Contemporary Endocrinology
Series Editor: Leonid Poretsky

Michael S. Freemark *Editor*

Pediatric Obesity

Etiology, Pathogenesis and Treatment

Second Edition

Humana Press

Contemporary Endocrinology

Series Editor:
Leonid Poretsky
Division of Endocrinology
Lenox Hill Hospital
New York, NY, USA

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To my Duke colleagues, who fostered my intellectual development and enriched my academic career, and to my wife, Anne Slifkin, who provided incisive critiques of portions of the narrative and who remains my best friend and loving partner in life

Series Editor Foreword

As obesity among adults has reached epidemic proportions around the world (affecting, for example, 1/3 of the US adult population) [1], it is becoming clear that the roots of adult obesity are often found in childhood. With attention to detail characteristic of pediatricians, Dr. Michael Freemark and an illustrious group of authors have produced a second edition of the volume devoted to childhood obesity that is unique in its scope and clarity of presentation. The authors cover extensively both genetic and environmental factors that lead to pediatric obesity, including its monogenetic and syndromic forms.

In addition to posing risks for children's health, childhood obesity increases the risk of adult obesity. The recent statement by the Endocrine Society [2] indicates that treating adult obesity with lifestyle intervention is an extremely difficult and only minimally successful effort. Prevention of obesity, therefore, should begin in childhood.

Managing obesity requires deep understanding of its biology. In this regard, the monograph edited by Freemark is an invaluable tool for all those involved in preventing and treating obesity, whether in individual patients or in public health programs. This book is highly recommended to a wide audience interested in containing the worldwide epidemic of metabolic disease.

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New York, NY, USA Leonid Poretsky, MD

Preface to the Second Edition

The first edition of this textbook, published in 2010, described an evolving epidemic of childhood obesity in the United States and other Western countries and the emergence in young people of serious comorbidities including insulin resistance, type 2 diabetes mellitus, hyperlipidemia, fatty liver disease, hypertension, and the metabolic syndrome. During the past 7 years, the worldwide prevalence of childhood obesity has soared, and the number of American children with severe (Class III) obesity has increased by 40%, with a predictable rise in the rates of life-threatening complications. The obesity epidemic has inflated medical costs dramatically, limited human productivity, and reduced life expectancy.

This second edition embodies all of the strengths of the original book but is deeper and broader in scope, with new chapters on emerging themes including metabolomics, genomics, and the roles of gastrointestinal hormones, the microbiome, brown adipose tissue, and endocrine disruptors in the pathogenesis of childhood obesity. Reviews of the effects of weight excess on cognitive performance and immune function complement detailed analyses of the biochemical and molecular pathways controlling the development of childhood adiposity and metabolic disease. Critical assessments of nutritional interventions (including new chapters on infant feeding practices and vegetarian diets) and superb reviews of behavioral counseling, pharmacotherapy, and bariatric surgery provide practical guidance for the management of overweight children. Penetrating analyses of the obesity epidemic in its social, cultural, economic, and political contexts highlight challenges and opportunities for obesity prevention and community action. The perspective is international in scope and reflects the expertise and experience of many of the leading figures in the field.

Despite extensive investigations into the mechanisms controlling food intake and weight gain, the precise roles of genetic and environmental factors and of nutrient balance and energy expenditure in the development and maintenance of childhood obesity remain, surprisingly, obscure. As in the first edition, I conclude each chapter with comments and questions for the authors that highlight the limitations of our understanding and the need for additional investigation. My premise is that better understanding of childhood obesity and its comorbidities will yield new approaches to prevention and treatment. It is this objective that I hope to achieve through the publication of this book.

Durham, NC — Michael S. Freemark, MD

The wise man says: I will eat to live, and the fool says: I will live to eat.

–Orchot Tzadikim, Germany, 15th century

To lengthen thy life, lessen thy meals.

–Benjamin Franklin, *Poor Richard's Almanack,* 1737

The rise of childhood obesity has placed the health of an entire generation at risk.

– Tom Vilsack, *Huffington Post*, 2010

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Part I

The Obesity Epidemic: A Global Perspective

1 Childhood Obesity in the Modern Age: Global Trends, Determinants, Complications, and Costs

Michael Freemark

Introduction

The first edition of this textbook, published in 2010, described with concern an evolving epidemic of childhood obesity in the United States and other Western countries and the emergence in young people of serious comorbidities including insulin resistance, type 2 diabetes mellitus, hyperlipidemia, fatty liver disease, hypertension, and metabolic syndrome. While the *rate of increase* in the overall prevalence of childhood obesity in the *developed* world has slowed, we are now witness to three ominous trends. First, the prevalence of childhood obesity has increased dramatically worldwide and now threatens even the most impoverished of nations. Second, the number of American children with the most severe and recalcitrant forms of obesity (Classes II and III) has increased progressively during the past 10 years. Finally, the persistence of severe obesity from childhood into adult life exacts a social and psychological toll on the individual, increases medical costs, limits productivity, and reduces life expectancy [1] (Fig. 1.1) owing to complications including myocardial infarction, renal insufficiency, cirrhosis, and liver cancer.

Extensive investigations conducted since the publication of the first edition have yielded new insights into the mechanisms by which

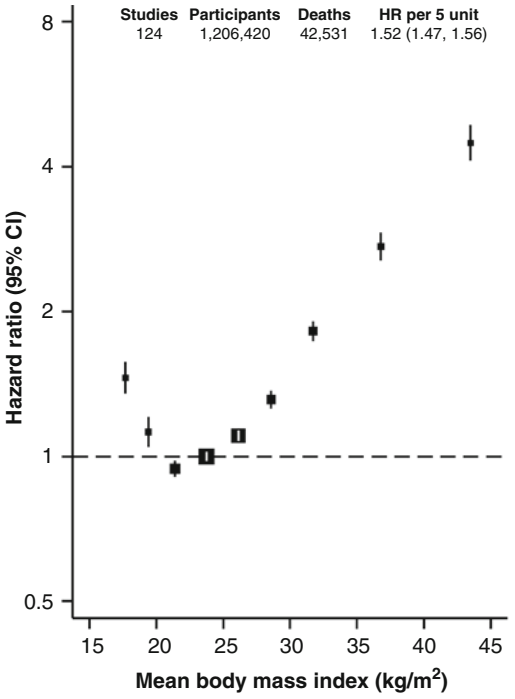

Fig. 1.1 Body mass index and all-cause mortality (ages 35–49) in four continents. (From Global BMI Mortality Collaboration. Body mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet. 2016 Aug 20; 388(10046):776–86. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)30175-1/fulltext)

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hormonal and metabolic factors control food intake and weight gain and have elucidated biochemