas (FA) by adiponectin and leptin levels and from goiters by serum leptin and resistin levels. FA could be differentiated from FTC and from classic PTC (CPTC) by leptin levels. On the other hand, CPTC differentiated from FA by leptin levels and from goiters by leptin and resistin levels. In conclusion, we found that serum concentrations of adiponectin, leptin and resistin may represent a new alternative approach to the diagnosis of thyroid nodules, especially for cases where fine

needle aspiration biopsy cannot give a definitive diagnosis, thus, avoiding more aggressive and unnecessary surgeries and interventions [125].

Conclusion

There is no doubt that adipose tissue is involved in many vital processes and its existence facilitates and improves several crucial events, such as insulin regulation, angiogenesis, energy balance, and the production of many immune system proteins and hormones. Although the processes that involve the adipose tissue and/or its products have their own molecular pathways, they also have the same common proteins through which obesity and adipose tissue might exert their role in carcinogenesis. Additionally they not only affect MAPK and PI3K insulin pathways, but also recruiting local inflammatory responses that could result in disease formation and progression. These are the main mechanisms through which obesity and the metabolic changes that it induces might be linked to thyroid cancers. Understanding these mechanisms might lead to different disease-preventing strategies, not only helping patients, but also sparing health systems worldwide to save money and direct money to more complicated cases, which require more complex treatment and care.

Declaration of Interest The authors have nothing to disclose. None of the authors has any competing interest.

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Depression and Obesity

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Introduction

The high prevalence and relationship between depression and obesity has largely been reproduced by epidemiological studies. A recent nutrition examination survey in England with 5600 participants confirmed an association between both disorders. Moreover, in this study Rethorst and colleagues found depressed individuals with elevated inflammation markers, C-reactive protein (CRP), are more likely to be obese and to meet criteria for metabolic syndrome (MetS) [1]. Indeed, obesity increases the risk of depression and depression is predictive for the development of obesity [2, 3]. In a recent systematic review and meta-analysis of longitudinal studies of overweight obesity and depression, 80 % of the studies showed evidence that obesity is prospectively related to depression, while 20 % of them showed evidence that depression is prospectively related to obesity [4–12].

As supported by most of the data, as obesity seems to occur "first", hence obesity in depressed individuals cannot just be causally explained by weight increasing side effects of antidepressant treatment strategies or as a collateral damage of the disease itself, resulting from symptoms of the disease. Indeed it has recently been shown that antidepressants might affect insulin secretion in major depressive disordered (MDD) patients [13]. However, selective serotonin reuptake inhibitors (SSRIs) are the only approved class of antidepressants with favorable effects on glycemic control, which might also have diabetogenic effects in the long run [14]. Since the two conditions depression and obesity are independent risk factors for cardiovascular disease (CVD) strategies/therapeutic regimens addressing both disorders are urgently needed not only facing predicted future global disease burden but also resulting individual and economic strains [15–18].

If the late life depression is a prodrome for AD and chronically impaired peripheral glucose metabolism is connected with late life depression, the comprehension of the neurobiological consequences of diabetes might have a high public health concern [19]. Indeed, an optimization of glycemic control and associated prevention strategies might modify not only depression but also the occurrence of dementia [19].

Behavioral and Sociocultural Factors in Depression and Obesity

One aspect leading to the relationship between these two disorders, obesity and depression, might result from behavioral and sociocultural similari-

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ties between depression and dementia where several behavioral and/or sociocultural factors result in both diseases or facilitate the occurrence of both diseases. Moreover, the symptoms of one disease, for example depression (inactivity, sleep disorders, carbohydrate craving and abusive substance consumption) can result in obesity (see Fig. 18.1). Factors which have been shown to be associated with both disorders are: gender, ethnicity, physical activity, alcohol consumption, physical health, weight history, interpersonal effectiveness and deregulated eating, stigma, marital status, age and body image (see Fig. 18.1) [5]. However, also the severity of obesity is associated with depression [20]. Obesity as such might also lead to depressive symptoms. This is in line with a longitudinal 20-year follow-up association study between depressive symptoms and body mass index (BMI), where women with excess body weight were more likely to have increased symptoms of depression 10 years later [21, 22]. One factor in this context might also be "emotional eating", which is associated with depression and obesity [21, 22]. Thereby depression might lead to anxiety and feelings of loneliness, as well as distress and emotional eating might improve mood changes but lead to obesity in the long term (see Fig. 18.1). This hypothesis is also in line with the observation that, despite metabolic improvements, bariatric treatment leads to a decrease of depressive symptoms but does not affect anxiety, suicides and overall improvement in psychiatric treatment [23].

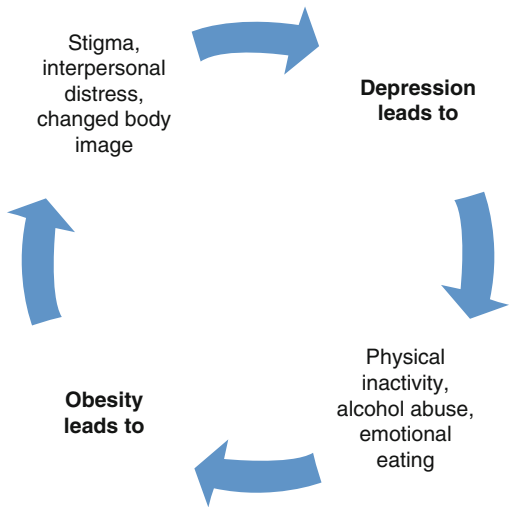

Fig. 18.1 Vicious circle between behavioral symptoms of depression and obesity

Biological Crosslinks Between Depression and Obesity

Obesity and depression have been postulated to be intrinsically linked and to share environmental factors, which might trigger both conditions. However, also biological systems of both disorders are strongly connected with severe metabolic dysfunction, which is initially manifested as an increased vulnerability of certain hormonal, peptide and protein profiles. Sugar has been postulated to be an addictive substance since it releases opioids and dopamine [24–26]. Addiction criteria of withdrawal symptoms, increase in tolerance level, eating unhealthy and risky meals, consumption of other drugs and inability to be abstinent can all influence obese patients consuming a high sugar diet.

Hyperglycemia has been shown to contribute to elevated levels of serum concentration of advanced glycation endproducts (AGEs) [27]. AGEs are pro-oxidant, cytotoxic substances contributing to chronic inflammation and diabetic complications [27–29]. Recently, Uribarri and co-workers suggested that serum AGEs (SAGEs) levels can be used to identify obese individuals at risk for developing MetS/Type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) [30].

In their study, SAGEs concentrations correlated with markers of insulin resistance and inflammation {homeostasis model assessment (HOMA), leptin, tumor necrosis factor-α (TNF-α) and receptor for advanced glycation end products (RAGEs)}. Also in depression, altered cytokine levels have been repeatedly reported [31]. Interestingly, a recent pilot study involving patients with different psychiatric disorders found the soluble AGE receptor, which is associated with atherothrombosis also regulated in depression and schizophrenia [32, 33]. These are preliminary results and need to be confirmed by further studies. Nonetheless, AGEs are interesting compounds for assessing pos-

sible interrelations between, and therewith treatment options for, depression and (non-healthy) obesity. Pioglitazone, an insulin sensitizer acting via peroxisome proliferator-activated receptor (PPAR-γ), got in focus as adjunctive therapy for depressed behavior of mice and men [34–36]. Furthermore, the drug target PPAR-γ is known to modulate AGEs levels and might be mechanistically linked to both diseases [37].

Hence the question to ask is when the process of deregulation/imbalance begins? Possibly it starts with prolonged exposure to stress, which leads to chronic elevation of glucocorticoids (GCs), which have been associated with depression and obesity onset, even prenatally [38–42]. Generally, it is believed that GC levels play several roles in coping with stressful conditions at the onset of obesity. It is well-established that, when receiving stressful stimuli, corticotropin-releasing hormone (CRH) is released in the hypothalamus, which stimulates the anterior pituitary to increase adrenocorticotropic hormone (ACTH). Subsequently, these hormones act on the adrenal gland to upregulate the levels of GCs for coping with stress. However, one of the main causes of depression is hyperactivation of the hypothalamic–pituitary–adrenal (HPA) axis with persistently increased levels of GCs [43]. Ample evidence demonstrates that GC levels regulate neuronal transmission and synaptic plasticity and are increased in MetS and obesity [44–49].

At the behavioral level, the increased perception of stress leads to increased episodes with depressed mood, sleep disturbances and less exercise which are connected with consumption of high-energy foods and carbohydrate craving, which in turn again lead to hormonal and metabolic changes as insulin resistance, dyslipidemia and hypertension. Furthermore, hyperglycemia/poor glycemic control, as measured by glycated hemoglobin (HbA1c), has been found to be associated with reduced hippocampal volume [50]. This morphometric feature/change is well known from studies investigating chronic life stress and chronic depression [51, 52]. Also, in elderly individuals (about 60–70 years of age) with "mild cognitive impairment", poor glycemic control was found to be associated with both poorer memory function and smaller hippocampal volumes [53].

Nutrition activated gut to brain pathways modulate appetite, digestive function, energy intake and mood. Firstly, dysfunction of peripheral expression and the transport of insulin-like growth factor-1 (IGF-1) in the brain might lead to depressive symptoms as IGF-1 leads to increased hippocampal neurogenesis and to central sensitization of insulin signaling [54, 55]. Also, in animal models assessing antidepressant-like effects such as the forced swim test (FST), administration of IGF-1 gave similar results compared to SSRIs and were shown to be blunted by serotonin depletion [56]. In rats, fluoxetine was found to upregulate the IGF-1 system in frontal cortex and thereby might affect frontal cortex neuroplasticity [57]. Interestingly, IGF-1 levels in cerebrospinal fluid increased in autistic children treated with the SSRI fluoxetine which might in turn reverse or protect from neuro-/excitotoxic effects in exposed brain regions, even though a recent Cochrane review found no evidence of effect of SSRIs in children with autism spectrum disorders [58, 59].

Also ghrelin, leptin and the lipid endocannabinoid system have been shown to signal from the gut to the brain. Interestingly, all these gastrointestinal hormones diverted interest in the regulation of mood and the treatment of depressive symptoms [56, 60, 61].

A significant association between leptin levels, depressed mood and sleep disturbances has been shown [62]. Leptin has been shown to be involved in hippocampal plasticity [63, 64]. Both, dexamethasone (a synthetic CG) and leptin seem to converge on glycogen synthase kinase-3β (GSK-3β) and are key regulators in controlling hippocampal neural progenitor cell proliferation, mood and response to psychiatric medications [63, 64]. Moreover, leptin can decrease the basal secretion of dopamine and feeding-stimulated dopamine release and it inhibits firing of dopamine neurons in the ventral tegmental area, whereas long-term blockade of leptin signaling in the ventral tegmental area increases locomotor activity and food intake [64–68].

The consumption of less carbohydrates increases ghrelin [69]. Ghrelin regulates central

system development and mood, exerts antidepressant effects in mice and men, influences the reward behavior and displays dopaminergic properties [64, 68, 70].

Central modulation of mood and chronic social stress regulate a number of signaling peptides influencing again nutrient sensing enteroendocrine cells, such as NPY, ghrelin, glucagon-like peptide-1 (GLP-1) and CCK [64].

In this context, chronic stress can elevate ghrelin levels by activation of the sympathetic nervous system and the increased ghrelin response then helps the subject cope with stress by generating anxiolytic- and antidepressant-like behavioral adaptations [71]. Therefore, obesity and major depression may both derive from a deregulated ghrelin feedback at brain regions regulating feeding and mood.

NPY was initially described as a 'co-transmitter' of sympathetic neurons, modulating the actions of norepinephrine in the cardiovascular system [72]. Later on, many other functions of NPY, in particular in the CNS were discovered, connecting NPY with stress response, food intake, energy balance control, sleep regulation, inflammatory processes and tissue growth remodeling [64]. NPY integrates complex responses of different body systems, such as reduction of anxiety and depression, inhibition of release of NPY, glutamate and GABA, angiogenesis and blood pressure regulation and regulation of circadian rhythms, bone formation and feeding response [64, 71].

CCK release can be triggered by social defeat stress and its increase can be prevented by antidepressant treatment [73]. Blockade of CCK receptors reverses depressive behavior in mice and prevents HPA axis hyperactivity [74]. In contrast CCK injection leads to increased serum corticosterone. Panic induction can be experimentally carried out by a bolus injection of CCK and a recent study associated decrease of CCK with mania [74, 75].

Gastrin-releasing peptide stimulates cell proliferation and displays a range of neuroendocrine activities [76]. This protein is distributed throughout the central nervous system and it is involved in regulating synaptic plasticity and aspects of anxious and depressive behavior in the hippocampus and in the amygdala [64].

Brain-derived neurotrophic factor (BDNF) is a mediator of food intake control at brain areas rich in BDNF receptors, including the hypothalamus. It is also involved in vagal afferent gastrointestinal impulses and thereby drives overeating and weight gain associated with increased meal size and frequency. The deletion of BDNF in the brain has been shown to lead to a metabolic phenotype characterized by hyperphagia, obesity, and increased abdominal white adipose tissue [77]. Contrarily, treatment of diabetic mice with BDNF lowered blood glucose, decreased lipid profiles and reduced histologic fatty liver phenotypes [78]. BDNF has been shown to be involved in vulnerability to overeating and weight gain in an obesogenic environment and is a key element in the vulnerability to depression and in antidepressant treatment [64].

BDNF Polymorphisms and Brain Volumes in Depression

Several studies have investigated the effect of BDNF polymorphism on brain volumes of patients with depression and bipolar disorder [79–83]. Several of these studies have focussed on the hippocampus, where BDNF has been shown to play a role in learning- and memory-dependent deficits in affective disorders and may be associated with declines in hippocampal volume. Previous meta-analyses have investigated the association between BDNF rs6265 and hippocampal volumes using MRI techniques in a neuropsychiatric patient sample [84, 85]. Both studies reported insignificant smaller hippocampal volumes for Met-carriers than for Val/Val homozygotes. This is in line with recent meta-analysis of neuropsychiatric sample including individuals that indicated an insignificant association between the SNP and hippocampal volumes [86]. In contrast, studies of the effect of the BDNF val66met in major depressive disorder and psychosis found that the status of Met-carrier and exposure to childhood trauma have an interactive effect on hippocampus volume [87].

The Effect of Nutrition and Microbiota on Obesity and Depression

The intestinal microbiota modulates gastrointestinal functions and influences intestinal permeability, mucosal immune function, intestinal motility, sensitivity, as well as activity in the enteric nervous system. Based mostly on preclinical studies (e.g. in a germ-free environment) the gut microbiome appears to modulate the development of brain neurotransmitter systems and thereby influences affective behavior, stress-related disorders and pain perception [88–90]. Indeed, microbiota perturbations with dietary changes, prebiotics, probiotics, or antibiotics can lead to addictive or depressive behavior [91, 92]. Consequently, restoring a certain gut microbiome might be a considerable (adjunctive) treatment strategy for depression and obesity [93, 94].

Viable Treatments, Which Overlap in Depression and Obesity

Statins have anti-obese properties and their use was associated with a significant reduced occurrence of depression [95, 96]. In mice, atorvastatin, a widely used cholesterol lowering drug, has been shown to significantly reduced immobility time in FST, a measure for antidepressant-like properties. The study suggested PPAR-γ and nitric oxide (NO) pathway to be at least partially accountable for the antidepressant-like effect of atorvastatin [97, 98]. It is in line with results from pre-clinical trials on insulin sensitizers such as pioglitazone. Further more, serotonin depletion abolished antidepressant-like effects of atorvastatin [99]. Also in severely depressed individuals, augmentation of citalopram with atorvastatin was superior to placebo in reducing depressive symptoms assessed with the Hamilton depression rating scale. Notably, in a rat model of atherosclerosis either administration of atorvastatin or escitalopram was associated with a more favorable blood lipid profile, as well as regression of atherosclerotic changes in the aortic wall compared to control animals [100]. However, a recently published large population-based study, which reported an increased risk of development of T2DM (adjusted hazard ratio 1.46; 95 % CI 1.22–1.74) in Finnish men taking statins revived the discussion on too uncritical use of drugs such as statins in certain populations [101].

Metformin is an antidiabetic drug and has proven to be effective as an antidepressant [102]. Certain antidepressant agents have been proposed to also act as antiobese drugs [103]. Substances exerting beneficial effects on both conditions are for example the thiazolidinedione/insulin sensitizer pioglitazone, which has been reported to ameliorate depression, or the serotonin norepinephrin reuptake antidepressant milnacipran, which has been demonstrated to improve metabolic parameters in diabetic patients [104, 105]. Phosphoinositide 3-kinase (PI3K) activity has been linked to insulin resistance and depression [64, 106]. Indeed, inhibition of PI3K leads to inactivity, memory loss, insulin resistance and depressive and anxious behavior [106]. In contrast, the use of docosahexaenoic acid seems to reverse depression, anxiety, plasma insulin and glucose increase and inactivity [106].

However, certain studies on metabolic effects of antidepressant drugs consider at least some of the favorable changes (e.g. of HbA1c, fasting blood glucose, BMI, total and LDL-cholesterol, serum triglyceride levels etc.) to depend on the antidepressant treatment response. So, treating one disease might, via behavioral changes, have positive influences on the other condition.

Therefore, behavioral changes, psychotherapy and exercise programs have been shown to be very successful to prevent and treat these disorders, obesity, T2DM and depression [107–109]. Thus, cognitive behavioral psychotherapy and light exercise therapy have been suggested possibly to be effective for both disorders. Another vision to develop therapeutics for both disorders depression and obesity might be a modulation of the microbiome via pharmabiotic or nutritional strategies [110] (Fig. 18.2).

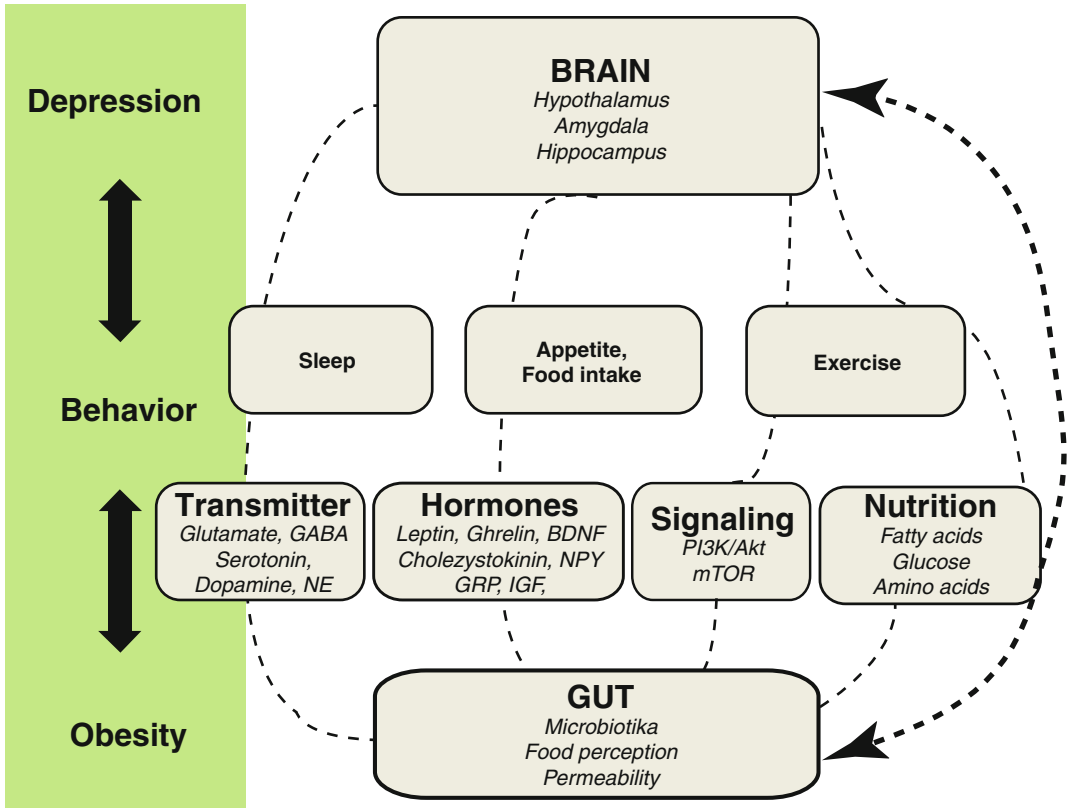

Fig. 18.2 Interplay between behavior, obesity and depression. Brain function (and depressive state) influences hormonal, nutritional, signaling and neurotransmitter function but is itself influenced by changes and negative feedback mechanisms resulting from behavioral adaptions to these changes. Abbreviations: gamma-aminobyturic acid (*GABA*), norepinephrine (*NE*), brain-derived neurotrophic factor (*BDNF*), neuropeptide Y (*NPY*), phosphoinositide kinase 3 (*PI3K*), mechanistic target of rapamycin (*mTOR*), gastrin releasing protein (*GRP*), insulin growth factor (*IGF*)

Conclusion

Depression and obesity contribute to enormous disease burden [2, 44] and more and more evidence supports these two highly prevalent entities to be bidirectionally interrelated [2–12, 44, 64]. Over the last few decades several hormonal/molecular pathways have been identified to be involved in the onset, maintenance, identification of treatment-associated biomarkers, indicating disease progression and risk for occurrence of co-morbidity, of depression, as well as obesity. However, exact mechanisms underlying progression from disease vulnerability to onset of clinical symptoms are yet to be fully elucidated and understood.

Recent studies revealed brain-gut circuits to be involved as potent mediators of both regulation of energy homeostasis and mood-associated processes. Drugs or nutritional agents that act on molecules, such as IGF-1, or NPY and subsequent regulatory cascades represent new treatment strategies that might have impact on neuronal circuits, crucial for respective psychiatric symptom manifestations, as well as on metabolic disturbances.

In this chapter, we reviewed selected promising and/or well established therapeutic strategies to be used in the treatment of psychiatric or metabolic disturbances and their potential additional affects on the respective other disease entity, as well as shared underlying

mechanisms. The findings might further challenge our understanding and classification of diseases like depression as evoked by McIntyre, who suggests depressive syndromes to be reclassified as "metabolic syndrome type II" [45].

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Obesity: Orthopaedics and Trauma Surgery

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Introduction

Obesity is defined as a body mass index (BMI) >30 kg/m^2 [1]. BMI is calculated by dividing a person's weight in kg by the square of their height in meters (kg/m^2) [1]. A normal BMI ranges from 18.5 to 25 kg/m^2. Adults with a BMI between 25 and 29.9 are considered overweight, and those with a BMI ≥30 are considered obese [1]. Severe obesity is defined as a BMI between 35 and 40, with morbid obesity defined as BMI ≥40 kg/m^2 [1]. Children and teenager (ages 2–19) are considered overweight if their BMI is between the 85th and 95th percentile and obese if above the 95th percentile for children of the same age and gender [1]. Obesity is known as a growing public health problem worldwide. In 2014, the Global Health Observatory estimated an obesity prevalence of 12.9 % in the World population [1]. According to 2008 World Health Organization (WHO) estimates, 1.4 billion adults were overweight and more than 500 million were obese, while more than 40 million children under the age of five were overweight [1]. The prevalence of obesity has nearly doubled between 1980 and 2008 [1]. Each year, at least 2.8 million people die because of the consequences of being overweight or obese [1].

Obesity requires specific considerations during surgery and there is now a peer-reviewed journal dedicated to this problem [2]. The orthopedic surgeon is not immune to this public health problem, and often is not well prepared to deal with this additional surgical and perioperative challenge [3].

In daily practice, orthopedic surgeons have to deal with two distinct categories of patients. First, patients who are overweight or moderately obese that are treated without being really prepared for the surgery despite the increased risk of complications related to their condition. The second category of patient includes those who are severely obese or morbidly obese who wander from hospital to hospital looking for a surgeon willing to operate on them. In this second group of patients, a multidisciplinary team approach is essential; in the least, a nutritionist, endocrinologist and psychologist should be supporting the surgeon-anesthesiologist team.

After reviewing pathophysiological and epidemiological aspects, the main focus will be on establishing broad principles for managing obese patients in the pre-, intra- and post- operative stages of orthopedics and trauma surgery.

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General Data

Pathophysiology

Obesity has historically been attributed to excessive consumption of high-calorie foods and a sedentary lifestyle, factors that are more widespread in patients with a low socioeconomic status. However, no strong causal relationship between these factors has been established, probably because several other factors come into play [4]. Obesity should not be viewed simply as a biomechanical problem leading to excessive loads and/or a physical problem complicating imaging, surgical approaches, procedures and skin healing [5]. It has recently been found that certain fat-derived hormones (adipokines) are involved in the development of obesity: leptin (pro-inflammatory) and adiponectin (anti-inflammatory). Although the mechanism of action is not fully understood, it is likely related to altered regulation [6] and changes in cell receptor sensitivity [4].

When added to a whole other series of pro-inflammatory and anti-inflammatory agents that are increased in obesity, the result is a low-grade inflammatory condition linked to cardiovascular and metabolic complications and infectious, wound healing or bone healing complications during orthopaedics and trauma surgery. These could also explain some of the failures of diet-related treatments.

A recent international, multicentre prospective study gathered demographic, clinical, laboratory and coronary imaging data from 13,874 patients. A clear link between weight and cardiovascular events, high blood pressure and diabetes was established. When looking at patients who were underweight, normal weight, overweight and obese, there was an increase in the prevalence of diabetes (7, 10, 15 and 19 %, respectively), high blood pressure (37, 40, 46 and 59 %, respectively) and hyperlipidaemia (48, 52, 56 and 56 %, respectively) as weight increased [7]. Multivariate analysis identified high BMI as an independent risk factor for coronary heart disease and >50 % coronary stenosis. Obese patients also had a higher risk of myocardial infarction leading to death than non-obese people [7]. This can be explained by the role of adipokines in blood glucose regulation and fat metabolism [5] with the complex cascade of biological events that follows. This cascade involves interleukins (namely IL-6, TNF-α and IL-12), which results in obese persons having a permanent inflammatory condition [7].

Furthermore, these adipokines seem to play an important role in the biochemical processes that trigger osteoarthritis [6]. Recently, the contribution of adipocytokines to the knee joint cartilage degradation, osteophyte formation, infrapatellar fat pad alterations and synovitis has been highlighted [8]. Clinical studies have shown relationships between adipokine levels and cartilage volume loss [6]. For example, leptin triggers the development of an intra-articular inflammatory condition that is responsible for breaking down collagen and then osteoarthritis later on [6]. This may explain why osteoarthritis is more common in the obese, not only in weight-bearing joints such as the knees, but also in the hands [6]. Research is on going to identify new specific antibody-based drugs to control the negative effects of adipokines [5].

Epidemiology

The Global Health Observatory estimated to achieve optimum health, the median body mass index for adults population should be in the range of 21–23 kg/m^2 [1]. In 2014, approximately 13% of the global population were obese. Variations are shown by country: 26.8 % in America, 23 % in Europe, and 10.4 % in Africa. However, some conclusions are often drawn:

- average BMI steadily increases with age;
- there is an inverse relationship between obesity and household income and between obesity and town or city size;
- nearly three times more overweight people have diabetes that is being treated or requires dietary modifications; this increases to seven times more in obese people;
- the prevalence in the association of three cardiovascular risk factors is more than ten times higher with obesity and five times higher when overweight.

The relationship between osteoarthritis, age, gender, nationality and obesity was evaluated in a two-part French and European study of 63,232 households [9]. Hip and knee osteoarthritis increased significantly with increasing age for both genders, and then become more pronounced in women above 50 years of age [9]. The prevalence of osteoarthritis was correlated with the prevalence of obesity in region (R: 0.92 for the hip and 0.54 for the knees) [9]. As well, adjusted Incidence Rate Ratio was found about 1.06 (0.93–1.20) for hand, 1.04 (0.99–1.09) for hip, and 1.23 (1.19–1.28) for knee after adjustment for obesity [10].

With the population getting older and heavier, and osteoarthritis being correlated to these parameters, the number of obese arthritic patients needing care will increase [9].

Financial Consequences

Financial Impact

The direct annual cost attributed to treating obesity and its related diseases (hypertension, diabetes, etc.) was estimated in literature:

- the direct annual cost reached 1.37 billion Euros when all care was included, even if it was not directly related to the obesity;
- an obese person needs twice as many medical products as a normal weight individual;
- in a 10 year period, the percentage of health expenses attributed to obesity went from 0.7–2 % to 1.5–4.6 % of the global budget, but this did not include certain costs incurred by and for obese individuals (diets, treatments, specific equipment) that are said to be invisible and difficult to track [11].

The excess cost of performing orthopaedics and trauma surgery in obese patients has not been evaluated. For each operated patients, height and weight must be recorded in the patient's file and discharge summary; depending on the type of procedure, potential comorbidities and duration of hospital study, obesity can increase the cost of the stay [12, 13]. Diagnostic codes were created to capture obese children and overweight children and adults. These are in addition to the other codes created in 2006 for obesity (E66), which allows to better evaluate the cost of hospital stays attributed to these patients [13]. But these diagnostic codes do not affect the procedure codes and do not take into account the problems encountered by a surgeon caring for an obese patient [13].

Medical Imaging

Since obesity has a direct effect on image acquisition, changes must be made when the bones and joints of obese people are imaged. These patients should be referred to a radiology center experienced in managing obese patients, particularly for axial imaging because the standard protocols often need to be modified [14, 15].

Changes must also be made to standard radiographs because the increased tissue thickness in these patients increases photon scatter and reduces contrast [14, 15]. To get around these problems, the voltage must be increased but this in turn reduces the contrast even more. Increasing the exposure time increases the risk of motion artefacts during the acquisition [14, 15]. To avoid this phenomenon and improve the image, the user must narrow down the collimator beam, which reduces the field of view, reduces dispersion and reduces the need to increase voltage or exposure time [14, 15]. This is particularly true for joints near the trunk, notably the spine, shoulder and hip [14]. Not only is this a significant problem during preoperative imaging, it is even more challenging during the intra-operative period for trauma cases when fluoroscopy is used; this requires the surgeon to work with a classic fluoroscopy unit that allows the collimator to be adjusted [14]. These challenges extend to the postoperative period, especially when working with the hip [14]. The EOS® Imaging System (EOS®, Paris, France) may be able to capture better quality images without increasing the irradiation dose. It is currently being evaluated in the United States on obese patients [16].

During axial imaging, waist size and weight are more relevant than the BMI itself [14]. For a standard CT scanner, the weight limit is 202.5 kg (450 lbs) and the maximum gantry diameter is 70 cm (27.5 in) [14]. CT scanners suitable for obese people can accept patients with a waist size greater than 90 cm (36.5 in) [14]. An open MRI must be used for imaging, but there is still a limited number of available en MRI. This had led to the development of specialized imaging centers to improve the care of these patients.

Perioperative Period

Materials

The hospital environment must be adapted before the surgical treatment can start: beds, chairs, wheelchairs, bathrooms, and surgical tables. A standard surgical table is built to support a patient weighing up to 180 kg (400 lbs). Wheelchairs and patient lifts may have the same weight limitations. Moreover, specific instrumentation is required for surgical procedure for the obese patient [17].

Information

Although many operated patients are overweight, published complications rates are similar to patients having a normal BMI [15]. When caring for an obese patient, the patient and the patient's family must be informed of certain data before the surgical procedure gets under way (Table 19.1):

- in obese patients with a BMI between 30 and 40 kg/m^2, the risks of thromboembolism and infection are doubled;
- in patients with BMI >40 kg/m^2, general mortality is twice as high as for a normal weight individual [14], post-surgery mortality rate is nearly 4 % [18], anaesthesia and surgery times are significantly higher [18] and infection rates after TKA or THA are nearly 5 % [19].

In a recent study looking into the mortality rate in a population of 1.46 million Caucasian adults, general mortality, with all causes combined, was higher in overweight patients (RR: 1.88) and obese patients (RR: 2.51) [14]. The relative risk was even higher when these patients underwent surgery [20].

Table 19.1 Ten key points

Key points
1. In 2014, 13 % of the worldwide population were obese with a BMI >30 kg/m^2
2. Obesity is an orthopaedic challenge because of increased loading and the patient's pro-inflammatory state related to fat metabolites
3. Obese patients have difficulty walking, which leads to falls and increases the number of comminuted fractures in the extremities
4. Diabetes and comorbidities must be controlled as well as possible before any surgery
5. Morbidity and mortality of obese patients during the perioperative period is significantly greater than in patients with BMI <30 kg/m^2
6. During hip and knee arthroplasty, the infection rate is nearly 5 % in obese patients and nearly 10 % in obese, diabetic patients
7. Anesthesia and operative time are significantly greater in all published studies
8. Significant improvement in pain and function scores have been reported in various studies, although functional scores and long-term implant survival is lower than in patients with normal BMI
9. Arthroplasty will not trigger weight loss and bariatric surgery does not help reduce complications during the arthroplasty procedure
10. One of the key aspects of care lies in informing the patient and his/her family

BMI body mass index

Risk of Medical Complications

Medical consequences of obesity, especially heart and lung problems, have a direct impact on perioperative management and the consequences of anaesthesia [18]. One third of patients having a BMI >40 kg/m^2 had to be admitted to intensive care and 9 % needed respiratory assistance [18]. Anaesthesiology teams must be especially vigilant with these patients, and anticipate the possibility of a difficult intubation, including laryngoscopic intubation [18]. Doses of antibiotics and anaesthetics must be adapted to the distribution volume [18]. Spinal anaesthesia or local anaesthesia is potential solutions for limiting the respiratory complications seen with general anaesthesia, but these alternative methods are difficult to carry out and take more time [21].

Patient Position

The patient must be positioned carefully. Even though the soft tissues are fairly thick, obese patients are at risk for pressure sores and nerve compression [19]. When the surgical procedure allows it, lateral decubitus will make ventilation easier [18, 19].

Incisions

In trauma and elective surgery, the incision size must be adapted to the BMI to provide good exposure and minimize tension on the skin, which is quite fragile in these patients [22].

Prevention of Thromboembolism

Obesity is a risk factor for thromboembolic events [23]. The standard recommendations for duration of use of anticoagulants apply to these patients [23]. There is no published data or official recommendations on the need to prescribe anticoagulants to an obese patient for a procedure where anticoagulants are typically not used, such as arthroscopic meniscectomy [23]. However, mechanical prophylaxis is recommended [23]. Compression stockings and bandages are not well tolerated by obese patients. This is why plantar pump systems called intermittent pneumatic compression devices are heavily used in the United States [23].

There are no dose recommendations for prophylaxis drugs and no study up to now has been able to identify a dose that prevents thromboembolic complications without greatly increasing the risk of haemorrhage for obese patients [23]. In the United States, the AAOS does not recommend either low-molecular weight heparins or new oral anticoagulants, which is consistent with ACC/AHA and ACCP guidelines [23]. Although there are no clear recommendations in terms of dose or duration, it is also important to prevent venous thrombosis in obese patients undergoing surgery in the upper limb [23].

How Orthopaedic and Trauma Surgery are Affected by Obesity?

Children and Teenagers

The prevalence of childhood overweight and obesity has risen substantially worldwide in less than one generation. In the USA, the average weight of a child has risen by more than 5 kg within three decades, to a point where a third of the country's children are overweight or obese [24]. Obesity has a direct impact on a child's quality of life, as it impairs mobility and produces a slower, more tentative gait [15]. Elevated leptin levels in obese children and teenagers also affect bone density, leading to greater bone fragility [15]. Knee, foot and back pain are statistically more common than in a control paediatric population [15]. Obesity also has a biomechanical impact on growth plates by making bones mature more quickly; genu valgum and genu recurvatum deformities are also more common, no matter the gender [15, 25].

Obesity and Trauma in Children

A link between obesity and paediatric fractures has been suggested recently. Obese children have greater fracture risk relative to healthy children, especially in the forearm, femur and lateral humeral condyle [22, 26]. Various groups have estimated the rate to be 1.6 times higher than in the general population. In addition, these fractures are occurring with lower-energy trauma in overweight children and occur mainly in distal part of the forearm [22, 26].

Databases have shown the risk of extremity fractures following high-energy trauma is higher in obese children, but the risk of brain trauma is lower [22]. These children and teenagers also have more anaesthesia-related problems because of higher baseline blood pressure and a higher frequency of asthma and sleep apnoea [22].

Materials used during surgery must be adapted to the child's weight. This is particularly true for femur fractures, where rate of complications such as wound healing problems, non-unions and malunions is higher with obesity [26]. These observations are especially true for unstable femoral fractures treated by flexible intramedullary nailing [26]. When the child's age allows it, these fractures should be stabilized through standard IM nailing [26].

With long bone fractures, obese patients have a similar number of complications and time to return to activities relative to a control

group [26]. But there were more complications in trauma cases involving obese children: pressure sores (1 % vs. 0.2 %), DVT (0.7 % vs. 0 %), re-fracture, infection, wound healing problems [22, 26].

Recommendations in paediatric trauma surgery can be summarized as follows: inform parents of potential anaesthesia and complication risks and choose an appropriate bone fixation material during surgery [26].

Obesity and Elective Surgery in Children

In Blount's disease or pathological tibia vara, a strong correlation was found between BMI and the magnitude of genu varum. The failure rate of standard hemi-epiphysiodesis treatment was higher in children with a BMI >45 kg/m^2 [25]. There is also a positive correlation between obesity and genu valgum, especially in girls [27]. Some advocate performing epiphysiodesis in severe genu valgum secondary to abnormal lateral femoral physis in girls; this abnormality has been attributed to micro-trauma, obesity and genetic predisposition [27].

Slipped capital femoral epiphysis has higher prevalence, occurs earlier on and is more often bilateral in overweight or obese paediatric populations than non-obese ones [28]. It has also been shown that reducing BMI after treatment of slipped femoral epiphysis on one side reduces the risk of it happening on the other side [28].

In scoliosis, the effectiveness of external corrective devices (e.g. corset) is reduced and the effectiveness of conservative treatment using a corset in obese children and teenagers is often limited [29]. There are more kyphosis deformities after surgical treatment, but no significant increases in morbidity and mortality [29].

A trauma or orthopaedics case presents a golden opportunity to refer an obese child to a team specialized in childhood obesity [30]. Weight loss programs in children in combination with suitable sports activities have led to excellent results in terms of weight loss and limitation of orthopaedic complications related to obesity [30].

Adults

Traumatology

Obesity and Fracture Types

Obese patients are exposed to select types of musculoskeletal injuries and their mortality rates are higher when subjected to high-energy trauma [22, 31]. Cross-sectional studies in the United States have shown that adults going to the emergency room after an injury have a 15 % higher likelihood of being injured if they are overweight and 48 % higher likelihood if they are morbidly obese [22, 31, 32].

In motor vehicle accidents, obese people are relatively protected from abdominal and pelvic injuries because of their soft tissues [33]. However, they are more likely to incur a pelvic ring injury, because energy absorbed by the abdomen is transferred to the pelvis. They are also more likely to fracture peripheral structures such as the distal femur, ankle or calcaneus and also experience degloving injuries [32–34].

Even with low-energy trauma, they have a tendency to experience comminuted fractures with skin and soft tissues injuries, especially at the distal end of long bones [31, 34]. Knee dislocations following low-energy trauma have also been described in obese people, with a high rate of neurovascular complications, which may require amputation of the leg [22]. In the upper limb, fractures following low-energy trauma are also more common because of ambulation problems related to large amounts of soft tissues, leading to falls onto an outstretch arm, often causing comminuted fractures [31].

The relationship between bone density and obesity is not well defined. It was initially thought that overweight and obese patients had higher absolute bone density, but this difference disappeared when the values were adjusted to the lower BMI in the control group patients [22]. The increase in the overall bone density found in obese patients is probably not enough to compensate for the excess loads placed on the skeleton, especially during falls onto the arms [22, 31].

After menopause, obese women take more falls than non-obese women, however the former group experiences fewer proximal femur fractures, probably because the fall is cushioned by soft tissues around the proximal femur [22, 32]. Research is now being done into how leptin could prevent osteoporosis and potentially even replace oestrogen [5].

Imaging Evaluation

The care of obese trauma patients first requires greater attention during the patient information stage and when evaluating the injury [20, 22]. For example, because of the thickness of soft tissues at the proximal femur, obese patients have a higher risk of having an undetected fracture above an ipsilateral fracture of the femoral shaft [20, 22]. The radiology adjustments recommended earlier on must be followed. Axial CT scanning must be systematically requested when standard radiographs are inconclusive or not of good enough quality, despite narrow collimation of the beam [20, 22]. With articular fractures, intra-operative arthrography, feasible but probably difficult to perform, could be used to optimize screw placement in femoral neck and proximal femur fractures [20, 22].

Technique and Fixation Choices

Cast immobilization of the limbs and temporary or permanent traction are very difficult to achieve in obese patients. Obesity makes any indication for conservative treatment difficult thereby forcing the surgeon to perform internal fixation. For example, immobilizing a humerus fracture along the chest of an obese woman causes arm abduction, which could be detrimental to fracture alignment [32].

The biggest problems occur with femoral IM nailing. Retrograde nailing is preferred over anterograde nailing since bleeding, surgical time and irradiation are lessened [22, 32]. But if the type of fracture requires anterograde nailing, the patient should be placed in lateral decubitus and the trochanter entry point moved laterally [32]. The largest possible nail diameter must be used, with multiple screws providing static locking to optimize the construct stability in as these patients have trouble achieving partial weight bearing. As a consequence, the risk of non-union and secondary displacement is higher in obese patients than in normal ones [32]. There are no scientifically based recommendations on the type of implant to use. But materials having the potential for contact welding must be avoided in obese patients.

Complication rates are higher in obese patients relative to patients with normal BMI. The complication risk is 6.8 times higher and the need for re-operation is 4.7 times higher in pelvic ring fracture patients having BMI >30 kg/m^2 relative to ones with BMI <30 kg/m^2 [33]. In distal tibia or tibial pilon fractures, obesity was thought to have protective effects relative to skin problems. But evidence of the opposite now exists [33]. In a register including 867,282 patients admitted for proximal humerus fractures, obesity was found to be one of the factors increasing the risk of complications and duration of hospital stay [35].

Elective Upper Limb Surgery

Obese patients are more likely to experience micro-trauma injuries to their upper limbs than patients with normal BMI because of their motor control problems [22]. Carpal tunnel syndrome is also more common, but weight loss has no effect on nerve conduction speed [22]. Obese patients also have more rotator cuff injuries [36]. After rotator cuff repair, there is a significant improvement in function and quality of life, even if the surgical outcomes are worse than patients having normal BMI [36]. With shoulder arthroplasty, obese patients experience significant improvements in function and pain over the long-term, but have more surgical and perioperative problems and higher complication and failure rates than patients with normal BMI [37]. Similar findings were reported for arthroplasty of the lower limb.

Elective Lower Limb Surgery

A clear link has been established between osteoarthritis and obesity, not only due to excess mechanical loads but also due to the biological

effects of adipokines on cartilage. The obesity effect is more efficient in the knee than the hip [5, 6, 8]. The Canadian arthroplasty register has shown that a person with BMI >30 kg/m^2 is 8.5 times more likely to need a joint replacement than someone with a normal BMI; this relative risk increases to 18.7 times if BMI >35 and to 32.7 times if the BMI >40 [4, 22]. Also, obese patients are operated an average of 10 years earlier than patients with a normal BMI. Weight loss is effective not only for symptoms but also the kinetics of the pathology [4, 22].

One may think that operating on obese patients once they can no longer walk will help them to lose weight once they recover normal function and can expend more calories [38]. But a recent meta-analysis has shown that only 18–49 % of patients had lost a significant amount of weight 1 year after the surgery; however many of the included studies had important limitations (patients lost to follow-up, differences in follow-up methods) [38]. Patients cannot be told to expect weight loss after surgery [38]. Thus it seems more logical to ask patients to lose weight before the surgery to reduce the magnitude of symptoms. But this weight loss is often difficult to achieve, even when a team of nutritionists and endocrinologists surrounds the patient. Before performing a regular procedure on a menopausal obese woman having followed high-protein diets, her calcium and phosphate levels must be measured. This type of patient often has significant deficiencies, especially in vitamin D, which may make bones more fragile [22].

Another question often asked when working with morbidly obese patients (BMI >40 kg/m^2), is the need to have them undergo bariatric surgery before arthroplasty. A recent American study clearly found the answer to be "No" [39]. This level II study included 125 patients undergoing total knee arthroplasty. The anaesthesia duration, total operative time, tourniquet time, length of hospital stay, complication rate after 3 months, and transfusion rate were compared between three groups of patients: TKA before bariatric surgery, TKA within 2 years after bariatric surgery, and TKA at least 2 years after bariatric surgery in patients having maintained their initial weight loss. The group with the TKA at least 2 years after bariatric surgery had significantly lower anaesthesia time and operative time, but there was no difference in complication rate and length of hospital stay. The authors concluded that the complication rate was elevated in all three groups and that none of the three solutions were ideal, even if the patient had lost weight due to the bariatric surgery, maintained the weight loss and the metabolic adaptation period had passed [39].

Beyond the mortality and the respiratory and thromboembolic events described earlier, infection is the main problem in these patients. A study with 7181 TKA and THA patients showed an increase in the infection rate from 0.57 % in patients with a normal BMI to 4.66 % in patients with morbid obesity [19]. Diabetes doubled the infection rate, independent of the presence of obesity (RR: 2.3) [19]. In patients who are morbidly obese and diabetic, the infection rate was 10 % [19]. The authors questioned whether it was justified to operate on these patients, but this question remains unanswered [19]. But it seems of the utmost importance not to operate on these patients unless the diabetes is completely under control [19]. The patient information step must include this infection risk, which is relatively higher than in patients with a normal BMI. Since this risk is correlated to diabetes and increased in diabetic patients, diabetes must be well controlled and managed during the entire perioperative period [19].

Hip Surgery

Obesity increases the duration of anaesthesia, operative time, and the bleeding, complications and dislocation rates during hip surgery. The surgical approach does not influence the outcome, as long as appropriate retractors are used [40]. With minimally invasive surgery, the skin incision should be at least one third as long as the BMI value (9 cm for BMI of 27 kg/m^2 and 11 cm for BMI of 33 kg/m^2). The fracture risk is not increased, despite the cortical index being lower. Since the risk of instability is higher, devices reducing the risk of dislocation must be available when elective total hip arthroplasty (THA) is performed. But there is currently no data to support

recommending systematic use of dual mobility cups, even if they are beneficial in patients at risk for dislocation, with obese patients being part of this at-risk group [40]. Other groups have shown that THA is successful even in obese people, with almost no increase in complications (other than wound healing) and excellent functional results. The authors concluded that obese patients should not be denied the opportunity to have THA solely based on their BMI [41]. In case of arthroscopy procedure of the hip, obese patient had lower absolute patient-reported outcome, but showed similar gain in hip improvement [42].

Knee Surgery

With total knee arthroplasty (TKA), the likelihood of intra-operative surgical problems can be anticipated by calculating the anthropometric suprapatellar index, which is the ratio of the length of the lower limb to the suprapatellar circumference. The surgery will be more challenging if this ratio is less than 1.6 [43]. In patients with BMI >35 kg/m^2, intramedullary tibial cutting guides should be used instead of extramedullary ones to reduce the likelihood of errors related to soft tissue volume [43]. Although it seems logical to use a tibial extension keel because of the larger forces being applied to the tibial component, no clinical or biomechanical data support this practice [43, 44]. Since polyethylene wear is not common at the knee, using a thicker tibial component is not recommended, because it would lead to the tibial cut being made more distally in lower-quality bone, and a higher risk of loosening [43, 44]. Although some studies have found that unicompartment knee arthroplasty provides less good results in obese persons, this procedure is not absolutely contraindicated. It is actually recommended by some authors because morbidity and mortality are lower than TKA in this at-risk population [22].

Obesity limits the survival of the arthroplasty and also reduces clinical functional scores, mainly due soft tissues reducing the amount of knee flexion [44, 45]. Nevertheless, it is important to note that improvements between the preoperative and postoperative condition are often greater in obese patients than ones having a normal BMI [46]. Patient satisfaction trends are similar.

Conclusion

Treating musculoskeletal injuries in obese patients is a genuine challenge for the orthopaedic surgeon. In every case, the surgeon, patient and family must be aware of the potential complications and risk of death, infection or failure because of the obesity.

In traumatology, the need to perform surgery is rarely brought into question. In elective orthopaedic surgery, the expected benefits of the procedure must be balanced with the perioperative risks. Any diabetes must be fully controlled and associated diseases managed to reduce the risks as much as possible. Specific measures must be taken relative to anaesthesia, patient positioning, instrumentation and surgical approaches.

Although significant improvement in functional and pain scores have been observed, the functional scores and long-term survival of the joint replacement implants are lower than in patients with normal BMI, while morbidity and mortality are higher. But despite this elevated complication rate and the problems encountered, the quality of life in obese patients can be significantly improved through a surgery that is increasingly in demand. In the coming years, the care of obese patients must be optimized in a multidisciplinary manner, without forgetting about prevention.

Disclosure of Interest The authors declare that they have no conflicts of interest concerning this article.

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New Technology in the Assessment and Treatment of Obesity

20

Sofia M. Ramalho, Cátia B. Silva, Ana Pinto-Bastos, and Eva Conceição

Introduction

With the demand of weight loss interventions, likely to continue its upward trend over the next decades, the question remains on how to continuously monitor and support obese individuals, particularly at long-term basis. Moreover, as the burden of the obesity rates increases in health care centers, the development of alternative delivering strategies gains attention. In an environment of limited resources, the recent development of new-technology based programs seems to be a promising area to deliver cost-effective interventions to a wide number of individuals.

The use and access to various new technology based devises are increasing globally. In 2014, 44 % of the households worldwide had internet access at home and three billion (40.4 %) were internet users (78 % in developed countries, primarily in Europe and Americas, and 32 % in developing countries) [1]. Most of non-internet users (90 %) were from developing countries [1].

Moreover, 4.55 billion people worldwide are estimated to possess mobile phone(s), being 1.75 billion smartphone users. Consequently mobile-broad usage is increasing globally, with 84 % of penetration in developed countries and approximately 2.23 billion users worldwide [1, 2]. Furthermore, it is estimated that by 2017, 8 out of 10 mobile phone holders will own a smartphone [2]. The reality among adolescents, is not different: between 12 and 17 years old adolescent in the U.S. go online mostly using mobile devices, 78 % own a mobile phone and 47 % of those use smartphones [3].

Although the heterogeneity of existing data, Internet and technology are used transversely by age groups, from young people to the elderly. In spite of the physical and learning difficulties associated with the use of such technologies, in 2014, 77 % of the U.S elders owned a cell phone and 59 % report going online [4]. Additionally, a great percentage of minority populations also owned smartphones in the U.S. [5], emphasizing the importance of mobile technology as a privileged tool for clinicians and researchers in multicultural interventions.

In 2012, around 72 % adult Internet users in U.S. searched online for health information, whilst 52 % and 31 % of smartphones and cell phone owners, respectively, used their phone to search for medical and health information [6, 7]. Moreover, different types of technology tools such as mobile phones with advanced software applications (app), spreadsheets or websites are being used to track diet, weight, physical activity routine, blood sugar, systolic blood pressure, and sleep [7].

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Behavioral treatments are recommended as first line interventions for overweight and obesity, resulting in weight loss and its maintenance. However, the traditional behavioral treatments have a propensity to be especially complex, time demanding and expensive for provider and patient. Thus, programs delivered by digital platforms represent great potentialities since they combine the growing accessibility to digital technology and devices with the need of more effective treatments to overweight and obesity, capable of reaching a wide number of individuals at a low cost [8].

Digital Health and Obesity

Digital Health is a broad term that includes miscellaneous denominations such as mHealth (mobile health) and eHealth (electronic health), frequently describing health-related technology used in health care and public health. Hardware sensors, software applications, mobile electronic devices, web applications, Internet, social networking and wireless devices are some of the most used features in digital health interventions [7, 9]. In the context of obesity, digital health can provide pertinent interventions tools to patients and institutions in different areas such as health promotion, diagnosis, self-monitoring, treatment compliance (e.g. appointment attendance) and intervention programs [9].

Lifestyle choices importantly have impacts on individual's health, and unhealthy eating habits or diets, low physical activity levels or sedentary lifestyles have been associated with obesity [10]. Researchers and clinicians have been studying different strategies to train behavioral change skills via technological tools in order to promote health behaviors, prevent obesity-related lifestyles and, ultimately, prevent obesity [7, 11]. For this purpose, development of different delivering strategies for interventions aimed to increase health behaviors, such as physical activity, healthier eating habits and intake of healthy foods (e.g. fruits and vegetables) [12].

Traditional behavioral weight loss treatments are generally provided on a weekly basis for a period of 4–6 months, consisting in three key components: goal setting, self-monitoring, and stimulus control. In this context, psychoeducation on eating and physical activity can be implemented to provide an additional support to the trained skills. These behavioral interventions are usually offered as face-to-face individual treatment, group session or by digital technologies [8].

The greatest challenge in obesity treatment is long-term maintenance of weight loss. This difficulty is mainly due to the need for frequent medical appointments over long periods of time, which lacks feasibility and is often hard to maintain [13]. Thus, developing effective weight loss maintenance programs that are cost-effective and time-saving has become a health care priority [11].

Internet weight loss programs for obese adults have promising outcomes and may be a powerful alternative to overcome difficulties of long-term weight loss maintenance. Overall literature confirms several advantages regarding the use of new technologies in health behaviors programs: (i) potential to reach large numbers of individuals (ii) cost-effectiveness; (iii) availability to diffuse information; (iv) facility and readiness to use; (v) permits long-term patient-provider contact; (vi) guaranteed anonymity and privacy [7, 11].

Different functionalities of these programs are thought to have important roles for intervention. For example, self-monitoring, posts to bulletin boards, chat rooms, peer support and progress charts are features that have been associated with greater success [14]. Specifically, self-monitoring is one of the most relevant strategies on weight loss programs and is transversely used in digital based and face-to-face interventions for obesity. It allows regular monitoring of target behaviors, and, when combined with feedback strategies, it increases effectiveness of interventions improving physical activity levels and healthy eating [15].

However, adoption of digital technologies can have important implications that should be considered in the process of designing weight loss or weight control interventions. First, research suggests that implementation and adherence to these techniques for weight loss may be limited and, despite its apparent feasibility, it may vary depending on delivering strategies [15]. Moreover, the applicability of prevention or treatment

programs to different populations, digital literacy of particular populations and readiness of participants to use these programs or access to specific devices should be considered. In fact, researchers still need to explore new ways of delivering these techniques for weight loss interventions and to facilitating its implementation as well the compliance to these treatments [15, 16].

In the next sections of this chapter, current research on obesity assessment, prevention and intervention based on new-technologies will be explored. Specifically, we will discuss the use of mobile electronic devices, web-based tools, virtual reality and gaming, as well as other technological tools and methodologies such as Ecological Momentary Assessment (EMA) and Ecological Momentary Interventions (EMI) devices, that can be used to endorse and intervene on health behaviors related to weight loss and weight control.

New-Technology Devices and it Applicability

Mobile Electronic Devices

Mobile Electronic Devices (MEDs) are able to provide automatically individualized materials as well as to deliver content through equipment carried by the person. MEDs can include cell-phones, smartphones, personal digital assistants (PDA), tablet PCs and handheld video-game consoles [9, 17].

MEDs are thought to be effective in promoting health behaviors. For instance, mobile phones have the capacity to evaluate and to disseminate information, have input and output audio capabilities, and the opportunity to provide information and feedback for a large number of people [18]. The use of mobile devices also appears to enable effectively self-monitoring methods because they are portable, accessible, easy to use and convenient [15]. Additionally, mobile phones are not limited to a specific socioeconomic and demographic status, group or country, being currently a part of everyday life for most people [18]. For this reason, this type of devices may be an ideal instrument to use in programs for behavioral change and to promote healthy lifestyles [16].

For example, Personal Digital Assistants (PDA) have been effective in increasing adherence to self-monitoring of eating and physical activity, with a direct effect on weight loss and an indirect effect on weight-loss maintenance [19]. Previous research also showed that PDA increases adherence to self-monitoring, and that weight loss outcomes, when compared with the use of traditional paper diaries, are superior [20, 21]. However, PDAs are now obsolete and have been replaced by other tools, such as smartphones with self-monitoring apps [19].

On the other hand, short message service (SMS) is a specific tool of every mobile phone, which is increasingly used by most people. This tool seems to be efficient to promote behavioral changes, presenting specific advantages: accessibility at all times and everywhere; fast, easy and interactive communication; and is inexpensive [16, 22].

The effectiveness of text messaging has been studied for the last few years. Research has demonstrated that text SMS technology is effective in disease prevention and interventions specifically for weight loss, smoking cessation, and diabetes management [22]. Also, it may contribute to patient's readiness to change and to their willingness to seek help before treatment [18]. A recent meta-analysis on the efficacy of text messaging based in health promotion revealed that this tool has great potential for improving a range of health behaviors and health outcomes, including physical activity and tobacco cessation [23]. Nevertheless, some authors conclude that text messaging should not be considered a standalone model for behavior change, rather as a tool to assist behavior change methods [22].

In the context of obesity prevention and health behaviors, recent studies support SMS as a useful tool for behavior change interventions and to promote health behaviors [22], such as healthy eating or physical activity. Recent randomized control studies showed that daily tailored SMS and MMS increase fruit and vegetable intake relative to the baseline levels, when compared to control groups [12, 15]. For instance, Silva and colleagues implemented a program that uses text messaging as a tool to promote behavior change in children

providing support and feedback based on specific goals: decrease screen time, increase fruits and vegetables consumption and the number of steps per day (physical activity). This RCT showed that the group of children that monitored and received feedback through SMS had higher fruits and vegetables intake throughout the intervention phase, compared to the control group [24]. In addition, other authors suggest that children seem to prefer and be more compliant to new technological and interactive program than paper-pencil or other traditional monitoring tools [25].

The *Keep It Off* study tested the use of mobile phone as a weight maintenance strategy after successful weight loss. Intervention included a set of phone sessions focusing on key weight-loss maintenance behaviors and skills followed by continued self-monitoring and reporting of weight, feedback and check-in calls and, for those who experience a small weight regain, additional calls with a specialized coach. Data suggest that *Keep It Off* participants showed higher levels of physical activity, moderate levels of dietary intake, frequent breakfast eating, and frequent self-weighing [26].

Nonetheless, literature is yet full of mixed results and some studies did not find differences in terms of weight, eating behavior or psychological well-being in obese children after using similar programs including frequent monitoring of target behaviors and personalized feedback [27].

Despite the heterogeneity in research results, mobile devices seems to be an effective approach to increase physical activity, specially smartphone technology [17], the use of smartphones' applications ("apps") is growing in the market today, allowing a new generation of personal use. Therefore, this rapid growth in the use of smartphones has opened a new world of opportunities for use in behavioral health care [28]. Currently, research is exploring the development and evaluation of apps regarding the promotion of health behaviors, and has referred many potentialities of this tool in the specific context, such as: psychoeducation, resource location, tracking, monitoring and feedback [28], allowing individuals to receive information about everyday lifestyle choices that supports them to better care of their health.

Some studies have explored the use of mobile phones and users' view of apps with health-related content. Dennison and colleagues reported that precision, legitimacy and security of the data, effort required, immediate effects on mood, capacity to record and follow behavioral goals, ability to provide information, quick advice and goal-setting feature were the most desired functionalities of the apps [29]. Moreover, smartphone apps' interventions for obese adult showed more satisfaction, acceptability and patient adherence and lowest drop-out rates when compared with website and paper diary interventions [30].

Although there is great potential of these singular devices in weight loss programs, interventions combining different delivering devices, such as internet-based and SMS with personalized feedback, showed that combined technologies in a cultural integrated scheme optimize weight loss interventions in college students [31].

Despite the variability of apps focused on the engagement of healthy eating and physical activity habits to facilitate weight loss, the efficacy of the majority of these tools is unknown and very few included structured training in empirically validated weight loss strategies [7]. The heterogeneity of numerous apps available, absence of evidence and the lack of theory-based weight loss strategies in apps, together with the frequent software updates of MEDs can be important limitations when conducting clinical trials. Future studies should explore provider–participant communication, cost-effectiveness, ideal timing and regularity of interventions [32]. Certainly, there is a need of further investigation, but smartphones seem to have great potential that encourages its use in promoting healthier lifestyles and particularly in increasing physical activity [7, 17].

Web-Based Tools

Web-based tools are programs that can be accessed in any device connected to Internet including desktop or laptop computers or even smartphones. Recently, an increasing number of interventions designed to promote changes in health behaviors (such as physical activity,

tobacco use or eating) have been delivered via Internet and computer-tailored programs [33, 34]. Evidence shows that Internet methods are effective in treatment, but also in promoting healthy eating patterns and behaviors. In fact, effectiveness of this tool has been linked to the inclusion of a variety of behavior's modifying techniques, and additional interactive features [33].

Some considerations should be taken into account when designing web-based weight loss programs. First, different features such as social and professional chat-rooms, self-monitoring applications, customized meal planning, and weight tracker may have distinct impact on results and adherence to these programs [14]. Adherence is also predicted by frequent usage, interaction with a counselor and engagement on dialogue support [34]. Second, inclusion of social networking features and custom-made meal planning suggestions delivered via web-based weight loss programs are associated with increased number of days logged in the system. Additionally, the use of a weight tracker tool is correlated with increased weight loss [34, 35].

The use of web-based programs to carry out weight loss interventions is a widely under-evaluated area with divergent designs and results, which hinder generalization of weight outcomes [11, 14]. However, research points to a modest effectiveness of this type of programs regarding weight loss, suggesting that web-based weight loss interventions with counseling and personalized feedback features produce better weight loss results than web-based weight loss interventions with education features only [14]. In addition, recent findings shows that web-based computer-tailored programs can result in will to change to healthy diet and eating behavior, on personal awareness and on intentions related to intake of fat, fruit and vegetables [36].

Web-based programs also show promising results as weight maintenance strategies after weight loss interventions [37]. Despite initial lower weight regain associated with these interventions some authors suggested that there are no differences on weight regain or weight maintenance between interactive technology–based interventions and self-directed groups in longer-term assessments [37–39].

Overall, advantages of web-based interventions overlap with those of other technological devices. Internet-based programs can provide immediate and personalized feedback and information; with computerized technologies, the access to information is immediate, being easier find accurate and updated information; it allows anonymity of participants, provide mutual support and help the user to search for services at their convenience [40]. Additionally, computer-based programs can be designed in ways to make intervention appealing and entertaining, increasing the engagement and the adherence of the participants [40].

Gaming and Virtual Reality

Gaming

In the U.S. an estimated 58 % of the population (mostly young) plays video games. This is a technological achievement that could be incorporated and played using many digital devices (Internet on personal computers, game consoles, mobile phones, etc.), and can include a wide range of goal settings [7, 41].

Video games can be effective in promoting healthy lifestyles because of its capacity to involve solo players with the game and is a way to deliver health behaviors information and experience through an entertaining format [41]. Research demonstrates positive health-related changes resulting from playing video games, and the advantages of its use should be considered beyond entertainment [42]. For instance, Burns and colleagues developed one system that used a video game based on cognitive therapy to improve wellbeing and mental health, suggesting that this tool promotes engagement and knowledge among young people, and showed that female participants reduced their psychological distress and increased mental satisfaction [43]. Other studies underline clinical implications associated with video games, specifically improvement of patients' participation, knowledge and adherence to treatments designed for anxiety, burn pain, and others disorders [42].

Up to date, very few research have been published on the use of videogames for weight

loss or obese samples. However, there is preliminary evidence that video games are powerful tools for improving healthy eating, physical activity and nutritional knowledge in childhood and elementary school students [44, 45]. One study showed that a video game focusing on promoting healthy eating was highly accepted by school students, and the majority of students presented an increase in positive attitudes towards healthy eating, healthy eating self-efficacy and marginally significant increases in nutrition knowledge [45]. Despite this fact the overall capacity and advantages of video games, active video games (unlike hand-controlled video games), promote light to moderate physical activities and higher energy expenditure in children and youth. In fact, active video games played predominantly through lower body movements showed higher energy expenditure than active video games played mainly with upper body movements [46]. Research also shows some advantages of the use of video games: improve self-control through goal setting, imply focusing attention on precise behavioral modifications, promote entertainment and consequently intrinsic motivation to behavior change [41].

Still, little is known about the use of electronic or video games for health related behavior change. Future research on the use of video games should consider increasing challenging tasks including milestones in the game, which can be used to shape health behavior and, in particularly, weight loss [7].

Virtual Reality

Virtual Reality (VR) technology allows the construction of virtual scenarios analogous to the real world, thus not only providing a valuable clinical tool with a wide-ranging applicability to all-purpose interventions, but also to overweight and obesity behavioral treatment [10, 47]. In some VR technologies, such as *Second life Web* application, there is the possibility of creating a digital self-representation of the user (Avatar). This can be used to motivate health behavior through the *Proteus Effect* phenomenon, in which an individual generalizes the avatar performance and behaviors to the real world environment [7, 48]. As a result, for instances, VR users seemed to increase physical activity when their avatar does the same [47].

VR is a more immersive technology that stimulates further sensory modalities than typical interventions, and preserves ecological validity by rigorous control of situational parameters during the interventions. Furthermore, VR seems to be efficacious in improving weight loss maintenance, perhaps due a protected and confidential environment provided for self-training of behavioral weight management skills, which are supposed to reduce resistance in adopting new healthy behaviors [47, 48].

Sullivan and collaborators provided evidence for this effect in a randomized study that compared weight loss and weigh maintenance after use of *Second Life* virtual world application *versus* face-to-face interventions. Weight loss was superior in face-to-face interventions, but virtual reality showed greater effect on weight maintenance [48].

Virtual coaches can be an additional application of VR. In fact, these can be an affordable tool to increase treatment adherence in obesity, since when compared with human coach or support group, virtual coaches can be accessed frequently, delivering an immediate continuous support and assistance (e.g. through a smartphone) [7, 49].

Current literature supports the effectiveness of VR-based interventions to obesity treatment as well as to promotion of self-esteem, self-efficacy and reducing body image dissatisfaction. However, due to the wide range applicability of this technology, more research is needed to explore new interventions. Up to date, published studies include important methodological limitations such as small sample size and lack of follow-up data that compromise clear conclusions on the effectiveness of these treatment delivering strategies [10].

Ecological Momentary Assessment and Ecological Momentary Interventions

Ecological Momentary Assessment (EMA) and Ecological Momentary Interventions (EMI) are recently developed strategies based on the

potentialities of new technologies to provide a means to assess and deliver tailored interventions in "real time" (momentary) and in natural environment (ecological).

Studies with retrospective designs, laboratory-based and/or supported on self-report measures are unable of analyze temporally the course of ongoing behavioral, physiological and psychological processes in natural environment of participants due to limitations of data collection [50].

EMA is a type of behavior sampling technique that permits collecting "real time" data about variables of interest in individuals' natural environment. EMA can be employed to self-monitoring physiological, behaviors, affective and cognitive correlates focusing on immediate experiences (e.g., in the preceding 5 min), or on events that happened over longer time intervals (e.g., in the preceding 45 min) [51].

Originally, EMA used diaries or daily self-report questionnaires. Nowadays due to advances in technology, the signaling on EMA is conducted by handheld electronic devices such as personal digital assistants (PDAs), cell phones (e.g. text messages) [51], smart phones [52], programmable wristwatches, and web based computer programs [50, 51].

When compared to self-report measures, this is a wide-ranging and sensitive type of assessment technique, since it allows to obtain detailed measurements on a wide variety of factors, observing and collecting data on the natural environment of participants increasing ecological validity to data [50, 53]. Furthermore, these devices allow for on-time self-monitoring with several advantages over typical self-report methods, particularly due to the reduced retrospective recall bias [51]. Moreover, multiple assessments occur over time and temporal relationships among variables can be explored. These data allow more complex and nuanced research and clinical questions about dynamic associations and processes that occur over time. Summing it up, this is a sensitive methodology that can detect small behavioral changes, making possible or facilitating the study of more complex research themes [53].

EMA has been applied to the study of diverse populations such as eating disorders, attention-deficit hyperactivity disorder and borderline personality disorder [53, 54], and to investigate correlates of different variables related to obesity. For instance, previous studies have investigated emotional or physiological (e.g. hunger) precedents of different eating episodes, finding an association between these variables and compulsive eating [55]. Other authors, suggested that negative affection and interpersonal problems are associated with loss of control eating, and that mood and abstinence-violations were related to relapse crises in dieting [56, 57]. Situational variables have also been investigated with previous literature, bringing evidence to the association between television exposure, phone messaging and video game use with cravings for unhealthy snacks and sweetened drinks in different groups of adolescents [58]. Additionally, EMA studies suggest that individuals with higher weights tend to be more susceptible to the presence of palatable foods in the environment, supporting the importance of limiting exposure to good tasting high-calorie food [53].

Besides assessment, ecological momentary systems may serve as a tool to deliver tailored interventions. In obesity treatment, compliance with everyday healthy behaviors is crucial for weight control. Clinicians have long sought to extend their input into patients' everyday lives, developing tasks and daily-life activities to promote different skills between treatment sessions. The possibility of delivering intervention in patients' natural environment when they most need it provides the framework for Ecological Momentary Interventions (EMI) [59].

EMI can take many forms ranging from unstructured clinical recommendations, such as requesting problem solving or relaxation strategies for mood control, to more formalized and structured interventions, such as direct tips to cope when a binge-eating episode is anticipated. These systems can also automatically tailor EMI content based on participants' momentary input. Moreover, EMI can be used as a supplementary tool to ongoing treatments (medical or psychological), or could be implemented on their own [59].

EMI has been applied to different behavioral programs for smoking cessation, weight loss,

anxiety, diabetes management, eating disorders, alcohol use, and healthy eating and physical activity. However, communication between researchers and clinicians in different fields of expertise is still required to allow a comprehensive integration of these tools in the treatment of obesity. Nevertheless, EMI studies provide a very promising evidence-based strategy that allows for researchers and clinicians to assess, support, and interact with participants and patients in their daily lives, and to promote mental health conditions and health behavior change [59].

Additional Concerns About EMA and EMI

Despite the advantages of EMA and EMI mentioned above, implementation is demanding from researcher and participants. These can be expensive methodologies requiring programming expertise and possibly significant amounts of time spent training subjects on the use of particular programs and/or devices. For instances, depending on the EMA/EMI device, supplying the device itself may be necessary. Some of its disadvantages overlap with those of other self-monitoring procedures. EMA and EMI require motivation and extra-time dedicated to recurrently report on key-variables throughout the day. Consequently, this approach can be seen as intrusive, and since data are collected in the absence of the researcher, there is no external validation for authenticity [52, 53].

Discussion

New technologies represent powerful tools as an alternative assessment and treatment delivering strategies for weight control. However, the heterogeneity of study designs and the inclusion of different strategies in the programs (such as interactive chat session, feedback, self-monitoring, etc.) restrains the comparison across studies and compromises clear conclusions about its effectiveness on weight loss and its maintenance [32].

Recent literature reviews suggest that personalization of feedback information as well as strategies to promote social support during interventions (such as group chat session) are critical components of web-based weight loss programs [7, 14, 60]. On the other hand, a great concern regarding the utility of these treatment-delivering strategies is its attrition rate. In some studies, retention rate was not higher than 60 %, and research is still required to investigate the promoting adherence to these programs [14]. For instances, higher usage of these features may be associated with better outcomes, but little is yet known about which components have greater impact on weight loss maintenance and which reduce attrition.

Finally, despite meaningful weight changes associated with these interventions and their efficacy on behavioral modification, the effectiveness of these interventions in inducing weight loss is not comparable to face-to-face group or individual interventions [7, 14]. Thus, we believe that new technologies-based interventions may be optimized when used as supplementary strategies to ongoing face-to-face treatments or group programs, bridging the gap between clinical setting and patients.

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Obstetrical Risks in Obesity

21

Stefania Triunfo

Introduction

In the last decades, the prevalence of abnormal nutritional status has increased in both developed and developing countries, alerting the public health system for the possible risks both in terms of cardiovascular and metabolic diseases and economic impact for additional costs to prevent or manage the illness [1–6]. In Europe half of the adult population meet criteria for overweight (body mass index (BMI) 25–29.9 $Kg/m^{2)}$ or obesity (BMI≥30 Kg/m^2), while in USA the prevalence of obesity among adults exceeds 33 % with an additional 34 % categorized as overweight [7, 8].

Interestingly, the global health crisis is related to every age classes, assuming the aspect of transversal phenomenon. Indeed, overweight and obesity are unevenly distributed in the world, irrespective of age, in pre- and post- school children and in two genders. World Health Organization (WHO) estimated that the prevalence of children <5 years of age with a BMI >2 SD (equivalent to the 98th percentile) increased from 4.2 % in 1990 to 6.7 % in 2010 and is expected to reach 9.1 % by 2020, and more so in developed (11.7 %) countries (6.1 %) [9]. In USA the obesity prevalence has increased from 7 % in 1980 to nearly 20 % in 2008 in children aged 6–11 years and from 5 to 18 % over the same period in adolescents aged 12–19 years, respectively [10]. In European countries and regions wide variations in overweight and obesity prevalence estimates among primary-school children have been reported, suggesting the presence of a north-south gradient with the highest level of overweight found in southern European countries [11–13].

As reproductive aged women are a part of this trend, the effect of maternal obesity on the developing fetus is required to be investigated [14]. The prevalence of obesity in pregnancy is rising exponentially, as demonstrated by about 15–20 % of pregnant women enter pregnancy with a BMI which would define them as obese [15]. A strong link between obesity and adverse pregnancy outcome has also been identified for the mother and her child. The mother is more likely to develop diabetes (gestational), hypertensive disorders during pregnancy, and the pregnancy may end in a miscarriage, stillbirth or preterm delivery [14–16]. The baby could have important anomalies at birth, including neural tube defects, cardiovascular anomalies, orofacial clefts, hydrocephaly, anal atresia, hypospadias, cystic kidney, pes equinovarus, omphalocele, and diaphragmatic hernia [16–18]. The neonatal weight may also be bigger than normal, suggesting that the children of obese mothers go on to be

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obese in adult life. At delivery, the labour may be longer and can be associated with instrumental delivery, cesarean section and excessive postpartum bleeding [15–19].

Biologic Processes and Metabolic Changes in Pregnancy

The weight gained in pregnancy is the result of biologic processes and metabolic changes that promote the correct development of fetal programming [14]. Although the composition of weight gained during pregnancy varies across women, a general description can be assessed. Approximately 27 % resides in the fetus, 20 % includes the placenta, amniotic fluid and uterus, 3 % comprises breast weight, 23 % is made up of blood volume and extravascular fluid, and the remaining 27 % consists of maternal fat stores (insert Fig. 21.1) [14].

In early- to mid-pregnancy, underweight and normal weight women (pregestational BMI <25 kg/m^2) deposit fat in their hips, back, and upper thighs, which is thought to be important as a caloric reserve for late pregnancy and lactation [20]. Insulin secretion and sensitivity rise, favoring increased lipogenesis and fat accumulation, in preparation for the increased energy needs of the growing fetus [20]. However, women entering pregnancy overweight or obese (who may already have some baseline insulin resistance) do not have the same rise in peripheral insulin sensitivity in early pregnancy and little or no additional fat is accrued, perhaps due to a reduced need for extra caloric reserves [14, 20]. By late pregnancy, insulin resistance increases among all mothers and weight gain slows down, a normal physiologic adaptation that shifts maternal energy metabolism from carbohydrate to lipid oxidation and thus spares glucose for the fetus [14, 20].

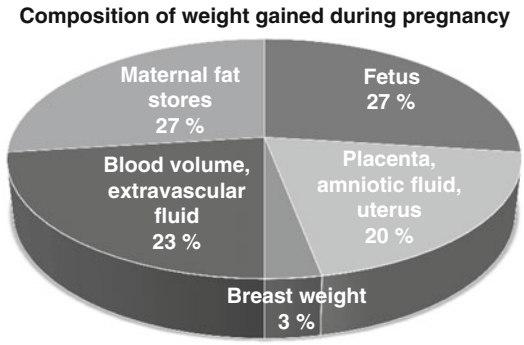

Fig. 21.1 Weight gained in pregnancy, as the result of metabolic changes, although it varies across women

The pattern of gestational weight gain is most commonly described as sigmoidal, with the majority of weight gained in the second and early third trimesters of pregnancy [14]. This complex of adjustments in carbohydrate and fat metabolism ensure that the fetus receives a continuous supply of fuel when its needs are maximal [14].

Identification of Abnormal BMI-Related to Risks for Pregnant Women

The consequences of obesity in non-pregnant individuals have been extensively described, including an increased risk of Type 2 diabetes (typical increase of 12 folds), hypertension (fourfold risk), myocardial infarction and colon cancer (each with threefold risk) angina, gall bladder disease and ovarian cancer (twofold risk) [21]. A recent meta-analysis has shown that for every increase in BMI of 5 kg/m^2 there is a 10 % increase in neoplastic mortality, 40 % increase in vascular mortality and a greater than 50 % increase in diabetic, renal and hepatic mortality [21].

In contrast, the impact of obesity on reproductive outcomes has only recently been the subject of significant research, probably due to the increased prevalence of obesity in women of childbearing age in recent years, with approximately one in five pregnant women in the developed countries are classed as obese at antenatal booking time [14–22]. A considerable number of studies have reported a clear association between abnormal maternal BMI and adverse obstetric and perinatal outcomes [14–23]. In the past, maternal hyperglycemia during pregnancy was thought to be one of the most important predictive factors of obstetric complications. Indeed, the obese population suffers from elevated blood glucose levels, insulin resistance and high rates

of overt diabetes. Also obese pregnant women are characterized by a significantly higher postprandial glucose peak value, increased 1- and 2-h postprandial glucose levels, increased time interval for glucose peak, and significantly lower mean blood glucose during the night [23]. Although, it is recognized the principal role of hyperglycemia, actually, it is accepted that other maternal parameters associated with obesity and/or over-nutrition during pregnancy are also involved including hypertriglyceridemia and the altered endocrine milieu associated with obesity condition (increased levels of insulin, androgens, and leptin), causing a number of maternal metabolic disturbances, such as insulin resistance, diabetes and increased blood pressure all of which influence fetal well-being [24, 25].

Generally, small weight gain may have additional benefits for the short- and long-term weight status of women and children. Compared with normal BMI women, obese women had significantly higher rates of preeclampsia, gestational hypertension, and gestational diabetes, and these rates increased with increasing BMI especially (trend-test $P<0.001$) [26]. Several research report a significant increase in the rate of induction of labour in the obesity category, from 25.3 % in women with normal BMI to 42.9 % in women with morbid obesity (aOR 1.67; 95 % CI 1.43–1.93) [14–17, 22]. Rates of primary caesarean section rise with increasing BMI and are highest in women with class morbid obesity (36.2 % vs. 22.1 % in women with normal BMI) (aOR 1.46; 95 % CI 1.23–1.73) (Table 21.1) [15–17, 26, 27]. Consequently, as a result of increased complication rate, more than 50 % of mortality cases during pregnancy, childbirth or the pueperium are of women who are either obese or overweight [28].

Table 21.1 Adverse pregnancy outcomes increased by obesity[a] and extreme obesity[b]

Complication	OR (95 % IC)
Maternal infection[a]	3.35 (2.74–4.06)
Maternal hemorrhage[a]	1.24 (1.2–1.28)
Postpartum haemorrhage[b]	3.04 0.96, 9.67
Pre-eclampsia[b]	4.46 2.42, 8.16
Gestational diabetes[b]	7.89 3.94, 15.80
Thrombosis[b]	Infinity 0.75, infinity
Induction of labour[b]	1.97 1.53, 2.54
Instrumental delivery[b]	2 (1.87–2.15)
Cesarean section[a]	1.17 (1.13–1.21)
Shoulder dystocia[b]	1.89 0.82, 4.34
Problems with epidural anaesthetic[b]	3.54 1.49, 8.42
Problems with spinal anaesthetic[b]	9.10 2.02, 41.00
Hospitalization[a]	2.84 (2.77–2.91)
Maternal intensive care unit admission[b]	3.86 1.41, 10.60

Data from [a]Heslehurst et al. [16] and [b]Knight et al. [27]

Impact of Abnormal Maternal BMI on Offspring Health

The fetal developing depends upon a complex feto-maternal interaction. This intricate interaction relies on several components: maternal nutritional intake, placental transfer mechanisms and uterine blood supply, which depend on maternal metabolic and cardiovascular condition. Maternal overweight and obesity is an obstetric risk factor due to its potential consequences for offspring, so its role should be considered in different epochs of pregnancy, as data of literature reported, due to specific impact of maternal nutritional status on obstetric outcome.

Risks in Pregnancy

In early pregnancy, obesity may increase pregnancy-loss rate in a mechanism that is still not dependent upon oocyte or ovarian function, but rather endometrial or placental [29]. Probably, an unfavorable hormonal environment characteristic of maternal obesity combined with the chronic inflammatory state associated with excess adipose tissue, may be the underlying mechanism, as demonstrated by observational data that propose weight reduction for reducing miscarriage rate in obese population [30, 31].

In addition, maternal obesity is associated also with the increased risk of twin pregnancy, dizygotic twin mainly, but it is not clear the mechanism that stimulate it because few studies are reported in literature [29, 31, 32]. The aspect that appears clear is related to additional risks in

pregnancy, not only for the maternal obesity, but also for the twin pregnancy, as known at high risk obstetric.

Another important topic that interests all the duration of pregnancy is the fetal ultrasound imaging, that results more difficult in obese gravid compared to normal-weight women [33, 34]. As a result, the antenatal detection rate for congenital anomalies is lower in obese women, resulting in fewer antepartum diagnoses and more affected liveborns and stillborn among births to obese mothers [34]. As described, the analysis of data collected in the FaSTER study indicates that the performance of second-trimester genetic sonography is influenced by obesity, with a significantly higher missed diagnosis rate for multiple minor markers and lower likelihood for detecting common anomalies in the obese population [35].

Suggestions on modality and timing of ultrasound scan in obese women indicate an elective transvaginal approach, as an alternative and more satisfactory window, in the late first-late second trimester in order to obtain a better evaluating fetal anatomy, reducing the limitations due to maternal nutritional status [34, 36].

The most important aspect is the limited power of imaging in detecting congenital anomalies in presence of maternal obesity; in this condition an increased risk of some congenital anomalies is more prevalent in the offspring of obese mothers or with elevate weight gain during pregnancy than normal-BMI pregnant. Generally, the increase in the absolute rate of specific congenital anomalies is increased with growing maternal weight. Actually, the prevalence of congenital malformations is 4.7 %, and the prevalence of relatively severe malformations is 3.2 % [33–36]. Particularly, maternal pregestational morbid obesity is associated with neural tube defects OR 4.08 (95 % CI 1.87–7.75), cardiac defects OR 1.49 (95 % CI 1.24–1.80), and orofacial clefts OR 1.90 (95 % CI 1.27–2.86) [36]. An increased risk of hydrocephaly, anal atresia, hypospadias, cystic kidney, pes equinovarus, omphalocele, and diaphragmatic hernia are reported [33–36].

Offspring of obese mothers are also subject to disrupted growth patterns (both growth restriction and overgrowth) [32]. Increased fetal weight and adiposity at birth increases macrosomia and difficulties associated with delivery of large-for-gestational-age infants. In these fetuses the estimated fetal weight can result more difficult than other cases both the maternal limitations and the decreased accuracy in macrosomic fetuses [36]. There is little to be done to technically improve the image obtained [36]. Delaying, repeating, or increasing the duration of the examination may only partially, if at all, mitigate the technical limitations that obesity imposes on visualization [33–37].

Risks in Delivery

Obesity condition is also associated with a marked increase in feto-neonatal complications including stillbirths, neonatal deaths, neonatal intensive care unit admission, preterm births and postterm pregnancy complications [16, 24]. The relationship between maternal obesity and fetal growth has shown that obese women have an 18–26 % increased chance of delivering large-for-date infants [38]. Indeed, macrosomic infants have an increased risks of shoulder dystocia and brachial plexus injury [16, 38]. Consequently, delivery of an obese pregnant woman remains a challenge due to possibilities both caesarean section and instrumental delivery (Table 21.1) [16, 27]. Given the high likelihood of operative delivery, even where vaginal delivery is attempted, the fact that ‘emergency’ caesarean section carries greater risks than ‘elective’ caesarean section, and the need for experienced members of staff if operative delivery is needed, one could argue that women with morbid obesity might be best delivered by elective caesarean section [16, 27].

Neonatal Risks

High maternal BMI has also effects on neonatal health. In view of the aforementioned higher rate of labor-related complications, it is not surprising that, after delivery, newborns of obese mothers show an increase in neonatal admissions to neonatal intensive care units with complications, such as neonatal trauma and incubator requirement [39].

In addition, an increased risk of stillbirth in the obese population has been described, compared with normal-weight pregnant women. Probably, the increase in stillbirth rate in obese women is presumed to occur due to the accelerated fetal growth induced by the fetal hyperinsulinemia and excess nutrient 'influx', in combination with uteroplacental insufficiency, which may lead to fetal hypoxia and death [40].

Influences on Maternal Obesity in Young Adulthood

Maternal body weight and weight gain during pregnancy influences intrauterine environment, causing permanent changes in the hypothalamus, pancreatic islet cells, adipose tissue and other body weight-regulating mechanisms of the offspring. Maternal pre-pregnancy overweight has been found to be an independent risk factor for infant and adolescence overweight and abdominal obesity [41]. As a result, lower gains may have additional benefits for long-term weight status of children, while women with higher gestational weight gains are also responsible of children with higher risks of high weight in childhood, during adolescence and adulthood [40–42].

Maternal prenatal over-nutrition may result in increased fetal adipose tissue deposition, consequently, as adipocyte number appears to be set in the first years of life, excess fat formed in early life may result in lifelong excess adiposity [42]. Besides, neonates with poor *in utero* nutrition may undergo catch-up growth or rapid weight gain. This early accelerated growth has been shown to adversely affect glucose metabolism, lipids, and blood pressure in adolescents who were born small, perhaps in part because most of the catch-up body weight distributes centrally and results in insulin resistance [40–42].

Some studies also suggest that children exposed to pregnancies complicated by metabolic conditions, such as diabetes, hypertension, and obesity, showed an increased risk of neurodevelopmental disorders, autism spectrum disorders and developmental delay, although interpretation of data is limited by lack of information on potential confounders [43].

Interventions Strategies

Concerns about the increasing rates of obesity in developing countries have led many policy makers to question the impacts of maternal and early child nutrition on risk of later obesity. Principally, the links between maternal obesity and adverse outcomes are strong and the ideal management results prevention, even if the increasing prevalence of obesity in pregnancy is going to change soon. Indeed, obesity prevalence suggest it is now pandemic, affecting populations across the age span, wealthy and impoverished nations alike, and without regard to traditional rural/urban divides [40].

The economic impact of inaction, or lack of effective action, is likely to be substantial as nations seek to manage the diverse health-related consequences against ever-increasing health-care costs [6, 14, 28]. The seemingly inexorable rise in infant and childhood obesity, associated with life-threatening co-morbidities such as early onset of Type 2 diabetes mellitus and cardiovascular disease, has raised concerns that current and future generations of children may be the first to die before their parents [10, 14]. Women of childbearing age, and especially those who are pregnant, must be considered a priority population for intervention, not least because pregnancy presents a 'window of opportunity' to reduce the burden of lifetime disease. Maternal diet and lifestyle factors affect fetal programming and hence influence pregnancy outcomes, including increasing the risk to the infant of developing (obesity-related) chronic diseases [41]. Furthermore women, as mothers, continue to play a central and traditional role in food provision and are thus influential in protecting their children against obesity and associated morbidities.

Understanding the links between obesity and adverse pregnancy outcome can inform effective therapeutic interventions. In non-pregnant individuals, diet and exercise are advocated to improve health. In pregnancy, there is limited evidence for the efficacy of diet and exercise although several trials are underway to test these interventions. Statewide (Queensland) Clinical Guidelines reflecting current best practice have recently

become available for the management of pregnancy-related obesity [14]. They provide advice regarding recommended gestational weight gain based on pre-pregnancy BMI, referral practices for multidisciplinary care including specialist support, and advice for the postnatal period, with demonstrated links to improved maternal and infant outcomes. Diet quality decreases with higher BMI categories and women who start pregnancy in the overweight or obese range are at higher risk of metabolic complications and assisted deliveries, and their infants are at higher risk of macrosomia, structural birth defects, perinatal death, and becoming obese in childhood. In addition, given the known links between obesity, elevated blood glucose, insulin resistance and adverse pregnancy outcome, an appropriate therapy for obese pregnant women may be metformin [14].

Maternal overnutrition and/or obesity during pregnancy afflict upon the developing child a fate of later-life overweight, thus creating a vicious cycle of epidemic scale. However, this mechanism is not a 'perpetuum mobile' [14]. Obese women and health care providers have it within their power to reverse the tide on the obesity epidemic. Dietary restriction and weight loss prior to pregnancy are proven strategies to improve infant health outcome.

Pregnancies after bariatric surgery are less likely to be complicated by gestational diabetes mellitus, hypertension, preeclampsia, and macrosomia than are pregnancies of obese women who have not undergone such surgery [44]. Bariatric surgery prior to a planned pregnancy is the best strategy for reducing obesity-related complication for mother and child. In unplanned pregnancies, controlled or minimal weight gain during pregnancy may also mitigate the impact of obesity and produce a dramatic positive impact on pregnancy outcome [44].

Pregnancy also provides a 'window of opportunity' in which obese women are more susceptible for lifestyle interventions such as diet and exercise counseling, thus allowing health care givers to intervene [28].

However, observational studies indicate that some obese pregnant women, especially those who are heavier, lose weight during pregnancy. Furthermore, some obese pregnant women may intentionally lose weight. The safety of weight loss when pregnant and obese is not substantiated; some observational studies suggest that risks associated with weight loss such as preeclampsia are improved, but others indicate that the incidence of small- for-gestational infants are increased. It is important to evaluate interventions that are designed to reduce weight in obese pregnant women so that the safety of weight loss during this period can be established. The advice for obese women in managing their weight during pregnancy is that weight loss should be avoided, and weight gain should be between 5.0 and 9.1 kg [14]. Moreover, it is mandatory that further research is conducted to evaluate the safety of interventions for weight loss when a woman is pregnant and obese for reducing associate risks.

Conclusions

The obesity epidemic has resulted in more overweight/obese women before and during pregnancy, determining obstetric complications such as gestational diabetes, hypertension and preeclampsia and affecting fetal growth. In addition, maternal obesity offers an altered genetic, hormonal and biochemical environment for the developing fetus/embryo and influences fetal growth and organ development. The offspring tend to have higher birth weights and more body fat, and carry an increased risk of obesity and cardiovascular diseases later in life as result of abnormal fetal programming development. The ideal management of maternal obesity is prevention. Further research is urgently needed to understand these links, in order to be able to develop therapies, and improve short-and long term pregnancy outcome until adult life of neonates from overweight or obese mother.

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Bariatric Surgery in Obesity

22

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Introduction

Obesity remains a worldwide epidemic, and its incidence is increasing exponentially. According to the World Health Organization's projections, 1.7 billion people are considered overweight, and at least 400 million adults are obese [1]. In the US alone, nearly 33 % of the population (97 million) are obese, and approximately 10 million people are morbidly obese (or class III obesity BMI≥40) [2].

Over more than two decades, bariatric surgery has become widely accepted as the most effective and long-lasting treatment for morbid obesity. The 1991 National Institute of Health (NIH) Consensus Conference, after reviewing the available data, concluded that Roux-en-Y gastric bypass (RYGB) and vertical banded gastroplasty (VBG) were safe and effective procedures for weight loss in patients with a body mass index (BMI) of 40 Kg/m^2 and above or 35 Kg/m^2 with serious medical complications of obesity [3]. Since then, bariatric surgery has surged in growth and popularity, resulting in increased recognition in the medical community, and culminating in the recognition of bariatric surgery as a separate specialty. Among the many factors that contributed to this steep rise in the field of bariatric surgery, a central factor is the ability to perform the procedures with minimally invasive techniques (laparoscopically). Following the first report of a LRYGB in 1994, the widespread ability of performing these complex procedures with significantly improved patterns of morbidity and mortality has reflected positively on the entire specialty [4].

Although initially lengthy and challenging, the laparoscopic operations were always characterized by decreased wound infections, bleeding, ventral hernias and shortened hospital stay, while achieving comparable weight loss results to the open technique. This is especially true in a population of patients in whom open operations had high rates of short and long-term complications. The clinical evidence of the safety and efficacy of these procedures has increased tremendously since then, and complications rates have reached astonishingly low percentages. Critical factors in these remarkable successes are the standardization of the techniques and also the implementation of dedicated multidisciplinary teams and appropriate commitment from the administrative perspective. The adoption of the Centers of Excellence (COE) program has served to maintain the high standards throughout the specialty. Long-term outcomes have also clearly shown to be superior to simple lifestyle changes and even

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intense medical interventions surgery in several randomized control studies, especially in the case of type II DM [5].

Overview of Bariatric Procedures

Historical Procedures

Initially, the indirect discovery that either removing or bypassing the intestine would invoke weight loss lead to the development of the first bariatric procedure, the jejunoileal bypass (JIB), performed initially by Henriksson, and then by Kremen [6, 7]. Although very effective for weight loss, and in spite of variations such as the jejunocolic bypass (JCB), the significant postoperative morbidities related to diarrhea, electrolyte disturbances, vitamin deficiency, and liver failure lead to the abandonment of such procedures [8].

Traditionally, the different weight loss procedures are based on two different concepts: restriction and malabsorption. The idea behind the *restrictive* operation is to create a smaller gastric reservoir by different means in order to regulate the amount of calories ingested. The willpower and patient's participation play a key role in the success of these operations; in fact, the feedback (feeling of restriction and decrease in appetite) provided by the operation itself will gradually decrease and leave more potential for the resumption of maladaptive eating behaviors.

The *malabsorptive* operations implement key changes in the gastrointestinal anatomy, which reduces the amount of intestine in contact with food. This, in turn, causes a decrease in opportunity for biliopancreatic secretions to digest the nutrients. Although these procedures provide a stronger feedback mechanism, the patient's understanding and motivation remain a key factor for success.

In general, the procedures that combine restriction and a lesser degree of malabsorption are among the most commonly utilized currently (i.e., gastric bypass [GBP]), and most long-term published results are from studies utilizing these procedures. Furthermore, the procedures with a variable degree of malabsorption (GBP, biliopancreatic diversion with or without duodenal switch [BPD±DS]) tend to result in better weight loss, but also a higher likelihood of macro- and micro-nutrient deficiency [9].

As the relationships between diet, gut, and brain hormones have become better understood, the mechanisms of action of these procedures, as well as their classifications, have significantly changed. The terms *restrictive* and *malabsorptive* are now less commonly utilized and the procedures are better characterized based on the relative effect of the gut hormones.

Restrictive Operations

Vertical Banded Gastroplasty

Gastric volume reduction (gastroplasty) can be obtained in many different configurations. One of the most popular gastroplasties was described by Mason in 1982 (Fig. 22.1) [10]. This procedure consists of the creation of a narrow gastric pouch based on the lesser curvature of the stomach and separated by the rest of the organ by vertical stapling. In order to maintain restriction, the outlet of this pouch is narrowed by using a synthetic, fixed band. This procedure gained popularity quickly

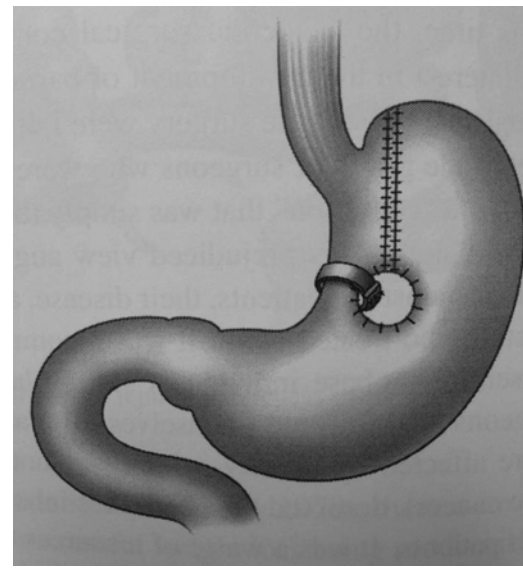

Fig. 22.1 Vertical banded gastroplasty (VBG). A narrow gastric pouch is created from the lesser curvature by dividing this are from the rest of the stomach. The outlet of the narrow pouch is restricted by implanting a fix band (Source: Nguyen et al. [51]. Page 40. Springer 2015)

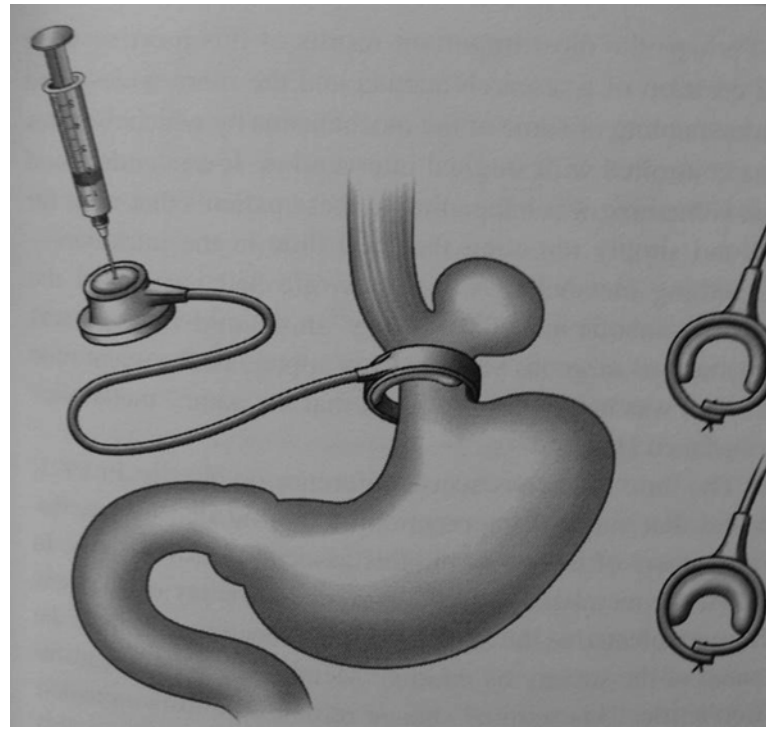

Fig. 22.2 Laparoscopic adjustable gastric banding (LAGB). An adjustable band is placed close to the esophago-gastric junction. The band is connected to a subcutaneous port in order to be adjusted in diameter with the injection of saline solution (Source: Nguyen et al. [51]. Page 41. Springer 2015)

because of the relative safety of the operation and the respectable weight loss results (excess weight loss [EWL] of up to 68 %) [9]. However, long-term studies have shown a significant number of complications, such as dysphagia, band erosion, and gastrogastric fistula with weight regain [9]. Based on these results, the procedure is now considered virtually of historic interest.

Laparoscopic Adjustable Gastric Banding

The concept of restricting the gastric reservoir by the virtue of extrinsic non-adjustable bands was initially developed by Wilkinson in 1978 and applied more extensively by Molina in 1980 [11, 12]. The evolution of the devices in their adjustable form, initially with open techniques and then laparoscopically, occurred in 1985 in Sweden by Hallberg and Forsell, and in 1986 in the US by Kuzmak [13, 14]. Another simpler restrictive operation is LAGB, in which a medical device is implanted in the proximal portion of the stomach, virtually dividing the stomach in two parts, proximal and distal to the implant itself (Fig. 22.2). The implant is constituted by an inflatable balloon that can be adjusted in order to artificially restrict the outlet of the proximal gastric pouch. Once the correct tightness is found, the patients are supposed to eat only small portions and feel satisfied. The restriction should also be sufficient to provide satiety in between scheduled meals. Although theoretically effective, in reality the maladaptive eating behaviors of the patients and the need for an intense follow-up, coupled with high long-term complication and reoperation rates, has led to a decrease in the popularity of this procedure. Several studies have reported reoperation rates up to 20 % because of either failure of weight loss or complications, such as erosion, slippage, chronic gastroesophageal reflux, and dysphagia [15].

Laparoscopic Sleeve Gastrectomy

Laparoscopic sleeve gastrectomy was initially described as part of a more complex malabsorptive operation—BPD-DS [16]. In fact the partial resection of the stomach along the greater curvature is identical for both procedures (Fig. 22.3). However, due to the significant potential morbidity in high-risk

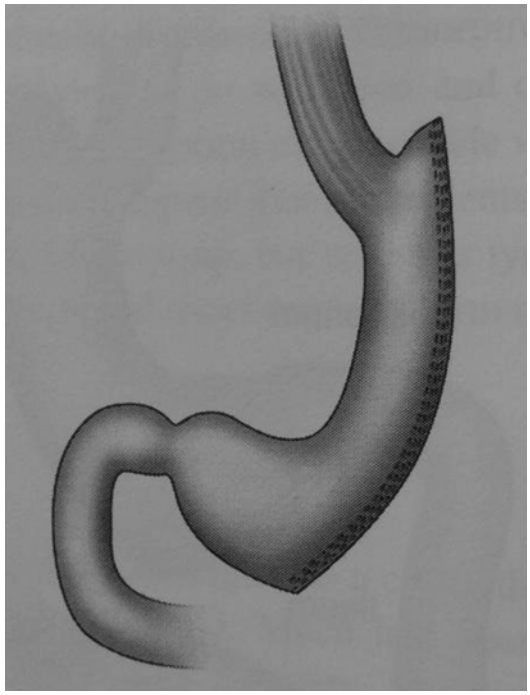

Fig. 22.3 Laparoscopic sleeve gastrectomy (LSG). The majority of the stomach is resected leaving a narrow, lesser curvature based reservoir (Source: Nguyen et al. [51]. Page 44. Springer 2015)

patients, the BPD-DS was broken down into two operations performed 6–12 months apart. The first step was the simpler and safer LSG, followed by the completion of the BPD-DS with malabsorptive intestinal resections and re-anastomosis [16]. However, during the close follow-up after the LSG stage, it was observed that 94 % of the patients continued to experience significant weight loss and comorbidity resolution and never progressed to the full BPD-DS. Since then, LSG has gained incredible popularity among bariatric surgeons, to the point that the worldwide trend of operations has shifted and LSG is currently the most commonly performed procedure worldwide [17]. Although originally considered effective based only on its restrictive nature, LSG has been shown to effect significant changes in the gastrointestinal hormonal milieu [6].

The procedure's growth is mainly due to its overall technical simplicity, respectable weight loss, and resolution of comorbidities. The apparent technical simplicity, however, should not be interpreted to mean that LSG is a procedure that can be safely performed by any surgeon; several potential pitfalls of this procedure exist and can lead to great morbidity and mortality. Recently a North American regional bariatric group used their own data to convince the Center for Medicare and Medicaid to allow the execution of this procedure outside the bariatric COE status [18]. The lack of scrutiny and follow-up in non-COE centers can potentially lead to increased morbidity after LSG. Furthermore, some controversies remain regarding several key technical aspects of the procedure. Several consensus conferences have published guidelines on the technical execution of LSG; however, variability remains in the literature. Overall, it is fair to say that the medium and long-term results of LSG are closer to LRYGB than other restrictive operations such as LAGB [15].

Malabsorptive Operations

Biliopancreatic Diversion – Duodenal Switch (BPD-DS)

In 1979, Scopinaro described the biliopancreatic diversion (BPD) in which a distal gastrectomy is accompanied by a Roux-en-Y reconstruction with a short common channel [19] (Fig. 22.4). Besides the excellent weight loss result, this mostly malabsorptive procedure has been associated with higher degree of diarrhea, protein malnutrition, and micronutrient deficiencies. In order to reduce marginal ulceration, Hess initially and Marceau later, combined the BPD with the duodenal switch (DS) described by DeMeester for reflux gastritis and a sleeve gastrectomy (SG) in the modern BPD-DS [20] (Fig. 22.5). Although more commonly performed now than the BPD, the technical complexity and the potential for nutritional deficiency relegates the BPD-DS to a mere 2 % of the bariatric procedures performed worldwide [7].

Combined Procedures

Roux-en-Y Gastric Bypass

The RYGB remains the gold standard for surgical weight-loss, constituting about 70 % of the procedure performed. In fact, during the last decade

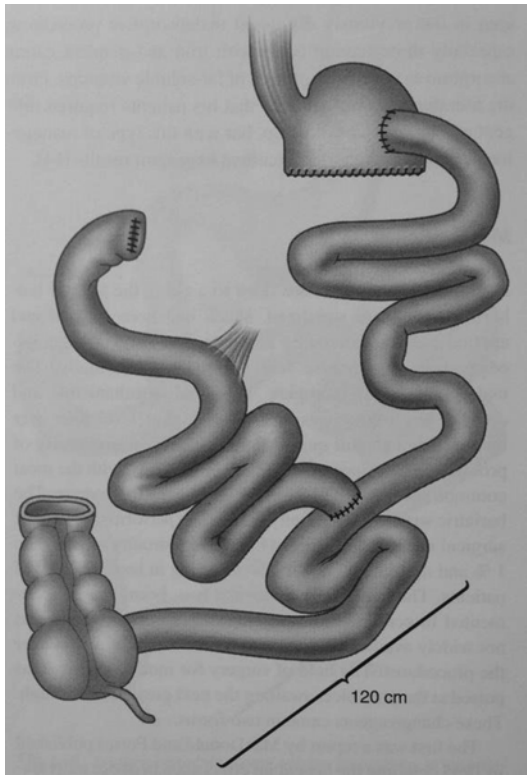

Fig. 22.4 Biliopancreatic diversion (BPD). A distal horizontal gastrectomy is accompanied by a Roux-en-Y reconstruction with a short common channel, determining high degree of malabsorption

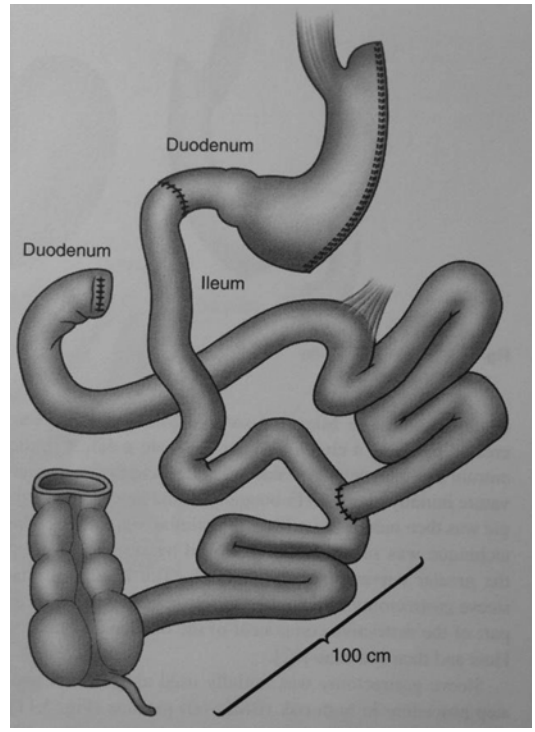

Fig. 22.5 Biliopancreatic diversion with duodenal switch (Source: Nguyen et al. [51]. Page 43. Springer 2015)

the number of RYGB has increased by 125 % between 2004 and 2007 in US academic centers [21]. Also, the approach to RYGB changed over time with currently an excess of 85 % of RYGB performed laparoscopically.

In 1967, Mason described RYGB for the first time [22]. The idea was to create restriction via the combination of a small gastric pouch (15–20 cc) completely partitioned from the upper stomach and a restrictive gastrojejunal anastomosis. The malabsorptive component derives from bypassing a variable length of jejunum, creating an alimentary limb of 100–150 cm (Fig. 22.6). Several variations on the original description have been described. One of the major changes pertains to the shape and volume of the gastric pouch. In fact, the original horizontally oriented pouch that included some gastric fundus was replaced by a vertically oriented one based on the lesser curvature, in which the entire

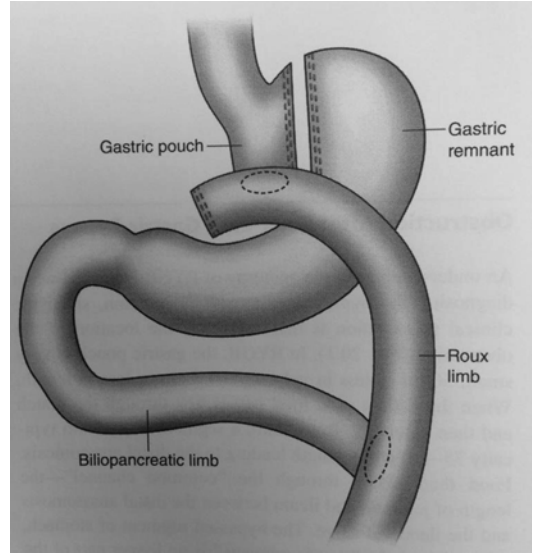

Fig. 22.6 Gastric bypass. A 15–30 cc gastric pouch is combined with a Roux limb that will carry the aliments of variable length (usually 100–150 cm) (Source: Nguyen et al. [51]. Page 230. Springer 2015)

Table 22.1 Changes of the entero-hormones after bariatric surgery

	Origin	Satiety	Glycemic control	GI motility	RYGB	LSG	LAGB	BPD	BPD-DS
GLP-1	L-cells	↑	↑	↓	↑	↑	No Δ	↑	↑
GIP	K-cells	No Δ	↑	No Δ	↓	?	No Δ	↓	↓
Ghrelin	Oxyntic	↓	No Δ	No Δ	↓	↓↓	No Δ	No Δ	↓↓

GLP-1 glucagone-like peptide-1, *GIP* glucose-dependent insulinotropic polypeptide

gastric fundus is excluded. The RYGB, in its most commonly performed version, LRYGB, is now considered the gold standard operation for weight loss, though recent statistics reflect that LSG has surpassed LRYGB as the most common procedure in the US [17].

Mechanisms of Action

As previously mentioned, the traditional concept of restriction and malabsorption as sole mechanisms of action in bariatric procedures has been revised based on the recently discovered interactions between gut, brain and adipose tissue. Body weight homeostasis is centrally regulated with the influence of mediators secreted both in the intestinal tract and adipose tissue [23]. It is the complex interaction between these hormones and the hypothalamus that will ultimately determine the energy expenditure and need for food intake [24]. Besides the weight regulation, the complex interaction between gut, adipose tissue, and brain play a key role in glucose homeostasis. In fact, diabetes improvement and resolution after bariatric surgery has been reported much sooner than weight reduction [25, 26]. This suggests the presence of independent pathways and hormonal changes after bariatric surgery. Some of the most commonly accepted mechanism of action theories are described here:

Enterohormones

The close interaction between the pancreas and intestine and their secretions is known as enteroinsular axis. The principal mediators of these close interactions are GLP-1, GIP, peptide YY, oxyntomodulin, cholecystokinin, and ghrelin. The quantitative secretion of these mediators is altered after the different bariatric operations (RYGB, BPD-DS, VSG) (Table 22.1). Interestingly, not all of the procedures cause variation of the same mediators, and some other operations, such as LAGB, do not seem to cause alterations at all.

Here we describe few of the enterohormonal changes after bariatric surgery.

Ghrelin

Ghrelin (growth hormone releasing peptide) is one of the first hormones proven to change after bariatric procedures, in particular RYGB [27]. The hormone is linked to the secretion of growth hormone and has a stimulating effect on the appetite by directly affecting the hypothalamus. Under normal circumstances, the level of ghrelin increases in between meals and falls in response to meals. However, obese individuals appear to have a blunted response with a decreased suppression of ghrelin after a meal [28]. More recently ghrelin has been shown to directly inhibit insulin, and as such, indirectly affects glucose metabolism negatively, maybe by suppressing adiponectin [27, 29]. In general, ghrelin levels have been found to be permanently lowered after LSG as opposed to after RYGB (when levels can increase again over time), and this is likely due to the complete removal of the gastric fundus, the primary location of the oxyntic glands [30]. However, these findings have not been consistent and negative studies have been published as well [31].

Glucagon-Like Peptide-1 (GLP-1)

This peptide is released by the L-cells of the ileum and colon in response to the ingestion of meals. Under normal circumstances, this hormone increases insulin secretion following ingestion of glucose (incretin effect) and it suppresses

postprandial glucagon secretion and gastric emptying (ileal brake), with the final result of inducing satiety [32, 33].

Due to the location of the secreting cells, mostly in the distal ileum, the rapid transit of the food bolus seen after intestinal bypass procedures (RYGB, BPD, BPD-DS) causes an increase in this hormone [23, 34]. On the contrary, procedures that do not affect the absorption of nutrients and do not affect the transit time seem not to have any effects on the postsurgical levels of GLP-1 [35]. If this theory is correct, the post-LSG increase of GLP-1 can be explained by the accelerated gastric transit time [36]. Once again discordant evidence exists, and, in fact, in longer follow-up studies, the increased satiety did not correlate with a significant increase of GLP-1 [37]. Certainly GLP-1 could play a role in the weight loss mechanism after bariatric operations, and also appears to play an important role in glycemic homeostasis [23].

Glucose-Dependent Insulinotropic Polypeptide (GIP)

GIP is mainly secreted by the K-cells of the duodenum and proximal jejunum. As its name indicates, GIP is an insulinotropic hormone, and as such, causes an increased postprandial insulin secretion and pancreatic ß-cell hyperplasia [38]. Although GIP does not affect intestinal motility, it causes increasing lipogenesis [33].

Similar to the other two hormones described above, the literature is discordant on the changes of GIP after bariatric surgery. Generally the levels of GIP decrease after RYGB and BPD because of the bypassing of the proximal intestine, and no changes are reported after LAGB [35]. The changes of GIP after LSG remain undetermined.

The Role of the Adipose Tissue

Initially the adipose tissue was thought to be just a way for the organism to store excessive ingested calories and lipids. Over time, though, it become clear that not all adipose tissue is the same. In fact, the peripheral accumulation of adipose tissue has been associated with peripheral and hepatic insulin resistance, whereas the visceral fat has been identified as an endocrine organ [39]. The visceral adipose tissue is then responsible for the production of the "pro-inflammatory" cytokines such as TNF, interleukin-6, and leptin in obese patients [40].

Among the different hormones, a few will be reviewed below.

Leptin is normally secreted by white adipose tissue. Although it is inversely related to the level of hunger [41], obese individuals have an increased baseline concentration of leptin, and the levels decrease after weight loss [42]. It has been shown that the reduction in energy expenditure caused by the decrease in leptin could determine the loss of efficacy of diets long-term [43]. As is the case for many of the other hormones discussed, the mechanism of weight loss cannot be attributed to a single compound. In fact, post-RYGB patients who remain obese present a similar decreased level of leptin as successful post-RYGB. This data suggests a more complex interaction of mechanisms to justify post-bariatric weight loss other than just a single agent [44].

Adiponectin

Adiponectin also produced by the white has been linked to insulin sensitivity and fatty acid oxidation [45]. Obese individuals present a lower baseline level of adiponectin, and as expected, weight loss, including post bariatric surgery, causes an increase in its levels [43, 46].

Role of Robotics

The use of robotic platforms for laparoscopic surgery was approved in 2000 in the United States [47]. This new technology was initially adopted by surgeons who worked in fixed quadrants with narrow confinements, such as the pelvis (i.e., urologists and gynecologists). The utilization of the robotic platform allowed surgeons to fast overcome the learning curve of some complex laparoscopic tasks, such as intracorporeal suturing. Also, the ability to have high definition and three-dimensional views enhance the ability of delicate dissections. Additional advantages of the robotic

approach are improved ergonomics and stability of the camera. Based on the above-mentioned potential advantages, utilization of the robot has increased significantly and has expanded into additional surgical subspecialties, such as colorectal, bariatric, and foregut. However, a recent review of the University Health System Consortium Database, which includes several academic medical centers and affiliated hospitals in the US, reported a low utilization of the robot in general colorectal and bariatric surgery [48]. According to the same review, the only advantage of the robotic assisted laparoscopic approach over the laparoscopic approach was found in the reduced length of stay for Heller myotomy and cholecystectomy. As expected, the use of the robotic platform increased the costs by an average of 21 % [48]. Furthermore, longer operating room times have been reported [49, 50]. For procedures involving multiple quadrants, hybrid laparoscopic and robotic approaches have been reported. In fact, although the procedures are classified as "robotic," in reality a variable portion is truly performed with the robot. Sometimes the robotic component is limited to the suturing part of the gastrojejunal anastomosis alone, whereas the rest is performed using conventional laparoscopy. The limited adoption of robotic platforms in bariatric operations is probably related to this variability in technique and extent of the operation done truly "robotically", as well as to increased costs, operating room times, and lack of data on improved benefits.

Conclusions

Bariatric surgery has evolved over time. The adoption of laparoscopic techniques has made bariatric surgery very safe. Also, more long-term studies have shown the efficacy of these procedures against the multiple metabolic derangements associated with obesity. This has been particularly shown in cases of type II DM. Different options exist, and it appears that the mechanical post-bariatric procedure component is just one of the mechanisms of action involved in weight loss following bariatric surgery. More data exist on the metabolic and hormonal effects of these procedures.

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Underlying Physiological Mechanisms of Bariatric Surgery

23

Diana Vetter and Marco Bueter

Introduction

Obesity is detrimental to health and challenges public health systems worldwide. Bariatric surgery to date is the best method not only to reduce, but also maintain body weight loss in the long-term. Further, bariatric surgery reduces obesity-associated morbidity and is the only method so far with a proven mortality benefit [1–4].

The most common bariatric procedures are Roux-en-Y gastric bypass (RYGB), and Sleeve gastrectomy (SG) [5]. The more recently developed SG creates a gastric sleeve tube which remains after 85 % of stomach excision [6]. Today, the most common form of bariatric surgery worldwide is RYGB combining restrictive and intestinal bypass elements. Here, a small stomach pouch is created and connected to the distal small intestine – the "Alimentary limb" [7]. The proximal small bowel remains attached to the remnant stomach and is termed the 'Biliopancreatic limb' draining gastric secretions and bile into the distal part of the "Alimentary limb" [7]. The joining of the alimentary and biliopancreatic limb conduits creates the characteristic "Y formation" allowing mixing of drained digestive enzymes with food as they pass through the "Common channel" into the colon [5]. Unexpectedly, bariatric surgery and in particular RYGB has been shown to ameliorate or even cure type 2 diabetes, the metabolic syndrome and to have profound effects on the cardiovascular system [1]. These changes are seen as early as 2 days after surgery, thus long before significant weight loss has occurred. In today's practice, patients with a Body Mass Index (BMI) of over 40 kg/m^2 or with a BMI over 35 kg/m^2 plus significant co-morbidities may be referred for bariatric surgery [8].

Currently, the RYGB is the most commonly performed bariatric procedure among the available bariatric surgical techniques. Along with significant body weight loss, the RYGB operation is characterized by a multitude of effects. Patients with RYGB report to have reduced hunger, increased satiety, and a change in food preference toward more healthy food products (less high fat content and less sugar) [9–12]. In addition, changes in energy expenditure have been postulated as RYGB rats have been found to show increased energy expenditure after surgery. However, only few studies have been able to replicate this finding in humans [13, 14]. Further, increase in renal salt excretion as well as changes in renal water handling have been described [11, 15].

The underlying physiological mechanisms of these clinical observations are not fully understood. While caloric malabsorption and mechanical restriction do not seem to be major factors in this respect, changes in levels of circulating gastrointestinal hormones such as peptide YY

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(PYY) and glucagon-like-peptide-1 (GLP-1) are believed to play an important role [10, 16–18]. Other mechanisms include increased bile acid concentrations and an altered composition of gut microbiota [19, 20].

This chapter aims to provide an overview regarding key findings in respect to underlying physiological mechanisms of the RYGB procedure which is by many considered as gold standard in bariatric surgery. Sporadic reference will also be made to Vertical Sleeve Gastrectomy (VSG) where appropriate.

Clinical Effects

Body Weight Loss

Similar to the clinical findings in RYGB patients, RYGB-operated rats or mice show a rapid and significant body weight loss compared to sham-operated animals [13, 14, 21]. Rats typically lose about 20 % of their presurgical body weight. In some animal models, body weight is slowly regained over time but without reaching body weight of controls. Also, not all patients lose similar amounts of weight, and some may even regain most of their body weight that was lost initially. It has been described that patients who reached a 40 % body weight loss within 2 years after RYGB ("Good responders") showed higher postprandial GLP-1 and PYY levels when compared to patients who lost less than 20 % of their initial body weight ("Poor responders") [10]. This suggests that gut hormone levels may play an important role for individual body weight loss after RYGB.

Reduction of fat mass largely accounts for the decrease in body weight, while lean body mass is typically preserved or proportionally less reduced [14, 22, 23]. RYGB-induced changes of body composition at least in rats seem to mainly reflect the result of caloric restriction [14, 21]. Liver weight may be unchanged, but liver fat content typically decreases after RYGB [24, 25]. The reduction in hepatic steatosis after RYGB may be related to changes in key signaling pathways that control hepatic lipogenesis and fatty acid oxidation, as well as changes in the mitochondrial function in hepatocytes [26, 27]. On the other hand specific changes in the skeletal system indicate a marked decrease in bone mineralization and bone weight with potentially negative consequences on bone stability [28, 29].

In contrast to the initial idea that weight loss after RYGB could be due to mechanical restriction and caloric malabsorption, reduced eating and increased energy expenditure seem to be of predominant importance for weight loss [14, 30]. While the role of mechanical restriction and changes in energy expenditure after RYGB will be discussed later in this chapter, there is evidence that the total digestive absorptive capacity of the small bowel is still sufficient to avoid maldigestion and subsequent caloric malabsorption after proximal RYGB [14]. This may at least partly be due to the massive hypertrophy of the small bowel that is observed predominantly in those gut segments that are still in contact with nutrients, thus the alimentary, and the common limb [14, 31, 32].

Change of Eating Behavior

Rats after RYGB eat about 40 % less than weight matched controls [33]. Not only is the amount of food intake altered, but also the meal pattern. Further the preferred food quality shifts toward less sucrose and less fat foods.

Effect of RYGB on Food Intake and Meal Pattern

Both patients and rats after RYGB eat and drink less, and ingest smaller meals at a slower eating rate [21, 34]. Furthermore, meal frequency is increased which however does not compensate for reduced meal size. As changes in meal pattern are present in both humans and rats, they are unlikely to be due to nutritional counseling. Instead, they are likely to be of physiological origin, for example through altered feedback signals from the gastrointestinal tract to brain areas that control food intake. The traditional

dogma that meal pattern changes after RYGB are caused by mechanical restriction can be challenged for several reasons. First, neither humans nor rodents show an increased water intake after RYGB which would be an expected attempt to overcome a mechanical barrier. Second, food intake after RYGB has been shown to be modified by administration of somatostatin analogs such as octreotide. Somatostatin blocks the release of satiating gastrointestinal hormones and induces an almost twofold increase in ad libitum food intake in RYGB patients [10]. Third, RYGB rats that have been food deprived over a period of 2 weeks are actually able to increase their food intake to a greater extent than sham-operated counterparts indicating that an increase in food uptake after RYGB is possible if metabolically required [35]. Fourth, ingested food has been shown to pass into the jejunum rapidly after RYGB which is in contrast to the concept of a mechanical obstacle [36–39]. Finally, the diameter of the gastrojejunal anastomosis after RYGB is not associated with differences in body weight loss in RYGB rats [40]. Thus, multiple facts argue against a "fixed ceiling effect" for food intake due to mechanical restriction after RYGB surgery.

In fact, the reduction of food intake after RYGB seems to be voluntary, as pre-meal hunger is not higher and post-meal satiation is not lower in RYGB patients when compared to controls despite reduced food intake [9, 10, 16]. It seems plausible that changes in the gut-brain axis may at least partly be responsible for reduced hunger and increased satiety after RYGB surgery as blood levels of the anorexigenic gut hormones GLP-1 and PYY are increased postprandially after RYGB. Both hormones activate neurons in the brainstem, mediating satiety and can even provoke aversions at high concentrations [41, 42]. A causal connection however has to date not been demonstrated. In addition to reductions in food uptake, some data also indicate significant alterations in food preferences after RYGB surgery as patients and rats choose to eat less high-fat and sugary foods in favor of lower energy dense alternatives [11, 12, 43].

Potential Physiological Mechanisms of Roux-en-Y Gastric Bypass

Changes in Energy Expenditure

RYGB rats spontaneously eat less than sham-operated rats [14]. However, sham-operated rats that receive similar amounts of food as consumed by RYGB rats ("pair fed") still have a greater body weight than the RYGB rats. Furthermore, sham-operated rats require 40 % less food than RYGB rats to maintain a similar body weight ("weight matched") [14]. As caloric malabsorption has been shown to have only a minor role in weight loss after RYGB, these differences may be very well due to changes in energy expenditure after RYGB. In fact, increased energy expenditure after RYGB has been observed in several studies [13, 14, 30, 37, 44]. Interestingly, changes in energy expenditure as observed after RYGB have not been demonstrated for VSG [45, 46].

Increased energy expenditure after RYGB surgery is unexpected, as body weight reduction by severe food restriction such as dieting usually leads to an adaptive physiological response to reduce energy expenditure; this "starvation response" helps the body to minimize the potential negative effects of long-term energy restriction in a state of negative energy balance [47]. RYGB seems to prevent or at least reduce this adaptive response, i.e., body weight loss in RYGB rats is not associated with the same decrease in energy expenditure that parallels weight loss by food restriction [13, 14, 48]. In some, but not all studies, the change in energy expenditure is paralleled by a lower respiratory quotient indicating that fat oxidation is increased over carbohydrate oxidation. However, the latter may be rather related to body weight loss than representing a specific surgical effect as body weight-matched sham-operated controls show a similar response.

At present, mechanisms underlying altered energy expenditure after RYGB remain unclear. Neither increased spontaneous physical activity nor higher body temperature can explain these findings. Lastly, the small intestine is massively hypertrophied after RYGB in rats with increase

in total weight of 75 % [14, 31, 32]. As the small intestine has been estimated to make up for about 20 % of the rat's oxygen consumption, this hypertrophy will increase oxygen consumption, and may at least partly explain higher energy requirement and ultimately body weight loss [49, 50]. In a seminal paper, Saeidi and colleagues have recently shown that energy metabolism in the gastrointestinal tract is reprogrammed in a way that the gastrointestinal tract becomes a major organ of glucose utilization, which possibly helps to secure its increased metabolic needs [51]. However, changes in energy expenditure after RYGB seem to be less consistent in humans compared with most animal models, which may be due much higher heterogeneity of study populations in humans compared with laboratory animals [48, 52–55].

Alterations of Taste and Food Preference

RYGB in humans and rats decreases the preferential selection of sweet and fatty foods and fluids [22]. RYGB rats prefer low-fat to high fat diet in comparison to controls and weight-matched sham controls in a two-choice test protocol [11, 21, 56]. Further, RYGB rats display reduced preference for higher concentrations of sucrose or fat than sham-operated or intact rats [11, 21, 56]. Studies in humans indicate that the detection threshold for sucrose seems to be shifted to lower concentrations after RYGB when compared to preoperatively and that the preferred sucrose concentration decreased after RYGB [11, 57]. However, studies on the impact of RYGB on appetitive behavior in rodents and humans have produced mixed findings and it remains unclear whether there are fundamental shifts in the palatability of high-fat and sugary foods after RYGB or simply a decrease in the motivation to ingest them. Learning processes are implicated because the changes in food preferences appear to progress with experience. An issue is whether food preference modulation after RYGB is due to basic shifts in palatability (taste aversion, conditioned or unconditioned) or due to learned adjustments in feeding behavior that minimize negative visceral signals during meals (conditioned avoidance).

Regarding the mechanism of fat-induced aversion after RYGB it has been speculated that elevated GLP-1 and PYY levels may contribute to this response because both hormones activate neurons in the brain stem areas that mediate aversive responses [41, 42]. However a causal role of GLP-1 or PYY in the fat aversion after RYGB has not been formally tested.

Role of Conditioned Taste Aversion in Reduced Fat Preference

Reduced consumption of high fat meals may be due to a conditioned taste-aversion. In other words, rats may reduce their fat intake with time as they learn that this will help them to avoid gastrointestinal symptoms such as malaise or nausea [12]. At least results in this respect are uniform [12, 21, 58]. Rats do not completely cease fat intake after RYGB and the preference for lower-fat foods progresses over time, suggesting that the taste aversion is not so profound, but more a learning process over time [12, 21, 44].

Changes in Food Reward After RYGB

Aversion and reward are two sides of one coin in the same category of taste processing. Dopamine signaling is intimately involved in mediating reward-related behavior, and major brain regions involved in reward processing are the mesolimbic areas in the brain [59]. Brain activation has been found to be reduced after surgery in the brain reward areas, and it was typically more pronounced when food items with high caloric density were presented [15, 60, 61, 62].

Overall, a decrease in the reward value of food may be partly responsible for the decrease in eating after RYGB, and, in particular, for decrease in calorically dense high-fat and sweet food items. Miras et al. recently tested the willingness of RYGB patients before and after surgery to work for sweet and fatty candies in a so-called progressive ratio test; individuals had to produce increasing numbers of mouse clicks

on a computer to obtain the candy reward, and the results were then compared with normal-weight controls [63]. Interestingly RYGB patients were much less willing to work for the reward after the operation, and this reduction appeared to be more pronounced in patients with a bigger BMI loss. The mouse clicking for a non-fat, non-sweetened vegetable candy was not affected. In other words, the reward value after RYGB was reduced selectively for the sweet and fat reward [63].

Role of Altered Levels of Gastrointestinal Hormones

The gut-brain axis is believed to be a major component for the control of eating and depends largely on the release of gastrointestinal hormones. The idea that blood-borne factors may play a role in reduced food intake post-RYGB comes from a seminal experiment from Atkinson et al. who demonstrated that the injection of postprandial plasma from RYGB rats into intact rats reduced their food-intake which was not the case when recipient rats received plasma from either fasted bypass- or sham-operated animals [64]. Postprandial levels of satiating gut hormones such as GLP-1, PYY, amylin and cholecystokinin (CCK) are increased after RYGB surgery. The fact that administration of somatostatin analogues that block gut hormone release leads to an increased food intake in RYGB patients and rats, respectively, further supports an important role of altered levels of gut hormones for a change in eating behavior after RYGB [10, 65]. Gastrointestinal hormones have either an orexigenic or anorexigenic action on food intake. Among these, ghrelin is the only known hormone with an orexigenic effect, whereas CCK, pancreatic polypeptide (PP), PYY, GLP-1, oxyntomodulin (OXM), glucagon, gastric inhibitory polypeptide (GIP) and amylin have been demonstrated to have an anorexigenic function.

Gut Hormones After RYGB

Gut hormones, in particular the L-cell products GLP-1 and PYY, also amylin and CCK are consistently increased after RYGB surgery [9, 10, 66–68]. Increased secretions of GLP-1 and PYY are also typical observations after VSG [30, 69, 70]. The combined action of these satiating hormones provides a plausible explanation for the decrease in meal size observed in RYGB rats. The blood concentration of ghrelin, in contrast, seems to decrease after RYGB, which theoretically could be associated with a reduced drive to eat; however, data about changes in circulating ghrelin are rather inconsistent and their relevance remains not entirely clear [9, 67, 71].

Causal Role of Elevated GLP-1 and PYY Levels in the Treatment Success of RYGB Surgery

The association between elevated concentrations of gut hormones like GLP-1, PYY, CCK and amylin, and reduced eating after RYGB is compelling; but evidence so far is more correlational than causal [9, 66, 67, 72]. On the one hand, pretreatment with PYY-specific antiserum has been shown to reverse the effect of bypass on eating in rats [9]. On the other hand, PYY knockout mice did not lose body weight after RYGB surgery and PYY receptor antagonists were unable to increase food intake in RYGB rats [73–75]. The reason for these discrepant results remains unclear.

Findings a causal role for GLP-1 were similarly inconclusive; neither blocking GLP-1 signaling by using GLP-knockout mice nor administration of a GLP-1 antagonist exendin-9 in rats was able to reproducibly prevent RYGB-mediated effects on eating, weight loss, or energy expenditure [28, 75]. More specifically GLP-1 receptor blockade increased food intake in RYGB rats, but not in sham operated controls in one study, but food intake was increased for both sham- as well as RYGB female rats in another study [28, 74]. Furthermore, GLP-1 knockout mice receiving RYGB or VSG showed no significant difference in weight loss when compared to GLP-1 wild type controls [75, 76]. One possible conclusion is that mechanisms behind reduced hunger and increased satiety after RYGB are not dependent on one single hormone alone, but on an entire

cocktail of hormonal changes. As mentioned above the postoperative increase of orexigenic gut hormones is individually different and may account for the big variability in weight loss after RYGB [10].

Interestingly, adding PYY and GLP-1 antagonist exendin-4 to RYGB rats led to the same increase in food intake as in sham operated rats, indicating, that the sensitivity to these hormones is maintained after surgery despite the higher postprandial or partially also baseline levels of these gut hormones after RYGB in rats [28, 65].

Effect of Gut Hormones on Glucose Metabolism

Interestingly, although not all findings are unanimous, hormones like GLP-1 are important factors for the improvement of glucose metabolism after RYGB, VSG and other types of bariatric or metabolic surgery [13, 69, 70, 77–80]. It is however clear that an altered milieu of gastrointestinal hormones after RYGB is not the only mechanism underlying the beneficial effects on glucose homeostasis, as a recent study reported that pair-feeding in obese patients produced beneficial effects on glycemic control similar to those seen in patients after RYGB [81].

Potential Mechanisms of Increased Gut Hormone Levels After RYGB

After RYGB gut morphology changes in specific gut segments: there is a marked increase in wet weight of the small intestine in rats after RYGB which is due to muscular and mucosal hypertrophy in the alimentary- and in some models also of the common channel, but not in the biliopancreatic limb [14, 31, 32, 66]. Mechanical or chemical factors may be involved. Increased release of GLP-2 from intestinal L-cells facilitates intestinal hypertrophy in conjunction with intraluminal factors such as stimulation by nutrients. Overall, hypertrophy of certain intestinal segments in RYGB animals may represent an adaptive response to optimize nutrient digestion and absorption in the postoperative anatomically novel situation where nutrients and digestive juices mix more distally than under physiological conditions. Further, L-cell secretions can also be triggered by the parasympathetic nervous system [82]. Whether this effect is altered after RYGB is unknown.

Interestingly, together with mucosal and muscular hypertrophy the density of enteroendocrine cells remains unchanged. This translates into an increase in the absolute number of L-cells. Undiluted nutrients in the alimentary limb may activate L-cells that are present in higher number in the proximal small intestine, thus inducing more GLP-1, PYY and perhaps CCK. Also, bile acids directly stimulate L-cell secretion and may represent a potential mechanism of postprandial upregulation of preprogulcagon and PYY and secretion of GLP-1 and PYY [83, 84]. Interestingly, the mRNA expression per cell of preproglucagon (for GLP-1) and PYY was only increased in the common channel and not in the alimentary channel, although both limbs were hypertrophied post-RYGB [84]. Thus, the presence of bile acids and gastric and pancreatic juices are necessary in addition to the stimulus leading to small intestine hypertrophy for activation of gut hormones. However, intestinal hypertrophy might not be mandatory for stimulated gut hormone levels, as the elevated gut hormones can already be observed within few days after surgery, i.e., at a time when this hypertrophic response presumably is still negligible.

Role of Altered Levels of Bile Acids

Circulating bile acid (BA) concentrations are decreased in obese compared to lean individuals. RYGB leads to elevation of circulating BA, thus normalizing circulating BA concentrations [15, 85–87]. This effect seems to be long-lasting, as elevated BA levels in rats with RYGB have been observed at postoperative day 8 and also at later time points in diabetic ZDF rats.

Interestingly, BA levels markedly increase in the portal vein, but not systemically after food intake. In contrast, systemic BA levels are dramatically increased after RYGB. It has therefore been hypothesized that increased BA levels may be linked to the metabolic improvement

after RYGB as bile acids (BAs) have been suggested to directly affect carbohydrate and lipid metabolism, as well as potentially energy expenditure via the intracellular BA receptor, FXR. The latter is suggested to be required for bariatric surgery-induced effects on body weight, glucose and lipid metabolism. Further, BAs may increase energy expenditure after RYGB, but again this has not yet been tested [88].

The increased systemic BA levels have also been hypothesized to be responsible for elevated GLP-1 and PYY levels after RYGB for example by stimulation of the L-cells. However, the stimulation of L-cells by BA works via TGR5 receptor that is located in the luminal membrane of L-cells [89]. Thus, the effect would not be mediated by elevated systemic BA and intraluminal bile acid concentration after RYGB has not been tested to date. Accordingly, a recent study implies that bile acids are probably not responsible for the early increase of GLP-1 and PYY post-RYGB [90]. In summary, the direct link between elevated levels of BAs and increased L-hormone secretion after RYGB remains unclear [91].

Changes in Gut Microbiota

Gut microbiota have been identified as important modulators of whole-body energy metabolism and have been claimed to not merely be a bystander of metabolic alterations but to play a causal role in the development of obesity under different feeding conditions [92, 93]. The composition of gut microbiota has been shown to be altered by RYGB [94–96]. Furthermore, transferring gut microbiota from RYGB mice to germ-free mice reduced their body weight compared to mice that received gut microbiota from sham-operated mice [95]. This effect may be linked to a decrease in low-grade inflammatory state observed after reduction in body weight, as RYGB-induced changes in the microbiota of the alimentary- and also the common channel are similar to alterations seen after weight loss by dieting [96, 97]. Gut microbiota heavily influences bile acid metabolism [98]; thus altered gut microbiota may be causal for altered bile acid levels after RYGB. As mentioned above, it remains to be clarified if the altered bile acid metabolism after RYGB is necessary for beneficial effects of RYGB on insulin sensitivity and whole-body energy metabolism [4, 77, 78].

Central Nervous System Contribution to the Eating-Inhibitory Effects of RYGB

It seems plausible that any signal-inducing change on eating behavior and probably also on energy expenditure needs to be transmitted to the brain. Such signals may be transferred to the brain either via vagal or non-vagal afferent nerve signaling or directly via blood circulation.

Findings on the role of vagal nerve preservation for weight loss after RYGB is conflicting. One study found pronounced weight loss when the subdiaphragmatic vagal innervation was preserved during RYGB surgery [40]. In another study vagal nerve dissection actually increased the effects of RYGB on body weight with no difference however on long-term outcome [99].

Remarkably little is known about specific effects of RYGB on the CNS centers that are involved in eating control. Most studies focused on the role of the melanocortin system due to its overall importance in the control of eating and body weight [100–107]. Thereby one functional Melanocortin-4-receptor (MC4r) gene is sufficient for weight loss after RYGB, whereas homozygous knockout animals lost less weight after RYGB [103, 106]. By comparing homozygote to heterozygote or control animals after RYGB the MC4r was found to be important for changes in energy expenditure, body weight loss and glucose metabolism after RYGB [103]. Interestingly, the site of Melanocortin-4 (MC-4) signaling in the brain seems to be decisive for the effect. For example, genetic introduction of MC4r in key autonomic neurons of the brain stem, including cholinergic preganglionic motor neurons of the dorsal motor nucleus of the vagus, reinstated the effect of RYGB on insulin sensitivity, but not on body weight or obesity. Reintroducing MC4r in cholinergic preganglionic neurons of both the

parasympathetic and the sympathetic system on the other hand reinstated the RYGB effect on eating, body weight and adiposity; in this case, the improved insulin sensitivity was only secondary to weight loss [103, 106].

The important role of the melanocortin system was supported by findings in humans with a specific variant of the MC4 gene (MC4r(I251L)), which is associated with a better metabolic status; in fact, carriers of this variant had improved surgery outcome [104, 106].

Summary

Obesity and its related comorbidities are detrimental diseases for the affected individual, and they remain major challenges to public health systems worldwide. Bariatric surgery is the only currently available treatment for significant and long-lasting body weight loss and reduction in obesity-related morbidity and mortality [3, 4, 77]. Thereby the RYGB influences eating and energy expenditure.

The main effects of weight loss after RYGB do not seem to be due to restriction and/or malabsorption, but decreased appetite and earlier satiation. In addition, preference for less fatty, less sweet food and increased energy expenditure after RYGB may contribute to increased weight loss. Thereby the positive effect of RYGB on weight loss and glucose homeostasis have been linked to changes in circulating levels of gastrointestinal hormones and bile acids [30, 45, 108]. Although research in this field is progressing, studies linking observed changes in a causal manner are still limited. More work is needed to uncover the necessity of the discovered alterations for the effects of weight loss and improved glucose metabolism after RYGB.

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Infant Nutrition and Obesity

24

Lisa G. Smithers and Megan Rebuli

Introduction

Infant nutrition is thought to set the foundation for taste and food preferences and for later health outcomes, including overweight and obesity (from now will be referred to as "obesity"). This way of thinking about infant nutrition fits within the concept of the 'developmental origins of health and disease' hypothesis; that events or conditions occurring early in life can have long-lasting effects on obesity (as well as other health problems).

In this chapter, we discuss evidence on a range of topics where there are suggestions that infant nutrition is linked to obesity. These topics include breastfeeding, the protein composition of infant formula milk and food, timing of when to introduce solids and which types of foods, as well as the role of parents. We adopt an inclusive view to the measurements of obesity, from the most commonly used measures of body mass index (BMI) and BMI z-scores, to weight-for-age and indictors of body composition, such as skinfold thickness.

The chapter is limited to infancy, which is defined as the period from birth to 12 months of age. The chapter only involves studies of healthy infants and we purposefully exclude studies of infants born preterm, low birth weight or infants with medical conditions that affect feeding, nutrition, growth and obesity. Thus, this chapter is not about clinical nutrition management of infants at risk of obesity, rather we take on a more general public health view of nutrition in the first year of life for the healthy full-term infant.

It is important to note that the information that follows is not a systematic review of the evidence. Furthermore, in many cases the evidence is imperfect, controversial, or where experts have not reached consensus. It is for this reason that we attempt to integrate evidence from multiple sources and where possible, we favor evidence from high-quality randomized controlled trials (RCTs) or by triangulating evidence from different observational designs. This also means that as new evidence is published, nutrition recommendations for infancy will change.

Breastfeeding and Obesity

The effect of breastfeeding on obesity has been explored in many different ways, from comparing infants who are fed breast milk versus formula milk (from now will be referred as "formula") fed, and the duration and exclusivity of breastfeeding. A vast body of literature has mostly involved longitudinal cohort studies but at times has included other study designs, making the field quite complex and difficult to summarize. An additional complexity is that while obesity rates have been increasing other secular

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Table 24.1 Summary of breastfeeding and obesity by different study designs

Type of study	Some advantages and limitations of design for breastfeeding research	Examples of evidence on the effect of breastfeeding on obesity
Randomized controlled trial	Balanced on measured and unmeasured confounders	No effect [2, 3]
Longitudinal cohort studies	Easier to collect but at risk of bias due to residual or unmeasured confounding	Lower obesity if breastfed [4–7] but no effect if adjusted for confounders [8]
Sibling-pair studies	Better control of unmeasured confounding of the shared home environment and maternal factors but has low power	Mixed findings; no effect and lower obesity if breastfed [9, 10]
Cross-population studies	Able to examine consistency of effects across populations with different confounding structures to determine whether effects may be due to confounding	No effect [11]

events have occurred, such as changes to the recommended duration of exclusive breastfeeding and composition of infant formula.

We have previously shown how observational studies can help with the interpretation of breastfeeding research [1]. Studies with novel designs such as sibling pair and cross-population studies can offer some useful insights but these types of studies have not been integrated well into past systematic reviews and have been largely underutilized when generating policy and advice around breastfeeding and obesity. This has resulted in many official statements suggesting that breastfeeding will help to reduce obesity.

This section involves a summary of key evidence on potential mechanisms of how breastfeeding might influence obesity and a discussion of results from different study designs (Table 24.1) in order to give an overview of evidence for breastfeeding and later stage obesity.

Mechanisms: How Is Breastfeeding Purported to Influence Obesity?

There have been several mechanisms proposed by which breastfeeding might affect obesity [12]. One of the most frequently cited mechanisms is that breastfeeding promotes an infants' recognition of satiety [13]. Parents who formula feed their infant are more likely to persist with feeding until a bottle is emptied and this is thought to 'override' the infants learning to recognize signals of satiety, which may be manifested at later ages as eating in the absence of hunger [14]. By comparison, mothers who breastfeed rely upon the infant detaching from the breast to determine when they have had sufficient milk. Another mechanism by which breastfeeding might affect obesity is through programming of growth. The patterns of growth between breast and bottle fed infants differ. Breastfed infants typically grow quickly in the first few postnatal months and then growth tapers off so that by the age of 1 year, the average formula fed infant weighs around 500 g more than a breastfed infant [15]. Since early growth trajectories are linked to later obesity, this evidence tends to point to breastfeeding reducing obesity through growth trajectories. Despite these hypotheses, it has been much harder to establish a causal effect of breastfeeding on obesity than one might expect. This is because mothers who chose to breastfeed differ in many ways from mothers who do not breastfeed, and this can result in biased effects in observational studies due to confounding.

Experimental Research

The most rigorous study design for testing causality is the randomized controlled trial (RCT). This is because the randomization process ensures that both measured and unmeasured

confounding factors are balanced across the treatment and control groups. Kramer et al conducted a large cluster-RCT involving a breastfeeding promotion program versus usual practice (n > 17,000), naming it the Probit trial. The trial resulted in large differences in duration and exclusivity of breastfeeding between the intervention and control groups. By 6.5 years of age, no difference was found between the intervention and control group's BMI, waist and hip circumferences, triceps and subscapular skinfolds [2]. At 11 years of age, children in the treatment group had more positive attitudes to eating than control group children; however there were no anthropometrical differences between the groups and no effect on BMI, fat and fat-free mass indices, percent body fat, waist circumference, and skinfolds [16, 17]. Neither were there any differences between the treatment and control groups in IGF1 levels, which regulate children's growth [3]. It is unlikely that there will ever be another large-scale RCT of breastfeeding such as the Probit trial and therefore this high-quality rigorous study provides us with the best available evidence regarding the effect of prolonged exclusive breastfeeding on obesity.

Observational Studies

Observational studies of breastfeeding and obesity have been summarized in many systematic reviews, the majority of which suggest that breastfeeding reduces obesity [4–7, 18]. The individual studies included in these estimates vary to the extent at which they adjust for confounding. Proper adjustment for confounding is crucial for obtaining unbiased effects from observational studies. Owen et al showed that when only the cohort studies that adjusted for important confounders of maternal BMI, smoking and socioeconomic position are included, the effect of breastfeeding on obesity is nullified [8].

Observational studies that use better methods for balancing confounders, such as propensity scores, or better control for confounding in the home environment, such as sibling-pair designs, have also reported no effect of breastfeeding on obesity [9, 10, 19]. Sibling-pair studies compare obesity outcomes of children who experience disparity in their breastfeeding exposure. If breastfeeding does affect obesity, the sibling who had a greater exposure to breastfeeding is hypothesized to have reduced risk of obesity. The sibling-pair design offers better control of confounding because much of the home environment is shared between siblings. On the other hand, sibling-pair studies are limited because it is unusual for siblings to have large differences in their breastfeeding exposure, which reduces the power of sibling-pair studies and raises concerns about whether the reasons for siblings being fed differently also contributed to differences in obesity between children.

Cross-population studies also offer unique insights into breastfeeding and obesity when the confounding structures differ between populations. In the UK and many other Western settings, women who are older, more educated or more advantaged tend to breastfeed exclusively and for longer durations than women who do not breastfeed. Whereas in Brazil, no strong association has been observed between socioeconomic position and breastfeeding, and in The Philippines women from lower socioeconomic positions tend to breastfeed their infants [11]. If breastfeeding truly reduces obesity rates, it would be expected to occur regardless of socioeconomic position. However, Brion et al compared data from UK and Brazil and found that there was no effect of breastfeeding on obesity in Brazil suggesting that the findings from the UK are probably confounded [11]. Unfortunately most of the observational evidence on breastfeeding has come from high-income countries and these studies will replicate errors of unmeasured or residual confounding.

In essence it has proven extremely difficult to tease out the causal effect of breastfeeding because the majority of studies on this topic have been observational. There has been little uptake of evidence from different study designs, perhaps because what other designs have to offer is not well understood. Unfortunately this partial use of evidence means that many health authorities promote breastfeeding as having potential to reduce obesity, which seems a lot less plausible when all the evidence is pooled together.

Protein and Amino Acids in Infant Formula

Foods with a high protein content are thought to elicit a greater satiating effect, particularly if there are high levels of glutamate, and this may also be the case with infant formulas. Mennella et al. have shown that infants fed hydrolyzed cow's milk formula (which has a high free amino acid content) consumed a lower volume of formula. In other trials, they have shown that formula with added exogenous glutamate reduced feeding times and overall energy intake [20, 21]. It is too early to suggest if glutamate or free amino acid contents have a direct effect on obesity. In fact, infants who were fed extensively hydrolyzed formula with differing whey to casein ratios had no differences in BMI at 10 years of age [22]. Thus more evidence is needed to determine whether the amino acid profile of formula influences obesity.

Contrary to studies of amino acids in infant formula, high total protein content has been linked to later obesity. The prevailing hypothesis is that protein stimulates an insulin and IGF-1 response, which in turn, promotes growth. However this is a complex association that changes with age [23]. Typically IGF-1 levels decrease through infancy to 9 months of age and then increase, which happens to be the opposite of BMI which steadily increases through infancy until around 9 months before decreasing until the adiposity rebound around 5–6 years [23, 24].

Recently there has been a move to reduce the protein concentration of standard cow's milk formula as new research has demonstrated a link between protein in formula and childhood obesity. The seminal paper on this topic describes a multi-centre double-blind RCT involving over 1000 European infants. Control group infants were randomized to be fed a standard protein formula (providing 2.05 g/100 mL until 5 months and then 3.2 g/100 mL from 6 to 12 months) or a lower protein formula (1.25 g/100 mL until 5 months and 1.6 g/100 mL thereafter) [25]. The fat content of the formulas was manipulated to ensure that the formulas were isocaloric. By age 2, infants fed the low protein formula had 0.5 unit lower BMI, 0.7 kg lower weight and no effect on height compared with infants fed the high protein formula [25]. Analysis of plasma at 6 months of age demonstrated higher levels of insulin, IGF-1, and essential amino acids in infants fed the high protein formula [26, 27]. Follow up at 6 years of age showed that differences in BMI between the groups persisted [28]. Together with other trials, the results suggest that lower protein infant formula may modestly reduce adiposity in childhood [29]. It is important to note however, that current infant feeding recommendations are that there is insufficient evidence to conclude that higher protein intake in infant formula increases obesity [30]. However, protein intake is very topical and undoubtedly more research is required on protein and obesity in the years ahead.

Why Is There No Effect of Breastfeeding on Obesity But Trials of Protein in Formula Suggest Lower Obesity?

A challenge for nutritionists is to explain the discrepancy between the Probit trial (in which a longer duration of exclusive breastfeeding showed no effects on obesity) and the formula trial (in which high protein content increases obesity). As discussed earlier, there are many differences in families of infants who are breastfed compared with infants who are fed formula. A key difference between the Probit (breastfeeding promotion trial) and the formula protein RCT is that Probit mothers had commenced breastfeeding in order to be eligible for the trial. This is often not the case with the infant formula trials, where women who continue to breastfeed (rather than feed the formula according to the trial protocol) are excluded from the analysis. While excluding the 'non compliers' seems logical when the purpose of the trial is to examine the effect of the formula, it includes results of two non-comparable samples: infants whose mothers persist with breastfeeding and infants who could be at greater risk of obesity because of individual, parental or family characteristics that result in them being fed formula.

Complementary Feeding

Complementary feeding refers to the introduction of solid foods to the infant's diet. There are two key issues to consider in regard to complementary feeding and obesity; the timing of *when* to begin introducing solids and *which* foods an infant should be fed.

Timing of the Introduction of Complementary Feeding and Obesity

Current recommendations for when to begin complementary feeding are reasonably consistent (Table 24.2). Generally, the recommended time for introducing solid food to the infant diet is around 6 months of age and no earlier than 4 months [31–38]. The rationale for the recommendations is based on the maturity of the infant's renal and gastrointestinal systems and the increased need for micronutrients, particularly iron and zinc [35]. Introducing solid foods too early (prior to 4 months) increases the risk of Type 1 diabetes, coeliac disease, atopy, allergy, respiratory tract infections and diarrhea, while introducing solid foods too late (after 6 months) is linked to faltered growth; iron, zinc, and other micronutrient deficiencies, and feeding difficulties or developmental delay [31, 35, 39–41].

It has been suggested that early introduction of solid foods may lead to obesity in childhood or later in life, potentially due to rapid weight gain following the initiation of solid foods. On the other hand, larger infant size has been identified as a reason for parents to begin solid foods earlier, which may result in reverse causality where early complementary feeding is the result of large infant size, rather than early feeding resulting in weight gain [42].

As with breastfeeding research, there is limited experimental data in relation to timing of the introduction of complementary foods and later obesity or weight-related outcomes. To date, the RCT evidence largely suggests no effect of timing on infants' growth rate including BMI [43, 44]. For example, Mehta et al [44] found no difference in fat mass or percent body fat of 12-month-old infants who were randomized to commence solids at 3 or 6 months of age. Similarly, Jonsdottir et al found no effect of

Table 24.2 Current recommendations guidelines for introducing solid foods

Organisation	Summary of key recommendations
American Academy of Pediatrics (AAP) (2012) [31]	Introduce solid foods at around 6 months of age. Include a wide variety of healthy foods and a range of textures. Food should be rich in iron and zinc
Australasian Society of Clinical Immunology and Allergy (ASCIA) (2010) [32]	Introduce complementary foods from around 4–6 months. There is no evidence to support delaying or avoiding introduction of potentially allergenic foods
British Dietetic Association (BDA) (2013) [33]	Introduce solid food at around 6 months of age, but not before 4 months and not after 6 months
European Food Safety Authority (EFSA) (2009) [34]	Introduce solid foods between 4 and 6 months, and not before 4 months
European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) (2008) [35]	Introduce solid foods no earlier than 17 and no later than 26 weeks. There is no evidence to avoid delaying introduction of potentially allergenic foods. Introduce gluten between 4 and 7 months, in conjunction with breastfeeding
Institute of Medicine (IOM) (2011) [36]	Introduce solid foods at around 6 months
National Health and Medical Research Council (NHMRC) (2012) [37]	Introduce solid foods from around 6 months, using a range of foods of appropriate texture and consistency. Begin with iron rich foods
World Health Organization (WHO) (2001) [38]	Commence complementary feeding at 6 months of age in addition to breast milk

introducing solids at 4 versus 6 months on growth trajectories, BMI or obesity outcomes up to 3 years of age [43].

Systematic reviews of observational studies examining the timing of solid foods and obesity are inconclusive [38, 40, 41]. In fact, the results of independent observational studies are conflicting. Three recent studies found no association between the timing of introduction of solid foods [45–47], such as Burdette et al who reported no difference in adiposity or prevalence of overweight among children at 5 years of age whose mothers followed the American Academy of Pediatrics (AAP) guidelines (Table 24.2) and those who did not [31, 45]. Even in countries with different cultural contexts, for example, research from Hong Kong's Children of 1997 cohort showed the lack of association between timing of solid foods and weight in childhood [46]. Therefore it may be that timing of complementary feeding does not affect obesity outcomes, rather it contributes to a complex pattern of behavior and lifestyle choices that may lead to overweight or obesity [46].

In contrast to the above reports, two longitudinal cohorts found that timing of introduction of solid foods was associated with overweight in later life, with one study reporting a 15 % absolute reduced risk of being overweight at 10 years of age if introduction of solid foods was delayed from 20 to 24 weeks and another finding that the risk of being overweight at 42 years of age decreased with every additional week of delay of solid introduction in infancy [48, 49]. Interestingly, Huh et al found no relationship between obesity at 3 years of age and timing of complementary feeding among breastfed infants however, among children who were not breastfed, there was 6.3 fold increased risk of being obese (>95th percentile) at 3 years of age if solid foods were introduced prior to 4 months, compared to if they were introduced between 4 and 5 months [50].

Macronutrients, Type of Complementary Foods and Obesity

Recommendations for the type of first solid foods focus on the prevention of malnutrition, allergy, atopy and the development of healthy preferences and eating patterns throughout life, rather than on obesity [31, 32, 35, 37]. While there is some observational research into the association between macronutrients and obesity, it is difficult to ascertain the specific effects of certain foods in infancy and later obesity [31, 32, 37, 51].

Energy balance for healthy growth is relevant in childhood as in any other life stage, and excessive energy intake during complementary feeding can result in additional weight gain [35]. Research suggests that breastfed infants may be better at regulating their energy intake than formula fed infants. As breastfed infants consume more solid foods they tend to lower their intake of breast milk; however adjustment of milk intake in response to solids is not observed among formula fed infants, resulting in greater overall energy intake by formula fed infants [51].

Healthy eating patterns and food preferences are established in early life and continue into childhood and adolescence [52]. Infants require a nutrient-dense diet to support rapid growth. Sugar-sweetened beverages and deep fried foods are examples of energy-rich and nutrient-poor foods that can displace healthy foods from the diet and result in taste preferences for high fat, high salt and high sugar foods, which may lead to overweight and obesity in later life if over-consumed [35].

Protein in Complementary Food

Evidence emerging between the types of proteins in complementary foods and obesity suggests that dairy foods are more obesogenic than meat products, which could be because milk is relatively high in protein and it is easy for infants to consume large volumes compared with meat or other protein-rich food [53]. Michaelson et al point out that protein from dairy foods make a bigger contribution to total energy than protein from other sources [53]. Others suggest that protein in the second year of life is more important for obesity, than during infancy [54]. Currently, the recommended macronutrient distribution range of protein in infancy is a maximum of 15 % of total energy intake for healthy development [35, 51]. More research is needed to substantiate the link between the type and quantity of protein in complementary foods and obesity.

Fat in Complementary Food

The quality and quantity of fat in the diet are important for healthy weight and development. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommend a macronutrient distribution range of at least 25 % fat, Young and Krebs suggest 30–40 % fat, but note that less than 30 % from high quality sources can also support sufficient growth and development [51]. There is limited research on the effects of fat intake in infancy and later.

Summing up of Complementary Feeding and Obesity

There is a lot of evidence about the introduction of solids, but the context here is the association with obesity. Based on the evidence from RCTs, it appears that there is currently little support for the timing of introduction of solid foods influencing obesity later in life. This is somewhat consistent with the inconclusive findings reported in the systematic reviews of observational studies. However, the evidence around *which* foods to be introduced is less clear, hence advice is to introduce a nutritious diet that supports the high nutrient demands of rapid growth in infancy. It is important to remember that infants begin to develop preferences for particular foods and therefore establishing healthy eating patterns from infancy might be an important strategy for preventing obesity later in life. At this point in time, official recommendations suggest that the evidence for the effect of the type and timing of solid food on obesity is inconsistent, however it is essential that recommendations are updated as new research emerges [30].

Genes Involved in Taste, Flavor Exposures and Obesity

The development of our taste and food preferences reflects an accumulation of our past flavor experiences, our culture and our genes. Genes directly linked with obesity will be discussed in more detail elsewhere in this book, however it is important to mention that genes associated with taste may impact on infants' willingness to consume certain foods. Genes have been linked to acceptance of bitter foods such as Karela (a tropical vegetable) and with preferences for umami or sweet flavors. It is possible that preferences for healthier or less energy rich foods might influence future risk of obesity. To date, the evidence on whether genes related to taste ultimately lead to obesity has been ambiguous [55]. Nevertheless, one of the most interesting studies to date is a Mendelian randomization study, which demonstrated that the ability to taste bitterness is linked to body weight among girls but not in boys [56].

Throughout pregnancy, the fetus is exposed to flavors from foods in the mothers diet and infants tend to show preferences for such foods [57, 58]. Similarly, studies have shown that exposures to different flavors during infancy, either by exposure to flavors in breast milk or infant formula, may have lasting effects on flavor preferences as an adult. For example, infants fed a formula flavored with vanillin resulted in a preference for a vanillin-flavored food in adulthood [59]. Mennella *et al.* have described this as a 'flavor bridge' that captures local and culturally accepted foods consumed by the mother to prime the fetus, neonate or young infant to the types of foods they will be introduced to once complementary feeding begins.

Although it is possible that genes for taste or early experiences of flavor may drive food preferences, ultimately the association with obesity is more complex because it is not the preference for particular foods but the excess intake of food that is needed to result in obesity.

Parenting, Food and Obesity

For many years, psychologists have known that different parenting styles are linked to children's behavior and this is also being studied in nutrition science. The four main parenting styles discussed in infant nutrition are founded on the concepts of parental responsiveness and level of control [60, 61]. Parents who are responsive to the needs of their children and exhibit high control over their food

choices are referred to as having an 'authoritative' style. It is implied that children of authoritative parenting do 'better' than children whose parents practice authoritarian (high control, low responsiveness), permissive (low control, high responsiveness) and uninvolved styles (low in control and responsiveness). Parenting styles are thought, at least in part, to drive parental monitoring, restriction of food and pressure for children to eat. To illustrate, an authoritarian parenting style might result in a parent demanding that their child consumes all of the food on their plate before leaving the dinner table. This requires the child to suppress feelings of satiety, which could lead to obesity over the longer term via poorer self-regulation of eating. A recent systematic review by Collins *et al* suggested that parenting styles have weak to moderate associations with the monitoring, restriction and pressure to eat among children aged 2–5 years [61].

While less is known about parenting styles during infancy and obesogenic behaviors, there are some clues from comparing parenting practices of breast and formula fed children. For example, mothers who breastfeed their infants tend to have a feeding style lower in control, are more likely to feed their infant on demand (vs to schedule) and less likely to pressure their children to eat [62–64].

Certain temperamental traits such as poor self-regulation and the use of food to soothe distressed infants appear to influence a parents use of obesogenic feeding behaviors, such as restrictive feeding practices [65]. Although there have been very few studies that examine associations between infant temperament and obesity, the limited evidence available suggests that some aspects of temperament might be linked to weight gain and later obesity [66–69].

Nutrition Interventions Beginning in Infancy to Address Obesogenic Behaviors

In recent years, a number of interventions have targeted the infancy period to reduce obesogenic feeding behaviors [70–73]. The range and content of these interventions is diverse. For example, one RCT involved modifying obesogenic bottle feeding behaviors, such as teaching parents to better recognize infant satiety cues, while others have targeted the timing and types of foods introduced when complementary feeding [74]. Some interventions have also included physical activity ('tummy time') and sedentary behaviors information along with the nutrition information [71, 72], which means that some of these RCTs are not solely nutrition-based interventions. These trials have produced mixed results with most demonstrating improved infant feeding, such as responsive feeding strategies, reductions in sugary drinks or greater fruit and vegetable intakes, or knowledge of obesogenic bottle feeding behaviors [70–72, 74]. Despite having high quality designs and comprehensively structured interventions for tackling obesity, the effects of these interventions have been disappointing. Increased growth was observed among infants whose mothers were taught strategies to reduce obesogenic bottle feeding practices. A small effect on infant weight (about ~250 g at 2 years of age) was reported from one trial and no effects were observed in at least two other trials [70–72]. The reasons for these inconsistencies are not clear but may be due to the choice of targets for the interventions, the timing or delivery of the interventions. Furthermore, it could be that obesity outcomes might not be manifested until children are older. Thus, despite our best efforts there appears to be negligible effects of well-designed, multipronged and rigorous interventions to improve nutrition in infancy and ameliorate obesity outcomes.

Conclusion

Nutrition over the first year of life encompasses an infants' first experience of consuming a solely milk-based diet, through the transition to solid foods, which begins around 6 months of age and includes new flavours and textures. At the end of the first year, the typical infant is a competent eater of most solid foods, and ideally, the infant consumes a wide range of healthy foods that are also consumed by the whole family.

In adults, the obvious role for nutrition on obesity is via overconsumption of energy, but

this is not the focus in infancy, where early life experiences are conceptualized as having longer-term or 'latent' effects on the development of obesity. The effect of breastfeeding has been most commonly studied, and despite some public policies suggesting breastfeeding reduces obesity, it appears unlikely that promotion of breastfeeding will ameliorate the obesity problem. Likewise, recently published randomized trials find little evidence to support the theory that the timing of the introduction of solids effects later obesity. A more likely strategy for preventing obesity appears among formula fed infants to be reducing the overall protein content of infant formula, while total free amino acid and glutamate in infant formula may be targets for future large-scale confirmatory trials.

It is certain that there will be a great deal of research invested in the testing of methods to reduce obesogenic feeding behaviors, and towards developing interventions for energy-appropriate healthier diets that are sustained throughout infancy into childhood and ultimately reduce obesity. This is especially important as the parenting interventions that have been tested to date have had negligible effects on obesity-related outcomes. Since there are few proven effective targets, there is great scope for future research. Finally, the uncertainty in evidence on infant nutrition and obesity means that this is an exciting area to watch as new evidence emerges and infant feeding recommendations are adapted.

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Disordered Eating and Obesity

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Introduction

The World Health Organization considers Obesity a current endemic disease in developed countries, with serious public health implications [1]. Obesity, defined as body mass index (BMI) ≥30, is increasing in prevalence in the US and globally [2]. It is estimated that approximately 35.8 % of the US population were obese in 2009–2010 [3]. Not only does obesity compromise physical health, it also has a great impact on psychological well-being, and is associated with poorer quality of life, greater psychological distress, disordered unhealthy food eating and poorer self-esteem [4].

More concerning is that the rate of obesity in children and adolescents is also increasing in developed as well in several affluent countries worldwide. Childhood obesity is associated with an increased risk of disorderly and binge eating symptoms, and psychopathology, including unattractive shape and weight concerns, as well the weight control methods [5]. This poses great concerns not only because of the unwanted health consequences related to both overweight and disordered eating [6], but also because these conditions may mutually perpetuate each other, with childhood overweight increasing the risk for disordered eating, and vice-versa [7].

Among other factors associated with obesity, problematic eating has been the focus of increasing attention due to its modifiable character. In fact, regular and healthy eating choices have long been associated with a healthier weight or with greater success in weight loss [8]. Nonetheless, the presence of disordered eating behaviors may compromise attempts to maintain healthy eating and weight loss. Some of these behaviors are challenging to assess, and may be underreported, requiring specific knowledge and training for accurate assessment and the design of effective interventions.

This chapter will focus on the characterization and the clinical importance of different eating behaviors leading to obesity in individuals. We will address problematic eating behaviors that appear to play an important role in obesity such as binge eating disorder, loss of control eating, grazing, night eating syndrome and emotional eating. Specific guidelines for the assessment and treatment of such problems will be provided.

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Binge Eating Disorder, Binge Eating and Loss of Control Over Eating

Binge eating disorder (BED) is a diagnostic category in the eating disorder section in the DSM-5 (diagnostic and statistical manual of mental disorders-5). It is defined as the presence of objective binge eating episodes (the consumption, over a discrete period of time, of an amount of food that is definitely larger compared to what a person would eat under the same circumstances), accompanied by the sense of loss of control (LOC) over one's eating, occurring at least once a week for 3 months, with the episodes followed by feelings of guilt and distress. These eating episodes are not followed by compensatory behaviors such as vomiting or laxatives/diuretic misuse [9].

In some cases, LOC eating is reported without the ingestion of large amounts of food (e.g. subjective binge eating episodes) [10, 11]. As LOC eating seems to be prevalent among obese individuals who do not meet full criteria for BED, assessing the different components of binge eating independently (sense of LOC and the amount of food eaten), has been suggested when working with obese population.

BED, binge eating or LOC eating are thought to be relatively frequent among overweight, obese and severely obese individuals, and their association with weight gain and obesity makes them target behaviors for clinicians working with this population [12, 13].

Special Considerations and Clinical Relevance of Binge Eating Disorder, Binge Eating and Loss of Control over Eating

Empirical studies have suggested that obese individuals who binge eat have higher rates of Axis I and Axis II mental disorders than overweight or obese individuals who do not binge eat [14, 15]. Other studies suggest that individuals with BED often report overeating in response to strong emotional demand [16, 17].

Binge eating is therefore not only associated with psychological distress, but is also associated with weight regain and poorer long-term outcomes in those with weight loss treatment. Since such problems occur rather frequently among obese and overweight individuals, targeting binge eating or LOC eating may result in better psychological functioning and weight loss treatment outcomes [18].

Despite not meeting full criteria for binge eating episodes, individuals who report LOC, regardless of the amount of food eaten, score significantly higher in psychopathological variables and distressed overeating [19]. In fact, research has shown that the sense of LOC is highly associated with psychological distress than to the amount of food ingested [19, 20], and some authors have suggested that LOC is actually the central aspect of binge eating.

In severely obese patients undergoing bariatric surgery, research has supported the importance of binge eating, BED or LOC. Indeed, in a recent review by Meany and colleagues, it is reported that despite the apparent normalization of eating behaviors after surgery in a significant percentage of patients, the emergence or re-emergence of these behaviors post-operatively results in less weight loss and/or more weight regain [10, 21, 22].

Binge eating symptoms are also frequently found in severely obese adolescents. Specifically, up to 30 % of overweight children and adolescents report episodes of LOC eating with or without consumption of large amount of food [23]. Obese adolescents who binge eat; also appear to have increased depressive symptoms, higher levels of anxiety, and lower self-esteem. Depression and anxiety seem be the very important dimensions, specifically associated with binge eating in severely obese adolescents seeking treatment [23–25].

Assessment

The assessment of binge eating in obese people poses challenges and that may require specific training. Traditionally, clinicians and researchers have sought to examine the presence or absence of LOC over eating and in those consuming extremely large amounts of food. As detailed

above, literature suggests that LOC should be considered regardless of the amount of food ingested. Nonetheless, the distinction between overeating and binge eating may require careful questioning and experience because of the great variety of foods eaten and also because the amount of food eaten is usually not as distinctively large as that consumed by bulimia nervosa patients [26]. Moreover, in obesity, binge eating episodes are not terminated with some kind of compensatory behavior as in bulimia nervosa patients [27, 28]. Additionally, literature suggest that that LOC should be assessed in a continuous rating scheme to identify gradient loss of control associated with different eating behaviors [29, 30], instead of in a dichotomous (present/absent) manner [29, 30].

In individuals who have undergone bariatric surgery, the resulting limited gastric capacity greatly alters the amount of food that can be ingested, and deciding on what constitutes a large amount of food is a challenge for both researchers and clinicians. However, post-surgery bariatric patients often report feelings of LOC and overeating, despite the amount of food eaten not being objectively large [22, 31]. Consequently, assessing this population requires detailed knowledge of these patients' eating habits, type surgical procedure received, and time elapsed since surgery [26].

In the youth, binge eating may be particularly difficult to assess because of its reliance on subjective experience (i.e. LOC, overeating) and retrospective recall (e.g. amount of food consumed). Concepts such as "out of control" or "unable to stop" once having started eating, are difficult for many children and adolescents to fully understand. Similarly, it may be difficult to determine whether an eating episode is definitely large in children and adolescents given their developmental requirements [7].

These behaviors can be assessed through self-report measures or semi-structured clinical interviews. The semi-structured clinical interview Eating Disorder Examination (EDE 16.0D), assesses eating disordered behaviors and eating disordered symptomatology [32]. It generates a global score and 4 subscales: restraint, eating concerns, shape concern and weight concern, and includes diagnostic items to establish eating disorders diagnoses. The new EDE version (17.0) allows for DSM-5 eating disorder diagnoses [9, 33].

Currently there are a considerable number of self-report measures designed to assess disordered eating, eating disorder psychopathology, and compulsive/binge eating. The Eating Disorder Examination-Questionnaire (EDE-Q 6.0) is a 28 items measure used to assess eating disorder symptoms and associated common characteristics [34]. Patients answer using a 7-point scale (i.e. 0–6) indicating the number of days out of the previous 28 in which particular behaviors, attitudes or feelings occurred. It also generates four subscales (restraint, eating concern, shape concern and weight concern).

The Binge Eating Scale (BES), is a 16-item self-report questionnaire designed to assess the severity of binge eating among individuals with obesity [35]. The scale examines loss of control over eating and associated binge eating features, such as eating more rapidly than normal, eating until feeling uncomfortably full, eating large amounts of food when not feeling physically hungry, and eating alone.

The Dutch Eating Behavior Questionnaire (DEBQ), contains 33 items, rated on a 5-point Likert scale (ranging from "never" to "very often"), assessing 3 patterns of eating, grouped in 3 subscales – "emotional eating", which includes 13 items, "external eating", including 10 items and "restrained eating", which includes 10 items [36].

The Eating Disorder Questionnaire (EDQ), a self-report, 110-item instrument designed to assess a variety of eating behaviors and attitudes toward weight, shape, and eating [37]. It also contains questions about psychological, medical and psychiatric history.

The Eating Disorder Diagnostic Scale (EDDS), is a 22-item self-report questionnaire that assess eating disorder diagnoses [38]. Individuals diagnosed with an eating disorder using EDDS also score significantly higher on other measures of eating pathology.

The Questionnaire on Eating and Weight Patterns-5 (QEWP5) is a 28 item self-administered measure designed to assess the presence or

absence of binge eating episodes, the frequency of such episodes, and additional required features for the diagnosis of BED [39].

The Three-Factor Eating Questionnaire (TFEQ), is a self-assessment questionnaire developed to measure cognitive and behavioral components of eating [40]. The instrument contains 36 items with a yes/no response format, and 14 items on a 1–4 response scale. It generates three subscales: cognitive restraint, disinhibition, and hunger.

Treatment

Various approaches for the treatment of BED have been tested, including pharmacological treatments and different psychological interventions. Cognitive–behavioral therapy (CBT) is the best studied and the well-established psychological treatment for BED [41, 42]. However results are mixed and interpersonal therapy (IPT) has shown comparable outcomes with some work suggesting its superiority in the long term maintenance of results [43, 44]. One of the major concerns about CBT and IPT is that, although they result in remission of binge eating, they do not lead to substantial weight loss. Behavioral weight loss (BWL) interventions have also been tested as single intervention and as supplementary treatment delivered sequentially to CBT for BED. Results show that either CBT, BWL and CBT+BWL interventions produce significant improvements in binge eating, yet CBT is more effective in reducing binge eating, and BWL is better at producing weight loss. Moreover, these treatments do not differ in their impact on depression and eating disordered symptoms, and there is no evidence that a combination of these interventions lead to better outcomes when compared to CBT or BWL alone [41].

As the burden of obesity increase in health care centers, the development of alternative delivery strategies is gaining increased attention. Guided self-help CBT is a type of treatment that can widely be disseminable. It can be considered as a brief intervention with promising results in reducing binge eating, and can be used by non-specialist in different health care centers. Usually considered as a first line treatment in a stepped care approach, it can be delivered when specialized treatment is unavailable [44]. This treatment provides participants with a CBT-based self-help manual, as well as regular brief meetings with a therapist or other health-care provider. Guided self-help has shown efficacy for BED without additional pathology, and to be more effective in reducing binge eating than BWL interventions in some studies [44, 45].

Internet-based intervention programs are another treatment delivery strategy currently undergoing research. Such programs offer several advantages that are detailed elsewhere in this book, including high accessibility, reduced costs and easy dissemination. Preliminary results show their great potentiality in BED treatment and major trials are undergoing to explore their effectiveness [46, 47].

Grazing

Grazing is an eating behavior characterized by a repetitive eating pattern. Different authors have used different concepts, often with overlapping characteristics. As a result, different but similar nomenclatures, such as snacking, snack eating, picking or nibbling or simply picking have been used, limiting the ability to compare across studies [29]. Recently, an international survey was conducted aiming at developing a consensus definition. Grazing was defined as the repetitive eating of small/modest amounts of food in an unplanned manner and/or not in response to hunger/satiety sensations. Repetitive consisted of eating more than twice in the same period of time with no prolonged gaps in between eating episodes. Additionally, two subtypes were suggested: (i) compulsive grazing – characterized by attempting to resist but resulting in returning to repetitively snack on food; and (ii) non-compulsive grazing – repetitively eating in a distracted and mindless way.

Grazing should be distinguished from intentionally fractionating meals into smaller portions to be repeatedly eaten. Conceição et al. presented guidelines to differential distinguish this from other eating episodes [29]. For example, after bariatric surgery, given the reduced gastric capacity it is rather common for bariatric patients to

intentionally fractionate their meals in order to ingest the necessary amount of food. The planned and anticipated nature of this behavior speaks to its difference from grazing. Grazing should also be differentiated from subjective binge eating episodes, which are defined as feelings of LOC over eating small amounts of food in a circumscribed (and not repetitively) period of time.

Special Considerations and Clinical Relevance of Grazing

Grazing was first reported in bariatric surgery populations because of its presumed association with negative weight outcomes. The altered gastric capacity after surgery greatly limits the amount of food intake, and some authors have suggested that those who binge eat pre-operatively may became grazers after surgery as a means of maintaining compulsive eating [48]. Moreover, the unplanned nature of this behavior is thought to result in excessive caloric intake and, ultimately, to have significant negative impact on weight outcomes [49]. Growing attention is being paid to the emergence of grazing postoperatively, due to its presumed link to compulsive eating and weight regain [29, 50]. Recent studies reported a high frequency (up to 40 %) of grazing in post-bariatric population [51], but little is known about this behavior in other populations. Some authors have reported a similar concept, picking or nibbling, in eating disordered patients [52, 53] and in community samples [54, 55], with frequencies as high as 95 % in college students, and ranging from 34.3 to 88 % in eating disordered patients. Therefore, these seem to be highly prevalent behaviors, with no clear association with psychopathology [29]. Some authors have not found association between body mass index (BMI), frequency of meals, binge eating, overeating, dietary restraint, or shape, eating and weight concerns, or compensatory behaviors, but other studies reported more negative feelings, poor compliance with treatment, poor health-related quality of life, increased psychological distress and disordered eating among individuals who present with grazing [53–55].

Assessment

The authors proposing the definition described above, developed a self-report measure and a semi-structured clinical interview based on the definition proposed. Rep(eat) is a semi-structured clinical interview including compulsory probe questions and subsidiary probe questions to identify grazing behavior and its sub-types. It assesses the preceding 4 weeks, asking for the number of days characterized by grazing and its associated features.

The Rep(eat)-Q is a 15 items self-report measure designed to assess behaviors, feeling and cognitions related to a grazing eating pattern. It generates a total score ranging from 0 (“never”) to 6 (“usually more than once each day”) with higher scores indicating a grazing-type eating pattern [29]. In addition Lane et al. presented 16 item questionnaire assessing cognitions and behaviors related to grazing, using a 5 point likert-type rating scale, from never (0) to all of the time (4) [55].

Treatment

There is no validated treatment for grazing. However, we believe that those who graze often respond to an adaptation of CBT and/or life-style interventions with a focus on regular and scheduled eating, stimuli control and training in coping skills to control overeating.

Night Eating Syndrome

Stunkard et al. first characterized the night eating syndrome (NES) in 1955. Since then a variety of terms have been employed to describe an eating pattern that concentrates on eating in the evening and during the night. Night eating syndrome is now often referred to as evening hyperphagia and/or nocturnal eating, designated following regular awakenings [56, 57].

NES is characterized by a constellation of symptoms that may be associated with a delay in circadian rhythms of food intake, including hyperphagia in the evening or nocturnal eating, in which sleep is disturbed to food consumption

[58]. NES typically begins in early adulthood and seems to be a lifelong condition with periods of remission and aggravation that might be related with stressful events [58–61].

In the latest definition offered by Allison et al. diagnostic criteria for NES included abnormally increased food intake in the evening and nighttime, manifested by a minimum of 25 % of food consumption after the evening meal, and/or nocturnal awakenings with conscious episodes of food ingestions, occurring at least twice per week. Significant distress and/or impairment in functioning also has to be present [58].

Additionally, three of these five clinical features are required: (i) morning anorexia; (ii) urge to food intake after the evening meal and/or during the night; (iii) insomnia; (iv) nocturnal awakenings with conscious food ingestions in accordance with the belief that it is necessary to initiate or return to sleep; and (v) depressed mood, frequently in the evening. All the above mentioned criteria must be met for a minimum period of 3 months [58–61].

Currently, NES is included in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as an "Other Specified Feeding or Eating Disorder", and some studies suggest that NES might be a risk factor for obesity. Indeed, 52 % of obese individuals with NES report a normal weight prior to the beginning of this problem. Connections between childhood obesity and NES have not yet been established [62].

Studies on the prevalence of NES indicate that approximately 1–1.5 % of general population suffer from NES, with no differences in gender and ethnicity [59, 62]. On the other hand, NES seems to be more frequent in individuals with obesity, comorbid psychiatric disorders, depressed mood, sleep and eating disorders [59, 60].

Special Considerations Concerning Associated Features of NES

BMI seems to be positively associated with NES, and the literature indicates a prevalence of NES between 8.9 and 25 % in morbid obese individuals. However, criteria used to make the diagnoses have varied widely across studies, which precludes the comparisons of the results [62]. In overweight and obese individuals with serious mental illness, NES is present in about 25 % the population [60]. In the severely obese candidates, NES rates have been estimated to vary from 8 to 42 % in gastric bypass candidates [59, 63].

NES is frequently associated with depressed mood, anxiety, elevated rates of substance use, other psychiatric disorders, low self-esteem, low sleep efficiency and eating disorders [59, 61], which suggests an acceptance of the clinical relevance of this problem, particular for its role in obesity trajectories and consequently in weight and diabetes management [59, 61].

In the differential diagnosis of NES, Sleep Related Eating Disorder (SRED), bulimia nervosa and binge eating disorder should be considered. In NES food intake occurs in the evening or night, and with no compensatory behaviors associated. Furthermore, in NES nocturnal ingestions are conscious, which contrasts with the described nocturnal ingestions in Sleep-Related Eating Disorder (SRED), a parasomnia in which food intake episodes occur with only partial or no awareness [57, 60, 61].

The presence of NES in bariatric surgery candidates does not seem be predictive of negative weight loss outcomes, uncontrolled overeating, grazing or NES in the post-surgical period. Also, NES prevalence rates are thought to decrease significantly after bariatric surgery [63]. Nevertheless in 6 out of 10 patients presenting with postoperative NES, the problem appears for the first time after surgery [64]. Lower cognitive restraint, increased social eating and eating when tired have been associated with post-surgery NES. However, no statistically significant differences on weight loss have been found between NES and non-NES bariatric patients [63–65].

Assessment

A diagnostic interview conducted by an ED expert is considered the best tool for the assessment of NES, although self-report measures can be used [62]. The Night Eating Questionnaire (NEQ) is a

standardized instrument composed by 14 items used to screen for NES behavioral and psychological symptoms and its severity [66]. NEQ produces a total score that ranges from 0 to 52 points, and evaluates morning appetite, food cravings, percentage of food ingested after the evening meal, mood disturbance, initial insomnia, nocturnal awakenings and awareness of nocturnal eating occurrences. This scale also shows good psychometric properties in the assessment of NES in children, and is thought to be more informative than parent report alone [67].

Other self-report measures of NES include the Night Eating Diagnostic Questionnaire (NEDQ), which is comprised of 22 questions, and yields a total score that enables one to distinguish NES and non-NES individuals [68]. Using the night eating diagnostic criteria, the Night Eating Symptom Scale (NESS) is a self-report measure that indicates severity of symptoms of NES in the previous 7 days, and can be used as a monitoring tool in treatment [69].

Treatment

More research is necessary to establish effectiveness of psychotherapeutic and pharmacological treatments for NES [59, 61, 70]. However, there is some evidence for the benefit of dopaminergic drugs, anticonvulsants, serotonergic-based pharmacological treatments, and cognitive behavior therapy, with the last yielding significant improvements in number of night-time ingestions, caloric consumption after dinner, depressed mood and weight loss [60, 70]. Psychoeducation, sleep hygiene, cognitive restructuring, physical activity, relaxation techniques and social facilitation seems to be key ingredients in achieving positive outcomes in psychotherapeutic treatments of NES [59].

Emotional Eating

Despite the lack of a standardized definition of emotional eating, it has been characterized as 'the tendency to overeat in response to negative emotions, such as anxiety or irritability' [71]. The concept of emotional eating evolved from psychosomatic theory (1964), which stated that those who engaged in emotional eating were unable to discriminate hunger from the physiological states that accompanied negative emotions.

Emotional eating is highly prevalent in adults, particularly in female adults who are overweight or obese and is thought to have a very low prevalence in young children [72, 73].

Associated Features and Clinical Relevance of Emotional Eating

Emotional eating has been associated with binge eating, which is often preceded by negative emotions [74]. Moreover, research has demonstrated that negative emotional states frequently serve as triggers for engaging in unhealthy eating patterns, and that eating in response to emotions increases food consumption [74, 75].

Emotional eating has been described as a dysfunctional eating behavior that may lead to insufficient weight loss after bariatric surgery. Emotional eating is thought to be common among pre-and post-bariatric patients, and has been associated with binge eating, grazing, "uncontrolled" eating and snack eating [76, 77]. Additionally, some authors have considered it a risk factor for poorer weight outcomes after surgery, although the data are inconsistent regarding its impact on weight outcomes after surgery [74, 77].

Research findings among overweight youth indicate that children who have LOC eating are more likely to report eating in response to negative emotions [78, 79]. Girls were more likely to report eating in response to depressive symptoms [79]. Adults with BED also report overeating in response to emotional triggers. Emotional overeating is an important area of research since it has been identified as a trigger for binge eating and disinhibitory eating among individuals with BED [16]. Overweight and obese individuals with and without BED also report emotional eating or increased food intake in response to emotional activation that may not meet criteria for objective binge eating [80].

Assessment

Two questionnaires assess this behavior. The Dutch Eating Behaviour Questionnaire (DEBQ) is a self-report questionnaire designed to assess eating-related cues and triggers [36]. It generates three subscales: restrained eating (DEBQ-R), emotional eating (DEBQ-EM), and external eating (DEBQ-EX). Items are rated on a 5-point Likert-type scale, from 1 (never) to 5 (very often), with higher scores indicating a greater tendency to engage in restrained, emotional, or external eating. The Emotional Eating Scale (EES) was designed to assess the relationship between specific negative emotional states and overeating [81]. This 25 items scale includes three subscales: anger/frustration, anxiety and depression. These three subscales reflect the emotional antecedents of emotional eating and, on each scale, higher scores reveal a greater tendency to eat in response to an emotional state.

Treatment

To the best of our knowledge, there are no validated treatments specifically for emotional eating. However, treatments designed for binge eating or disordered eating may improve emotional eating, such as mindfulness therapy [82]. CBT have also improved relevant psychopathological features of BED such as emotional eating [83].

Conclusion

Given the high rates of obesity and the key role of eating behavior in energy intake exceeding expenditure, targeting specific eating behaviors in obese population appear to be central for weight loss control. The fact that many of these behaviors do not meet formal DSM-5 diagnostic categories makes them understudied and often misidentified. Since disordered eating is associated with weight gain and compromises weight loss interventions, specific training to assess and identify different problematic eating behaviors may allow a more detailed understanding of the phenomenon of weight gain and weight maintenance.

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Physical Activity in Obesity and Diabetes

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Definition of Physical Activity

PA can be described as any bodily movement produced by the skeletal muscles with energy expenditure from the individual performing the activity [1]. PA can be structured, repetitive, and deliberate in nature such as regimented exercise programs or recreational sports, or non-structured occupational and domestic tasks that are carried out throughout the day as part of a routine, such as climbing stairs, lifting and carrying boxes, gardening or cleaning the house. Engaging in regular PA is beneficial for cardiorespiratory, metabolic, and musculoskeletal health, as well as caloric balance and psychological well-being [1].

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Need for Physical Activity in Obesity and Diabetes

PA is a known predictor of both obesity and diabetes, and is considered to be responsible for as much as 6 % of global mortality [2, 3]. While obese individuals may be sedentary because of lifestyle and general habits, it is also important to recognize that greater body mass and certain comorbid conditions such as arthritis and diabetic sensory neuropathy may make it difficult to move around, thus creating a vicious cycle of physical inactivity. While engaging in adequate amounts of PA can be challenging for obese diabetic individuals, it is probably the only intervention capable to improve overall physical fitness and reduce disability in this population.

In the context of obesity, PA is often prescribed to reduce cardiovascular morbidity and mortality. It has considerable influence on modifiable cardiovascular risk factors such as physical fitness, body composition and weight, and certain cardiometabolic markers [4]. Lifestyle interventions that include PA have shown to reduce mortality by about 30 % in those with coronary heart disease [5]. In those with diabetes, PA is also prescribed with the additional purpose of lowering blood glucose levels. The positive influence of PA on both glucose levels and cardiometabolic risk factors has been regarded as a reason to prescribe PA in individuals who are obese and have diabetes. The Look Ahead Trial is probably the largest randomized trial that tested the effect of lifestyle

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interventions (diet + physical activity) versus usual care on cardiovascular events (e.g., stroke, myocardial infarction) and mortality in obese individuals with diabetes. Notably, the study reported no significant differences in mortality rates over a period of 10 years between those who received lifestyle intervention and those who received usual care [6]. Although the results of that trial may call into question the value of PA, physical activity remains relevant in diabetes due to its positive effects on weight maintenance, glucose control, and non-metabolic parameters such as physical function, sleep, and mood [7].

PA plays a salient role in the management of obesity and diabetes, and its benefits are well documented [4, 8–10]. Several large randomized trials of PA in obesity, pre-diabetes and diabetes demonstrate positive effects of physical activity on physical fitness, weight control, glucose metabolism and insulin sensitivity [11–17]. Although the majority of the evidence has focused on exercise or structured PA, recently, the importance of reducing sedentary behavior and interspersing active lifestyle behaviors during one's daily routine, has also been elucidated in some studies [18–21]. Greater time spent in sedentary behaviors (e.g., watching TV, sitting at the desk, driving) was associated with a greater risk of weight gain and diabetes; conversely less sitting time, and longer periods of standing and walking are associated with a lower risk [3, 22]. Breaking up long periods of sedentary behavior with short 2–5 min bouts of standing, walking or any light to moderate intensity activity can increase total daily energy expenditures, and improve overall body metabolism [18–20]. Thus, emerging evidence also demonstrates the benefits of unstructured physical activity.

PA positively influences several aspects of cardiovascular and metabolic health. The role of PA on the key aspects of health that are integral to the management of obesity and diabetes are discussed below.

Physical Fitness

The most apparent and recognizable benefit of PA is improved physical fitness, and high fitness levels are associated with reduced mortality [23]. Cardiorespiratory fitness is an independent predictor of all-cause and cardiovascular mortality in obesity [24] and diabetes [25]; and is comparable to other predictors of mortality in this population such as high body mass index, elevated blood cholesterol, and hypertension [24]. A large longitudinal cohort of 25,714 men demonstrated that those who were obese with low fitness levels have about three to five-folds greater risk of death compared to normal weight men with good physical fitness [24]. In a sub-cohort of 1263 men with diabetes, those who were unfit had a two-fold greater risk of death than men with diabetes who were fit, after controlling for other mortality predictors such as family history or baseline presence of cardiovascular disease, hypertension, high cholesterol, and smoking status [25]. In a recent meta-analysis, overweight and obese individuals who were fit had similar risk for all-cause mortality as that of normal-weight fit individuals. On the other hand, obese individuals who were unfit had about a two-fold greater risk of mortality compared to normal-weight fit individuals [26]. Accordingly, improvements in physical fitness through PA are related to lower risk of coronary heart disease independently of weight loss [27]. Consequently, physical fitness is a modifiable risk factor for morbidity and mortality that should be regarded as key to influence health in the obese population.

Body Composition and Weight Loss

The recent obesity epidemic has been attributed to declines in regular PA due to changes in lifestyle habits in both occupational and recreational settings [28]. The risk of weight gain is estimated to be three to four folds greater in men and women who report low levels of PA compared to those with high levels of PA [29]. PA and/or exercise is a key component in weight maintenance and weight loss programs. Weight reduction for obese individuals is an important outcome as it can reduce the risk of developing diabetes. Studies in obese individuals with elevated plasma glucose levels and impaired glucose tolerance

demonstrated that weight losses between 5 and 7 % of initial body weight can reduce the risk for developing diabetes by 30–60 % [30–33]. Current recommendations for PA from the World Health Organization suggest at least 150 min per week at moderate intensity for health benefits [1]. These recommendations are also supported for the obese and diabetic populations, and are endorsed by several professional organizations such as American Diabetes Association, The Obesity Society, and American College of Sports Medicine [4, 9, 10, 33]. However, physical activity by itself without any dietary or caloric intake changes may only result in small (~2 to 3 kg) or no reductions in body weight when performed close or around the recommended levels [28].

For significant weight loss to occur, PA needs to be carried out at extremely high volumes that exceed the current recommendations. PA interventions that target 500–700 kcal per session on a daily basis can induce 5–8 % reduction in body weight [9, 16, 34]. Based on available evidence, the American College of Sports Medicine (ACSM) recommends between 225 and 300 min/week of physical activity at moderate to vigorous intensities for significant weight loss [9]. For weight maintenance, PA interventions performed at moderate to vigorous intensity between 150 and 250 min per week could be sufficient for preventing weight gain of more than 3 % [9]. The ACSM recommendations are also supported by the Obesity Society and American Heart Association [33]. Weight loss is more effectively achieved when PA is combined with a weight loss intervention, such as diet or surgery. PA also has value in maintaining weight after dietary programs and surgery. The combined benefit of PA and weight loss interventions are discussed in a section "Physical Activity combined with other weight loss interventions".

Aside from weight loss and maintenance, exercise can induce favorable changes in body composition by reducing fat mass, and increasing lean body mass [35]. Aerobic exercises are more useful in reducing fat mass, while resistance exercises help improve lean muscle mass [35, 36]. Greater lean mass is beneficial as the muscle plays an important role in glucose and lipid storage as well as their metabolism.

Glucose Metabolism and Insulin Sensitivity

PA also improves glucose metabolism. Glucose uptake by skeletal muscle is a process mediated by the GLUT-4 transporter protein on the plasma membrane of skeletal muscle cells. Importantly, the hormone insulin activates signaling pathways that increase the number of GLUT-4 transporters in the plasma membrane. Through this mechanism, insulin promotes increased glucose uptake and metabolism in skeletal muscle. However, in obesity, insulin signaling is impaired, and results in lower GLUT-4 membrane abundance, lower glucose uptake and metabolism. In the absence of adequate physiological compensation, insulin resistance can lead to hyperglycemia.

Skeletal muscle glucose uptake is increased both acutely and after prolonged training in exercising muscles [10]. Exercising can induce several adaptations within the muscle, which contribute to improved glucose transport and insulin sensitivity, including up-regulation of GLUT-4 transporter protein, increased blood capillaries, and enzyme adaptations [37, 38]. Although insulin stimulates GLUT-4 membrane translocation to enhance glucose uptake, muscular contractions also trigger the translocations of GLUT-4 protein via activation of AMP protein kinase pathway, independent of insulin [10]. Thus, even in presence of impaired insulin sensitivity exercise can facilitate glucose uptake.

Since skeletal muscle is the site for about 80 % of insulin stimulated glucose uptake, it can have a major influence on overall body glucose metabolism. Thus, activities that involve large muscle groups, and PA that induces increase in muscle mass would be expected to have favorable effects on glucose metabolism. The clinical outcome for long term glycemic control is the amount of glycated hemoglobin in the blood (HbA1c). Several studies of exercise in diabetes demonstrated that PA carried out at least 150 min per week at moderate intensity level can produce clinically meaningful reductions in HbA1c levels of approximately 0.4–0.8 % [10, 12, 17, 39–41].

Diabetic Neuropathy

PA can also delay the onset or slow down the progression of diabetic complications such as neuropathy. Although the evidence is limited, few studies that investigated the utility of exercise in modulating the symptoms and progression of peripheral neuropathy support the role of exercise in modulating neuronal damage. One 4-year randomized trial included 78 subjects with diabetes (Type 2 or Type 1) with no signs or symptoms of diabetic neuropathy, and compared the effects of an aerobic exercise versus no exercise on the development of diabetic neuropathy. The aerobic exercise consisted of four 60 min sessions every week of supervised treadmill walking at 50–85 % of heart rate reserve. At the 4 year follow up, vibratory perception threshold increased significantly in the control group, and the rates of development of motor neuropathy (17 % vs 0 %) and sensory neuropathy (29.8 % vs 6.5 %) were higher compared to those in the exercise group [42]. Two other smaller pilot studies demonstrated significant decreases in neuropathic pain and neuropathic symptom scores (as measured by the Michigan Neuropathy Screening Instrument) [43, 44]. Although the mechanisms by which exercise produces a reversal or reduction in neuronal symptoms are not absolutely clear, possible pathways such as reducing inflammation driven oxidative stress and restoring neurotrophin levels [45], and promoting nerve regeneration [46] have been suggested.

Cardiovascular Markers (Blood Pressure, Lipid Profile)

PA by itself may result in small changes in blood lipid profile (Low Density Lipoproteins or LDL, High Density Lipoproteins or HDL, Triglycerides). The overall evidence for physical activity induced improvement in lipid profile in those with obesity and diabetes have shown mixed results with a trend towards small improvements in LDL [10]. Combination of physical activity and diet is more effective in improving blood lipid profiles [47]. PA can also produce modest changes in systolic blood pressure without inducing changes in diastolic blood pressure [10].

Physical Activity Combined with Other Weight Loss Interventions

Although the focus of this chapter is on PA, weight loss is an important outcome in those who are obese and diabetic, and hence the combined effect of PA with additional weight loss strategies warrants some discussion. Physical activity when combined with diet or weight-loss surgery have more pronounced effects on weight loss, and can result in 5–10 % loss of original body weight [33]. Interventions that comprise diet and physical activity can also be effective in reducing the risk of diabetes in those who have impaired glucose tolerance or are pre-diabetic [48]. The utility of lifestyle interventions that focus not only on regular physical activity, but also on food intake habits have been tested in several large multicenter randomized trials such as Diabetes Prevention Program, The Finnish Diabetes Prevention Study, and the Look Ahead Study. The PA component in all of these large trials consisted of maintaining ≥150 min/week in moderate to vigorous intensity activities that included both aerobic and resistive exercises [32, 49, 50]. Diabetes Prevention Program and the Look Ahead study also used additional behavioral interventions to provide support, motivation and feedback to the subjects regarding their PA behaviors [32, 50]. Goal-directed and self-management strategies were used to empower and encourage subjects to maintain and adhere to their PA goals. In the Look Ahead Study subjects were also encouraged to adopt active behaviors during their normal routines, such as walking extra blocks to the bus stop or parking lot, or using the stairs instead of elevators, in addition to their goal of 175 min/week of moderate to vigorous PA [50]. The diet and weight management component generally consisted of reduction in fat and caloric intake. Subjects were also taught self-management techniques such as regularly monitoring food types and portions, and body weight [32, 49, 50].

The Look Ahead trial demonstrated that the intensive lifestyle interventions (PA and diet) induced a significant weight losses of 9 and 6 % of initial body weight at 1 and 4 years follow up compared to usual care that induced weight losses of 0.7 and 0.9 % during the same time frame. The same trial also demonstrated reductions in glycated hemoglobin (HbA1c) of 0.7 % at 1 year and 0.4 % at 4 years in the lifestyle intervention group compared to 0.1 % in the usual care group during the same time frame [47, 51]. Large trials in individuals who are prediabetic (impaired glucose tolerance or elevated plasma glucose levels) or at risk for diabetes such as the Diabetes Prevention Program and the Finnish Diabetes Prevention Study, also demonstrated that lifestyle interventions (combined PA and diet) reduced the risk of diabetes by 58 % [30, 52].

PA may also play an important role in preventing weight gain after substantial amount of weight loss through surgery or caloric restriction. A systematic review of longitudinal cohort studies that assessed PA behavior in obese individuals undergoing bariatric surgery reported that PA levels post-surgery were positively associated with weight loss after bariatric surgery [53]. Behavioral interventions that help identify and overcome barriers to PA and exercise, and employ methods such as goal-setting, motivational interviewing and self-management strategies are also useful in promoting unstructured or "free-living" PA. The use of behavioral interventions along with exercise in those with diabetes have shown to reduce glycated hemoglobin levels significantly (mean difference of 0.3 %) compared to usual care [21].

Optimizing Physical Activity Prescriptions

While some PA is always better than none, benefits of physical activity are dose-dependent and also require regular practice of PA to be maintained. In order to optimize the benefits of PA, prescribing the appropriate dose is key in managing those with obesity and diabetes. Along with dose, the current health status and physical condition of the patient must also be considered. While current recommendations for PA in adults suggest participation in at least 150 min per week of moderate physical activity (in continuous bouts of at least 10 min) or 75 min of vigorous physical activity, and muscle strengthening twice per week [1, 4, 10, 33], these recommendations may need to be modified in those with obesity and diabetes based on their goals as well as current health status. Table 26.1 provides a summary of recommended physical activity prescriptions in obesity and diabetes.

Exercise can be classified mainly into an aerobic training mode and resistance training mode. As aerobic and resistance training have different intentions (i.e., aerobic to improve cardiorespiratory fitness, and resistance for increasing muscle mass and strength), an exercise program that combines both would have optimal benefits for a patient. Resistance training can also improve insulin sensitivity and facilitate glucose uptake by improving muscle metabolic function [36, 54]. Results from a meta-analysis of exercise programs in obesity showed that aerobic exercises are superior to resistance exercises in reducing body weight, body fat mass, waist circumference, and improving cardiorespiratory fitness, and that resistance exercises were superior to aerobic exercises in increasing lean body mass and muscle strength [55]. With the exception of cardiorespiratory fitness (assessed by VO_2 max), which was significantly higher in the aerobic training programs and combined aerobic and resistance training programs, the differences between modes in all the other outcomes (body composition, anthropometry, body mass index) were small to modest [55]. These findings suggest that even though a combined aerobic and resistance program is ideal, the small differences between exercise modes suggest that an obese individual would benefit from either exercise mode. The small differences noted in the meta-analysis could also be attributed to the variation in exercise intensity (from low to vigorous) and volume (45–300 min/week), and relatively short duration of the program (2.5–6 months) [55], which further supports that appropriate exercise

Table 26.1 Recommended physical activity prescription in obesity and type 2 diabetes

Type of physical activity	Weekly dosage (intensity, frequency, duration)	
Aerobic or endurance (e.g. walking, swimming, cycling, rowing, arm ergometer, dancing)	At least 150 min/week (30 min/day in 5 days or 50 min/day in 3 days) at moderate intensity *Or* 60 min/week (20 min/day in 3 days) at vigorous intensity, for able individuals For higher benefits (e.g., weight loss) 225–300 min/week (60 min/day in 5 days) at moderate intensity	Moderate intensity produces increased breathing and sweating, but person is able to engage in conversation. Perceived effort is moderate or hard. Moderate intensity corresponds to 55–70 % of max HR (or 40–60 % of maximal aerobic capacity) when determined using an exercise stress test. Vigorous intensity produces increased breathing, sweating, and may be difficult to engage in conversation. Perceived effort is hard to very hard. Vigorous intensity corresponds to 70–85 % of max HR (or >60 % of maximal aerobic capacity) when determined using an exercise stress test.
Resistance (e.g., weight machines, therabands, free weights)	2–3 times per week, 5–10 exercises involving large muscle groups for both upper and lower extremity, intensity at 50–80 % of 1 repetition maximum Start with 3–4 sets of 10–15 reps or till muscle is near fatigue Progress to fewer sets of 8–10 reps, with heavier weights. Muscles should be fatigued at the end of the set.	
Flexibility exercises (e.g., stretching, yoga,)	2–3 times per week, with at least 30 s hold in each position. Flexibility exercises are indicated for improving joint range of motion, and may be included in addition to aerobic and resistance exercises, but should not be used as a substitute.	
Balance and Co-ordination (e.g., heel and toe raises, side-stepping, tandem walking, single leg stance)	2 times per week, 15–30 min/day, exercises are usually of light intensity and require minimal effort. Progress by making the exercises more complex to challenge neuromuscular control.	

Refs. [4, 8, 9, 33, 64, 71]
Abbreviations: *HR* Heart rate

dose (i.e., intensity, frequency, duration) is key for reaping its benefits.

Similarly, for adequate glycemic control both aerobic and resistance training are useful. Secondary evidence from systematic reviews and meta-analyses demonstrates that aerobic training alone, resistance training alone, or a combination of both can effectively lower HbA1c levels between 0.5 and 0.8 %, which is clinically relevant [11, 17, 40, 56]. Variations in individual study findings can be attributed to differences in exercise dose, study population characteristics, and methodological limitations, but overall available evidence supports either mode of exercise for glycemic control.

Either mode of exercise is beneficial provided the appropriate exercise dose is prescribed. Generally the use of moderate to vigorous intensities and higher training volumes (duration and frequency) to maximize benefits are advocated for physical fitness, weight loss, increase in muscle mass, and glycemic index [4, 8, 18, 57–59]. In persons with type 2 diabetes, cardiorespiratory fitness levels were improved by 10 % compared to non-exercisers when aerobic exercises were administered at an intensity between 50 and 75 % of maximum aerobic capacity (VO_2 max) for 49 min per session, 3.4 times per week with a minimum training of 20 weeks [60]. Similarly, for resistance training generally an intensity of 50–80 % of 1 repetition maximum, performed at least twice per week is recommended for improving strength and muscle mass. However, some emerging evidence also suggests that even exercises at low-intensity but high volume, and conversely high-intensity but low volume may also be beneficial for glycemic control [57]. Thus, when taking into account the

individual's goals, current health, and disposition towards exercise, dosage in terms of volume and intensity need to be modified in order to receive the most benefits of a PA program. Furthermore, for physiological adaptations to occur, a minimum of 8 weeks of regular PA is necessary, and then to maintain these physiological gains in the long run, PA needs to become a life-long commitment.

In addition to structured PA, incorporating active lifestyle behaviors throughout the day and in an individual's routine should be part of PA prescription. Simple changes such as decreasing TV-watching time, or reducing sitting-time at one's desk during work by introducing standing and in place marching breaks, using the stairs instead of elevators, and walking short distances instead of driving, can positively influence the body's metabolism. Breaking prolonged sitting periods (>90 min) with standing and walking activities is also recommended [4]. These simple active behaviors can be very easily incorporated into one's daily routine and do not need drastic planning. With the advent of activity monitors such as pedometers, accelerometers, and multi-sensory devices that provide information on real time PA, it is now possible to measure and monitor progress in PA levels throughout one's daily routine and not only during an exercise session. Activity monitors are capable of providing immediate feedback to both the patient and clinician in terms of amount of calories, number of steps, intensity and duration of activity, and can be used to set PA goals and reminders.

Lastly, supervision of a prescribed PA program is more effective in improving health outcomes, such as glycemic index and cardiorespiratory fitness, than merely the advice to stay active [12, 40]. Thus, when possible some amount of supervised exercise sessions should be encouraged when prescribing PA programs.

Practical Considerations When Implementing a Physical Activity Program

While the prescription of PA must be considered in order to optimize benefits, the PA program must be tailored to an individual's need and current health condition in order to ensure both safety as well as adherence. For obese individuals who are very sedentary and at high risk of cardiovascular disease, it might be worthwhile to receive medical clearance and undergo an exercise stress test prior to participating in moderate to vigorous PA [61]. In obese individuals with poor mobility and severe cardio-respiratory deconditioning it might be advisable to gradually progress from low intensity to moderate intensity exercise depending on their tolerance and response to exercise. A possible strategy for exercise conditioning could be as follows: start with non-weight bearing low intensity exercises (e.g., upper extremity and lower extremity strengthening with therabands or light weights), progress to weight bearing (e.g., marching in place, slow walking, mini-squats, lunges), and finally continuous aerobic exercises (treadmill walking, stationary bike). In order to reduce risk of injury or discomfort due to delayed muscle soreness the exercise sessions should also include a warm-up and cool-down period. Monitoring of heart rate, blood pressure and perceived rate of exertion are important in ensuring appropriate response and tolerance to exercise. Since the intention of exercise is to induce whole body changes in metabolism and composition, large muscle groups should be targeted when developing an exercise program. The physical impairments and functional limitations these individuals may have must also be kept in mind and additional exercises to maintain or improve joint range of motion (stretching or flexibility exercises), or balance and gait should be incorporated into the program.

When implementing a PA program in individuals with morbid obesity (Class II and III) there might be some barriers related to use of exercise equipment in gyms. They may have difficulty in using or getting on and off certain exercise equipment due to body size, and poor mobility. In such situations, accommodations should be made to the exercise program within the clinic or exercise facility. For example, choosing exercises that can be performed in seated or standing position and do not require one to step into or out of an exercise equipment is preferable (e.g., free weights, therabands, walking on a track, aerobics and light calisthenics).

In addition to general mobility, joint integrity must also be considered when prescribing physical activity. Osteoarthritis in the weight bearing joints is fairly prevalent in obese and diabetic individuals [62, 63]. High impact activities that stress the joints should be avoided (e.g., jumping, hopping and twisting). Lower extremity joint pain, stiffness and discomfort may also challenge participation in basic weight-bearing exercises such as walking on a treadmill; in which case, alternate forms of exercise that reduce loading on weight bearing joints such as water aerobics, swimming, rowing, arm ergometer, or recumbent biking should be considered. Similarly, resistive exercises in arthritis affected joints should be carried out within pain-free ranges, and preferably under supervision of a trained personnel to avoid injury and to maximize benefits [64]. Box 26.1 provides a list of general safety tips to prevent adverse events due to exercise.

Box 26.1. General Tips to Prevent Adverse Events due to Exercise for Obese and Diabetic Persons

In previously sedentary individuals with high risk of coronary artery disease, an ECG stress test and medical clearance is recommended prior to engaging in a moderate to vigorous physical activity program.
Drink sufficient water before and after exercise to prevent dehydration.
Use comfortable clothing with breathable fabrics.
Use comfortable tennis shoes or other walking shoes.
Perform regular foot care.
Ensure optimal room temperature to avoid dehydration due to excessive heat.
Avoid high-impact activities in arthritic joints of those with degenerative joint diseases.
Before and after exercise, perform adequate warm up and cool down to prevent injuries and reduce discomfort due to delayed onset muscle soreness.
Monitor vital signs such as BP and HR. In diabetics, also monitor glucose levels prior, during, and post exercise.

Refs. [8, 64, 65]
Abbreviations: *ECG* Electrocardiogram, *BP* Blood pressure, *HR* Heart rate

Obese individuals are also more likely to be on medications to control hypertension, lower cholesterol or for joint pain, and insulin or insulin secretagogues in those with diabetes. Some of these medications may alter exercise responses and thus, appropriate measures should be taken to avoid adverse events due to medication side effects. (Refer to Box 26.2 for altered exercise response due to specific medications). In those with diabetes, non-optimal glucose control (blood glucose >300 mg/dl or <70 mg/dl), and presence of diabetic complications can result in safety issues and impaired responses to exercise. Therefore, regular monitoring of blood glucose, checking for symptoms of

Box 26.2. Precautions due to Common Medications in Obese and Diabetic Persons

Diuretics	May affect fluid and electrolyte balance, hence adequate hydration prior, during and after exercising should be emphasized.
Beta Blockers	Blunt heart rate response to exercises and may increase risk of hypoglycemia unawareness.
Statins	May cause myalgia and myositis, and lower exercise tolerance.
Pain Medications	Non-steroidal analgesic inflammatory drugs (e.g., acetaminophen, ibuprofen) may not affect response to exercise, stronger pain medications such as opioids (e.g., hydrocodone) may cause drowsiness, impair cognition, and decrease reaction time.
Insulin or Insulin Secretagogues	Short acting oral insulin medications may cause hypoglycemia post exercise, therefore reducing dose or adjusting the timing of dose may help prevent post exercise hypoglycemia.

Refs. [8, 64, 65]

hyper or hypoglycemia, adequate hydration, and when applicable coordinating medications (especially short acting insulin) with exercise, and consuming carbohydrates prior to exercise, are necessary measures when exercising those with diabetes. In those taking insulin or insulin secretagogue drugs, there is a risk that exercise could precipitate hypoglycemia. But in subjects not treated with insulin or insulin-secretagogues, moderate intensity exercise poses a negligible risk of hypoglycemia [65], since counter-regulatory and endogenous insulin secretion responses to hypoglycemia remain intact. In case of non-optimal glucose control, the clinician should proceed cautiously with exercise provided there are no signs of ketosis and the patient is feeling well. (See Box 26.3 for precaution and absolute contraindications to exercise during non-optimal glucose levels.)

Precautions also need to be taken in presence of diabetic complications such as nephropathy, retinopathy and autonomic and peripheral neuropathy. In presence of diabetic retinopathy care should be taken to avoid strenuous activities that may induce Valsalva maneuvers or breath holding due to concerns with retinal detachment or vitreous hemorrhage. Individuals with autonomic neuropathy can have decreased cardiac responses to exercise, postural hypotension and are also more susceptible to hypoglycemia, and silent ischemia; hence, cardiovascular investigation prior to engaging in moderate to vigorous activities is indicated in these individuals [4]. In case of diabetic peripheral neuropathy, weight bearing exercises is also a concern for infection and foot ulcers due to skin breakdown. However, evidence to the contrary has been demonstrated, and studies have shown that weight-bearing exercises do not increase the risk to foot ulcers [66–68]. Appropriate practices for foot care and regular inspection of skin integrity should be undertaken by the health care provider and the patient, both prior to and during the course of a PA program. In case of skin breakdown or ulcer, the exercise or PA programs should be modified to include non-weight bearing and upper extremity exercises. These modifications can be made without compromising exercise intensity or volume.

Impaired balance and risk of falls is a major concern in older individuals with diabetic peripheral neuropathy due to reduced sensory and proprioceptive feedback [69]. In absence of any contraindications for weight bearing status (e.g., open ulcers on weight bearing part of the

Box 26.3. Precautions to Exercise in Presence of Non-optimal Glucose Levels and Absolute Contraindications to Exercise

Precautions during non-optimal glucose levels	Pre-exercise BG > 300 mg/dl or 16.7 mmol/l, and no signs of hyperglycemia or ketosis: Can exercise provided patient feels well. Ensure adequate hydration prior to exercising. Pre-exercise BG < 100 mg/dl or 5.5 mmol/l, no signs of hypoglycemia: Ingest up to 15 mg of carbohydrate prior to physical activity. Can exercise as long as patient is feeling well.
Absolute Contraindications	Signs and symptoms of hypoglycemia (BG <70 mg/dl) such as shakiness, pale skin, sweating, dizziness, headache, tingling sensation around the mouth, seizures. Signs and symptoms of ketosis (BG > 300 mg/dl and ketones >1) such as shortness of breath, dry mouth, nausea and/or vomiting; these signs medical attention. Alcohol ingestion ≤ 3 h prior to exercise.

Refs. [8, 64, 65]
Abbreviations: *BG* Blood Glucose

Box 26.4. Precautions During Diabetic Complications

Peripheral Neuropathy: Regular foot inspection and care, modify weight bearing exercises or substitute with non-weight bearing exercises in presence of foot lesions or ulcers, or neuropathic pain; reduced sensations and impaired balance can increase risk of falls, use support or observe caution while administering exercises that challenge balance and co-ordination to avoid falls.
Autonomic Neuropathy: Monitor blood glucose, and signs of silent ischemia such as orthostatic hypotension, dyspnea, and diaphoresis.
Retinopathy: Avoid strenuous activities that may cause breath-holding and Valsalva maneuvers (e.g., weight lifting), avoid head-jarring or positions with head below the waist level.

Refs. [8, 64, 65]

foot) PA programs should also incorporate exercises to improve static and dynamic stability. Although, the evidence for effectiveness of balance exercises in individuals with diabetic neuropathy is still scarce, and consists of few small trials of relatively low quality [70], the evidence of balance training in reducing the risk of falls in older adults is strong [71], and could carry over to older adults with diabetic peripheral neuropathy. Examples of static stability exercises are heel and toe raises, holding positions such as tandem stance or single leg stance, while dynamic stability exercises include tandem walking forward and backward, or side-stepping. These exercises can be made more challenging by use of less stable surfaces (foam or wobble board for static stability), or by adding upper body movements (for both static and dynamic stability). (See Box 26.4 for a concise list of precautions during exercise in presence of diabetic complications.)

Adherence to Physical Activity Programs

Benefits accrued through PA can fade over time when it is not carried out regularly or discontinued. Strategies to improve adherence to PA is crucial to maintain its long term benefits. Several factors may contribute to poor PA adherence, such as presence of multiple co-morbidities, poor exercise tolerance, and barriers, such as lack of motivation or emotional support, time constraints, or inaccessibility of exercise facilities. Prior to prescribing a PA program an assessment of the individual's readiness to incorporate PA as a lifestyle modification may shed light on whether they may or may not adhere to the program. An individual's physical, mental, social and economic circumstances also needs to be brought into perspective in order to tailor the PA program for optimal success. Lifestyle is not easy to change, and barriers to PA can be difficult to overcome if an individual lacks the will or readiness to implement these behavioral changes in his or her life. Behavioral interventions when applied along with PA interventions are beneficial and should be considered to keep individuals engaged, and to improve their adherence to PA in the long run [21]. Adequate counseling and education on the importance of PA can allay fears such as kinesiophobia and worries of injury or falls [72]. Self-management strategies that adopt a goal-oriented approach, (where individual sets his own goals) and provide regular feedback to the individual can improve an individual's self-efficacy and desire to bring about change [72]. Clinicians also need to help patients identify and discuss their barriers to physical activity and help develop strategies to overcome these barriers. For maximum benefits, PA programs that do not involve drastic changes in one's routine are more likely to be adopted. Time and travel constraints are very common barriers to PA. For instance, individuals who find it cumbersome or expensive to exercise in a gym or facility, or cannot put aside 30 min daily to exercise, may be more successful in becoming physically active by incorporating active behaviors that are interspersed throughout the day and in their daily routine.

Conclusion

PA is a key intervention for improving physical fitness, facilitating weight loss and preventing weight gain, also improving other cardiovascular markers such as lipid profile and blood pressure in obese populations. In

obese individuals with diabetes, PA is also effective for glucose control, and may also have a role in delaying or reducing certain symptoms of diabetic complications such as peripheral neuropathy. Current evidence based guidelines exist and can be used to prescribe PA safely and effectively in individuals with obesity and diabetes. There is also an added benefit for weight loss when PA is combined with other weight lifestyle interventions such as diet, bariatric surgery or behavioral therapies. Although regular practice of PA is recognized as the most important factor for sustaining its benefits, adherence to PA still remains one of the biggest challenges in this population.

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Obesity Prevention in Young Children

27

Ruby Natale, Catherina Chang, and Sarah Messiah

Introduction

Over the past 30 years, the number of overweight and obese young children has significantly increased worldwide making it a serious clinical and public health concern. Globally, an estimated 170 million children (of under 18 years) are now estimated to be overweight or obese [1]. The highest prevalence of childhood overweight and obesity occurs in upper-middle-income group in the industrialized countries, while third world countries normally show the lower prevalence rate. However, countries with overweight children continues to be a global health challenge, with prevalence rates growing fast in lower-middle-income group in each country [2].

These statistics are of particular concern because obese preschool children are five times more likely to be overweight during adolescence and four times more likely to be obese adults compared to their normal weight counterparts [3, 4]. These results show that, contrary to popular belief, children do not "grow out of their baby fat." In fact, excessive weight gain in the first years of life can alter neuronal development, metabolic and behavioral systems in ways that increase the risk for obesity linked chronic diseases such as Type 2 diabetes, cardiovascular disease, hypertension, and stroke in later life [5, 6]. As such, many reports have been showing that childhood-onset obesity will contribute significantly to increased morbidity and mortality in adulthood, particularly among ethnic minority groups who are disproportionately affected by many of these chronic conditions [7, 8]. Moreover, higher prevalence estimates of obesity among some ethnic groups are often underscored by low socioeconomic status. Children who live in economically depressed communities are less likely to have access to affordable fresh fruits and vegetables leading to be physically active [9, 10].

The current chapter examines the multiple factors associated with childhood obesity as well as prevention measures targeted towards would be obese young children.

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Early Childhood Interventions

Mostly children's health behavior including dietary and physical activities are determined during the preschool years when they are heavily influenced by their adult caregivers such as

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teachers and parents. Effective strategies to prevent obesity, therefore, should target these health linked behaviors during the preschool years. Poor quality nutrition intake and minimal amount of physical activities are the two major risk factors that challenge the maintenance of healthy weight in early childhood. Other modifiable risk factors include, television in the child's bedroom, minimal physical activity, increased portion sizes, and increased consumption of sweetened beverages before age 5 years [11–14].

A review based on meta-analysis summarized the effects of 64 obesity prevention programs seeking to produce weight gain prevention effect, 21 % produced significant prevention effects that were typically pre- to post effects. Larger effects were seen in programs that (i) targeted children and adolescents (vs. preadolescents) and females, (ii) were relatively brief, (iii) solely targeted weight control versus other health behaviors (e.g., smoking), and (iv) participants self-selected into the intervention. Other factors, including mandated improvements in diet and exercise, sedentary behavior reduction, delivery by trained interventionists, and parental involvement, were not associated with significantly larger effects [15, 16].

Preschool settings present significant opportunities for obesity prevention through implementation of programs targeting nutrition and physical activity. There is evidence of sustainability of some of these early interventions based on reports from intervention studies conducted in developed countries addressing obesity in early childhood [17, 18]. The success of many of these programs involves the inclusion of multiple stakeholders, including child-care providers, parents, children's health care providers, and child-care organizations [16]. Programs such as the Tooty Fruity Vegie, an intervention study involving 3- to 6-year-old children, parents, and child care staff in rural and regional NSW Australian preschools resulted in improved movement skills, increased fruit and vegetable consumption, and decrease in unhealthy food consumption among the children [19, 20]. The 1-year program was successful in sustaining some strategies 3 years beyond the end of the intervention.

Sustainable strategies from this program involved the ease in implementation of the use of newsletter tips, experiential activities for the children directed at food tasting, physical activity sessions, and policies such as the increased consumption of drinking water included as part of their organizational framework [19].

Another intervention study conducted with kindergarten children in the Haute-Garonne Department in France was also successful in response to simple measures aimed at increasing awareness of the effects of overweight on health and practices involving the periodic monitoring of height, weight, and follow up care by health care providers [21]. In terms of parental strategies, interventions aimed at behavior management of healthy eating and physical activity for parents and children at home environment have been successful with modification of some of these behaviors [22]. However, it is suggested for these practices to involve one item of intervention at a time, whether in the form of an interactive session or educational materials as combined interventions may be overwhelming for some parents [16]. Maintenance sessions may be necessary to sustain the effectiveness of the program in the longer term as the studies report parental interventions being effective only on the short term basis [16, 22].

The Nutritional Gatekeeper: Powerful Socializing Agents for Young Children

"Nutritional Gatekeepers" are the people who purchase and prepare food for a child, which disproportionately tends to be the role of mothers [23]. Nutritional gatekeepers are powerful socializing agents of young children, yet are an understudied and underutilized group. A review of the literature concluded that the role of parents and other family members, as well as parental lifestyle factors, deserve more study and should be incorporated into interventions [24]. The U.S. Department of Agriculture's (USDA) concept of the "nutritional gatekeeper" and the "Project M.O.M.: Mother's & Others & MyPyramid" campaign suggests that empowering the nutritional gatekeepers at both places, the

home and the childcare center will potentiate a lasting and effective impact on the health and nutrition of future adults.

Specifically, previous studies have shown a positive association between mother's self-efficacy regarding their children's eating habits and their children's actual healthy eating habits [25]. Additionally, parents shape the eating habits of their children, and subsequently their growth, thus diet modifications and interventions for children should also target parental dietary beliefs and behaviors [26]. Therefore, interventions that support the development of healthy lifestyle behaviors may be most effective if they target mothers' knowledge of healthy eating as well as their self-efficacy in these domains early in the children's life.

In our previous work, in the early childhood obesity prevention arena, we used the nutritional gatekeeper concept, supported by a social cognitive theory (SCT) foundation to formulate our intervention, Healthy Caregivers-Healthy Children (HC2) [27]. The SCT postulates that children learn new behaviors by observing and imitating models such as parents, teachers, and peers.

Specifically, the theoretical underpinnings selected from SCT, describes specific mediating factors that impact an individual's decision to make health behavior changes including perceived benefits of making the behavior change (positive health benefits), perceived control (who is in charge of food shopping and preparation), and self-efficacy for making changes (including confidence that barriers can be overcome) [28]. Accordingly, the adult "nutrition gatekeepers" were trained on effective role modeling including how their choices for food and exercise affect their children, their control over food shopping, and ways to overcome barriers to healthy food choices. The goal was to for adult caregivers (parents and teachers) set a healthy example to instill a lifetime of beneficial lifestyle habits for their children and students, as well as for themselves.

This focusing helps ensuring the core concept of SCT whereby children learn new behaviors by observing and imitating models such as parents, teachers, and parents. The researchers found that a strong relationship exists between parental role modeling and children's nutrition and physical activity. Other studies have also found parental modeling of healthy eating to be positively associated with healthy eating behaviors of the child, especially with respect to fruit and vegetable consumption [29, 30].

Socio-Ecological Model

Given that childhood obesity is a complex issue, requiring multidimensional solutions, experts contributed in the Institute of Medicine (IOM) early childhood obesity report [31], suggest applying a socio-ecological model (SEM) framework to examine the multiple effects that contribute to obesity [32].

According to SEM, health behaviors arise and are maintained through four interacting levels of influence: individual factors, interpersonal relationships, community (schools), institutions, and the greater macro-level structures and policy systems [32–35]. While individual-level behaviors factor into obesity rates, overarching social and environmental changes can have a broad, lasting impact on obesity [36]. Effectively, SEM principles suggest that creating an environment conducive to change makes it easier to adopt healthy behaviors and that childhood obesity prevention should address multiple levels and multiple sectors. Primary focus must be placed on factors within family, school, childcare and community environments that affect food intake and physical activity, emphasizing the role of the environment in relationship to health [37, 38].

It is important to address the role of the i**nstitutions and community**, by implementing best-practice policies (critical to intervention maintenance and an effective mediator of change) to regulate the types and quality of food that is brought into the childcare center, increase the amount of physical activity, and decrease the amount of physical inactivity/television viewing [12, 39–41]. One study incorporated the following IOM policy recommendations and Caring for Our Children standards in every treatment centers [42–44].

1. Drink Policy; water will be promoted as the primary beverage for staff and children; cow's milk provided will contain ≤1 % milk fat, and juice will be limited to once a week;
2. Snack Policy; Snack and meal time will incorporate fresh fruits and/or vegetables as often as possible; and
3. Physical Activity Policy; children will be physically active outdoor in the sun from moderate to vigorous activities for an average of about 15 min per hour of observation which means approximately 2 h of physical activity across a period of 8 h while in the daycare/childcare setting; and
4. Screen Time Policy; TV/videotape/computer viewing will be logged and limited to <30 min per week per classroom. On-site training and assistance to address barriers to implementation was provided.

Community Based Programs

Given that preschool children often spend majority of their days in childcare, it is essential to investigate the contributing factors that support or impede positive health practices. Specifically, child care provide an opportunity to modify many risk factors for childhood onset-obesity including increased physical activity, provision of healthy nutrition, healthy lifestyle education, and decreased screen time.

Previous studies in preschool settings have been successful in reducing the children's obesity by increasing their physical activities, reducing television viewing, and reducing the consumption of sweetened beverages [39–41, 45–47]. The majority of childcare setting studies conducted to date focus on individual-level intervention with few efforts targeting systemic policy-level changes that include evidence-based curricula and modifications to institutionally-provided meals and snacks [39, 48–50]. In fact, health and nutrition are often completely overlooked in the childcare setting because administrators and teachers feel they are under-qualified for effective delivery of the programs [51].

Community-based programs involving partnerships between stakeholders from the local community, school, and home environments present significant opportunities for the development of positive environments for young children [52, 53]. A media approach was found to be effective to encourage a change to 1 % (is it not too low) milk dietary practice in a local community in West Virginia who advocated for this campaign [54]. A community program involving municipalities, schools, and health centers in Portugal resulted in significant weight reduction, increased consumption of fruits and vegetables, and increased levels of physical activity as a result of the intervention [52]. Coordination of? may present some challenge-based programs on the magnitude of their success. Yet with the inclusion of key stakeholders in the planning and implementation of these programs, there are more opportunities to reach out to larger groups in the community through these efforts. Programs in France such as the EPODE (Ensemble Prevenons l'Obesité Des Enfants/Together Let's Prevent Childhood Obesity) developed to build capacity in the implementation of effective and sustainable strategies for obesity prevention in communities, have been successful through the inclusion of children, families, and local stakeholders with 90 % of its pilot communities becoming active. Other European and Latin communities have followed as a result of this success [53]. The program targets marketing, social communication, and partnership with community practitioners and leaders to develop and implement a local project in the promotion of healthier behaviors and the prevention of obesity [55]. Muevete Bogota in the capital city of Bogota, Colombia, and the Agita Sao Paolo in Sao Paolo, Brazil, are other examples of strategic partnership of national, international, public and private sector, and government initiative to promote physical activity and decrease in sedentarism in these respective countries [56, 57].

Healthy Inside-Healthy Outside

The Healthy Inside-Healthy Outside (HI-HO) program consisted of a 6 month intervention that included a developmentally, culturally, and linguistically appropriate curriculum that targeted preschoolers, including a childcare provider/

teacher and family-based component that addressed the dietary and physical activity patterns of the child [43, 58]. The program was designed to be culturally sensitive, given the ethnic diversity of the families, teachers, and administrators/staff at participating schools. For example, the curriculum was written in English and translated into Spanish to accommodate primarily Spanish speakers. Although the specific goals of behavioral changes were similar to previously validated programs implemented among minority children, the curriculum was modified to reflect the unique diversity of our study population [39]. Given that food, and thus nutrition, is an integral component of culture and specific intervention strategies were designed to account for this such as modifying recipes to reflect cultural preferences. In addition, the technical assistance portion of the program targeted cultural, cognitive, and environmental barriers to accommodate a low fat, high fiber diet that included more fresh fruits and vegetables. Technical assistance visits consisted of weekly teacher's meetings with a HI-HO specialist to ensure the implementation of a low fat, high fiber diet that included more fruits and vegetables with an emphasis on cultural barriers. Monthly parent dinners paralleled the information offered in the monthly newsletters, but also covered issues that are often of concern to parents of preschool children (e.g. how to introduce new foods, how to encourage eating more fruits and vegetables) and were culturally sensitive. Parents were encouraged to reduce TV viewing, increase physical activity, and model healthy eating behaviors for their child at home. For each of the six at-home activities that each family completed the task received a healthy snack bag. At the end of the program, parents that attended three or more dinners received a certificate of completion. This was not a weight-loss program, rather a health-maintenance or prevention program to keep preschool children on a healthy weight gain trajectory. Results revealed that 97 % of those children who were normal weight at baseline were still normal weight 12 months later. Additionally, approximately 4 % of those children who started the program overweight were normal weight by 12 months post intervention; two children who were obese at baseline dropped into the overweight percentile range at 12 months post.

Hip-Hop to Health Junior

Hip-Hop to Health Junior aimed to prevent obesity in minority 3–5 year olds by delivering a healthy eating and exercise intervention throughout Head Start programs in Chicago, IL. This study utilized a 14-week developmentally, culturally, and linguistically appropriate curriculum, which integrates diet and physical activity as well as a parent component [39]. Results indicated lower body mass index (BMI) increases in the intervention group at both 1- and 2-year follow-ups [48].

Healthy Start

The "Health Start" Project includes a reduction in the total and saturated fat content of snacks and meals to recommended levels of <30 % and <10 % respectively, to preschoolers in Head Start programs, and resulted in interventioned children achieving significantly lower total serum cholesterol as compared to children in the control schools [49].

Eating Right Is Basic Program

Eating Right is Basic program was developed at Michigan State University Extension/University of California as part of the Expanded Food and Nutrition Education Program (EFNEP). In this program were included lesson plans feature objectives, materials needed, preparation steps, lesson basics and concepts, activities, recipe suggestions, goal setting prompts, take home "assignments", and ideas for adapting the lesson for a target audience (ethnic/cultural groups, vegetarians, age groups, etc.). Example lessons included: Making the Most of Your Food Dollars, Quick and Easy Meals, Keeping Food Safe, Healthy Choices Away From Home, Live It, Don't Diet, Eating Right for Two, Feeding Your New Baby, etc. are the component for instructors which also included an overview and related fact sheets to help nutrition educators answer consumer questions. Information was presented in flip chart and

curriculum includes handouts and CD with PowerPoint presentation. It is designed to teach adults how to choose and prepare healthy, low cost meals. Research found that over 88 % of graduates made positive changes in eating habits. Fifty-five percent of graduates use information on food labels to compare fat or other nutrients in food more often than before. There was an increased effort in food preparation practices that reduce dietary fat and improved planning and budgeting practices to stretch food resources [59].

Childcare Centers Verses Family Childcare Homes

Normally there are two different environments in which childcare is provided. This includes family childcare homes and childcare facilities. Family childcare homes tend to be licensed to care for either 6 or 12 children. Childcare centers on the other hand tend to function more like a school with classrooms of typically 20 children of the same age.

There have been some studies that have examined the nutritional quality of foods served in these environments. One study conducted in 92 childcare centers found that the facilities exceeded mean fat levels by over 10 %, and the mean amounts of energy and nutrients were significantly lower than what is expected in the Child and Adult Food Care program [60]. A more recent study conducted in North Carolina in 20 childcare centers found that 50 % of milk consumed was whole milk and 75 % of the meat consumed contained high-fat or fried variety [61]. Regarding physical activity, one study found that when examining other factors like, gender and birth weight, the childcare center was identified as a strong determinant of physical activity in the children studied; it explained 46 % of the variation in activity. The authors concluded that the daily programming for these facilities may influence physical activity in these children and varies depending upon type of indoor space, supervision, gross motor play equipment, and various aspects of outdoor play area [62].

Much less is known about the quality of family childcare homes. One study conducted in Kansas in family childcare homes alone, found areas of concern included infrequent servings of low-fat milk, frequent use of unhealthy foods for celebrations, widespread use of television and videogames, and lack of appropriate indoor spaces for physical activity. However, most providers either met or exceeded childcare food standards related to serving fruit and vegetables [63].

Another study looked at comparison in quality between family childcare homes and childcare centers. Participants included 1042 childcare centers and 300 family childcare homes. They found that among centers and homes serving mainly ethnic minority preschool children most are displaying high initial levels of television viewing and low levels of providing health related lessons. Results indicated that in-home childcare (family childcare homes) performed better in respect to the following items: (i) limiting computer time (ii) providing health related lessons and (iii) serving fresh fruit (iv) limiting servings of rolls/bread and (v) limiting servings of fruit in syrup. Out-of-home facilities (childcare centers) reported higher ratings in engaging in outdoor physical activity and limiting television and video time. These differences point to the fact that family childcare homes and childcare facilities can learn from each other, and more attention should be paid to improving quality in these areas [64].

Ethnicity and Culture

Ethnicity and culture often play roles in childhood obesity. One study of 1104 children found that Hispanic-Cuban were significantly more likely to be overweight compared to other Hispanic ethnicities, as well as compared to non-Hispanic Black and non-Hispanic White children. In addition, Hispanic Other (which other?) had significantly high rates of obesity. The Hispanic Other participants were mostly from Central America [58]. Finding Hispanic children overall to be at higher risk for being overweight compared to Non-Hispanic children is consistent with the current literature [65, 66], yet differences by Hispanic subgroup are unique.

High rates of obesity among specific racial/ethnic groups have led researchers to hypothesize that susceptibility to overweight is partially explained by genetics. Thrifty gene hypothesis postulated by Neels is that an energy-conserving genotype leads to increased obesity in environments where food is abundant [67]. Pima Indians, originating from Mexico are hypothesized to possess the thrifty gene more in population than in Non-Pima Indians. Evidence suggests that Central Americans are anthropologically related to Pima Indians, and at a higher risk genetically for obesity [67].

Perception of Overweight

While there are multiple causal factors related to childhood obesity, parent (mis)perception of overweight, it has recently gained traction as a risk factor and has been shown to be heavily influenced by cultural and neighborhood factors [68]. Increased acculturation and years the parent has lived in the US have also been linked to higher rates of obesity in adults and adolescents but has not been extensively examined in parents of preschool-age children [69, 70]. Studies have reported that few parents think childhood overweight is a health problem, and is in more common in parents of young children (ages 2 to 6) versus parents of older children [71, 72]. Moreover, few Hispanic parents of obese children perceive their child to be obese [73]. These findings are even more powerful in the context of very young children because parents/caregivers are the primary mediator of a child's physical activity, eating behaviors, food preferences and security/insecurity during these important developmental years [74, 75].

Conflicting findings have been reported concerning the specific association between acculturation and childhood obesity risk. Low levels of acculturation have been associated with increased risk for obesity, while others report the converse findings [76–78]. One study reported acculturation was a significant moderator between food insecurity and BMI percentile among children of Latino immigrants while others have shown that higher rates of both acculturation food insecurity were associated with lower fruit and vegetable intake at home [78–80]. Few studies have examined the relationship between food insecurity and parent perception of child weight status, particularly in context of sub-cultural patterns of misperception of child weight among Hispanics. Give that values and beliefs about food, diets, nutrition, and healthy body weight vary widely among not only continents, but countries within continents it is important to consider sub-cultural patterns.

Country of origin differences were found in a recent study by Rosas and colleagues, who found that Mexican mothers born in the US underestimated their child's weight less than mothers born in Mexico [81, 82]. Eighty-two percent of US-born mothers were dissatisfied with their child's weight, as compared to 29 % of mothers born in Mexico.

Ethnic differences in parental perception have also been demonstrated in the literature. African American and Hispanic mothers were found to perceive their children to be thinner than their actual size [83]. Other studies have also confirmed a misperception of child weight status with Hispanic parents [84].

Acculturation may also play a role in perception. One study found that those caregivers who lived in the U.S. less than 10 years had greater odds of having an inaccurate perception of their child's weight status [58]. This further speaks to the importance of cultural variables in that in many Hispanic cultures, wherein a baby with larger girth is considered a healthier baby, and that young children will grow out of being overweight [68, 85, 86]. Newly arrived immigrants may continue to retain that belief pattern until they are exposed to the American culture, where being thin is better socialized throughout the media.

Furthermore, one study found significant differences in BMI and perception within Hispanic subcultures [58]. Almost the entire sample of parents who had an overweight child incorrectly perceived the weight status of their child. This rate is higher than others reported in the literature; rates of misperception with preschool

children have ranged from 60 to 82 % in other reports [72, 87–89]. The highest rates reported in the literature were with a sample of mainly low-income Hispanics in California, wherein 94 % of mothers misclassified their child as overweight, and 78 % of mothers misclassified their child to be obese [90].

Cuban-Americans and Central Americans parents may have different perceptions of healthy eating and physical activity than other Latino parents, which has led to higher BMI in these children, and more incorrect weight perception. However, it is also possible that social desirability may have been stronger for these groups than the other ethnic groups. Research has found that Hispanics have higher levels of acquiescing and answering in a more socially desirable manner compared to Non-Hispanic Whites [91].

First Transition Years Out of Preschool

With the transition out of the preschool years, there is a significant shift in environments as children move into the elementary school system. In this new setting, young children are then exposed to a different food environment, composed of different food schedules and different types of food choices [92, 93]. Physical activity practices also shift towards an increased focus on academic development and less time to engage in structured and unstructured physical activity [94, 95]. A focus groups study conducted with parents and teachers of first graders in a Hispanic community reported significant differences in their perspectives of the children's eating and physical activity practices in the school environment. Parents reported lack of time, financial constraints, and fast food being inexpensive as common factors that impacted on their preference for the children to have lunches at school. An interesting finding was the fact that they perceived sharing of responsibilities and expectations of teachers to becoming more involved in the modeling of their children's dietary and physical activity-related behaviors. School staff, on the contrary, raised concerns about parental practices associated with excess screen watching time at home and unhealthy food and snacks brought from home. Teachers raised concerns about delays in achieving academic curriculum, paper work, time commitment, and space constraints in the classroom as potential barriers to outdoor activities [96].

With the increased amount of time children spend away from home, schools present significant opportunities for children to engage in healthier lifestyles in the prevention of obesity. For changes in nutritional and physical activity practices to take place, administrative support would be necessary with the inclusion of specialized training and continuing education incentives for educators to engage the students in these health promotion behaviors. Screening programs can also be advocated in the school environment, targeting high-risk populations [97]. Simple, low-cost strategies may also be implemented to maximize the recess time for young children. Interventions such as playground markings (castles, mazes, hopscotch or other images) in the playground areas, activity-friendly outdoor equipment, activity zones for specific types of activities, and teacher involvement in the physical activities have had positive effects on children's increasing physical activity [98].

Portion Control in Young Children

Portion sizes have increased significantly during the past decades. Marketing of these large portions exceed national standards and are offered by retail vendors for a minimal cost [99–101]. Many young children are susceptible to large portions of energy dense, palatable foods, which leads to higher energy consumption and increased body weights [102, 103]. Report from the studies indicates the selection of food portion sizes in young children being influenced by external factors such as parent's parenting styles, parental feeding practices, siblings, peers, and visual cues from the food environment (size of serving spoon or dish) [14, 104, 105]. Factors such as the child's internal self-regulation, self-moderation, and food preferences also play a significant role

[106]. During the first 24 months of life, eating behaviors develop dramatically as children transition from the consumption of breast milk or formula milk to complementary foods and "table foods" in the home and child-care settings [107]. While infants and young children may have the ability to self-regulate their energy intake during meals, they are influenced by the parental feeding practices transitioned to parents from previous generations [108, 109].

Parent and other caregivers play a significant role in the food preferences and eating behaviors modeled at home and child care environments. Traditional maternal practices, including the "feeding to soothe" in response to infant crying and distress, frequency of feeding in response to food availability, offering of preferred foods, and large food portions, have been associated with increased weight status in infants and young children [107, 110]. As children get older and transition into the preschool years, with their increased autonomy and exposure to other social and food environmental cues in the preschool or child care setting, they learn to assert their own food agenda [111]. Parenting practices associated with controlling, restrictive, as well as indulgent parenting styles have also been associated with eating disorders and increasing dietary intake in the absence of hunger. The philosophy to "Clean up the Plate" has been associated with controlling practices associated with loss of self-control around food [112–114].

On the contrary, the "family style" or the practice of children serving themselves at the dinner table has been advocated by national organizations such as the American Academy of Pediatrics and American Dietetic Association [115–117]. This practice provides children with the opportunity to become involved in self-servings. It also contributes to the children's sense of self-control of their food intake [117]. To succeed in the promotion of healthy portion sizes for children requires collaboration at various levels, including government policies and programs, as well as additional research to determine more accurate methods to impart portion size information and recommendations for caretakers in childcare programs as well as school system [118].

Obesity Prevention in Children with Disabilities

Youth with disabilities comprise 13 % of school-age children in the United States [119]. Although pediatric obesity received a great deal of national attention in recent years, limited research exists on the causes, consequences, prevention, and treatment of overweight and obesity among children with developmental disabilities (DD) and other special health care needs. There is, however, an extensive body of research that demonstrates the higher prevalence of obesity among children with special health care needs and psychiatric disorders, particularly Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), and learning disabilities [120, 121]. Among youth aged 12–18 years, the prevalence of overweight and obesity was 42.5 % among those with ASD, 55 % with Down Syndrome, and 64.5 % with Spina Bifida, compared to 28.8 % among youth with no disabilities [122]. Factors that contribute to obesity in these populations need to be studied further due to the complexity of these disorders. What is known from recent data is that these children may have a higher propensity to become obese or overweight due to particular food preferences and restricted diets [123]. For example, children with ASD have been found to eat fewer vegetables, salads, and fresh fruits and consume high-carbohydrate foods and less fat than children without the disorder [124, 125]. Patterns of physical activity were also found to be related to obesity and overweight in youth with disabilities as a result of physical and sensory limitations, as well as cognitive impairments [126].

One study sought to improve the knowledge about the prevalence of overweight and/or obesity, key risk factors, as well as obesity-related chronic and secondary health conditions among children with special health care needs. One project was able to test the initial efficacy, feasibility and acceptability of an intervention program designed to reduce excessive weight among children with special health care needs [127]. A 3-year randomized controlled trial was conducted that examined the effectiveness of a multilevel

(parent, teacher, child) role modeling curriculum on obesity prevention within preschools. Thousand one-hundred and five children were recruited; 103 of whom were identified as having developmental disability (DD). Results indicated children in the control group ate less fruit/veggies at 6 months post-intervention period than they did at baseline, increased their junk food intake, and increased their sedentary behavior, while improvements were noted for the intervention group [127].

Conclusions

Because the prevalence of obesity (in general) appears on increase, there is increased attention towards prevention of obesity and overweight during early childhood years. Although rates of obesity among young children has decreased in recent years, almost one in four US children are overweight and over 8% are obese, emphasizing the need for programs specifically targeting this age group [128, 129]. Childhood overweight is strongly associated with increased child morbidity, increased adult morbidity, and decreased life expectancy.

The etiology of obesity among young children is complicated, multifaceted and as such offers no easy solution. Early childhood is an important period for developing dietary and physical activities and practices of child care facilities can improve children's dietary intake, physical activity levels, and energy balance. Young children are particularly at risk for obesity because they depend on adults for their nutritional needs and exercise at home as well child care environment [130, 131]. However, this? provides a unique opportunity to parents and teachers to intervene through assigning their role as nutritional gatekeepers for the young children in their care. For childhood obesity prevention programs to achieve long-term success, the nutritional gate-keeper must engage in healthy lifestyle behaviors and beliefs themselves. For young children, the nutritional gatekeeper is most likely the parent, but also may be teachers and child care center staff.

Since a large majority of children under age 5 years are enrolled in out-of-home child care, interventions to reduce risk of overweight during the preschool years may be most effectively and most feasibly implemented in the early child care facility. Community-based settings, therefore, can be part of a trans-site intervention in the battle against childhood obesity. Licensing regulations regarding nutrition, physical activity, and screen time vary widely among and within states and countries. Given that improvements in policies for child care settings could improve the diets and physical activity behaviors of millions of children and improve their health. National and international policy efforts to create child care environments that foster healthy eating and physical activity are highly encouraged. A comprehensive model that includes both policy changes and classroom curricula changes as well as a family-based component may be necessary to promote sustainable effects. All components should be sufficiently adapted to the cultural context and involve community members.

Regarding DD and special health care needs, the CDC recently recommended that schools provide their teachers and other school personnels with trainings on ways to include children with disabilities in activities that promote health and wellness [132]. There is a need for better knowledge and understanding about the scope of overweight and obesity, key factors contributing to the possible increased risk, and obesity-related chronic and secondary health conditions among children with special health care needs.

The literature also points to the important influence both ethnicity and parent country of birth have on their accurate perceptions of their young children. While research has confirmed ethnic group differences, studying subcultures within the Hispanic population has led us to find parental nativity is strongly associated with misperceptions and higher BMI among preschool age children. Those who did not recognize overweight, may especially benefit from an intervention approach target-

ing adopting a healthy lifestyle rather than weight management. Screening for inaccurate maternal perceptions with these populations may be the first step in this process. Furthermore, little is known about the effectiveness of interventions in low- and middle-income countries, and on the sustainability of interventions over time.

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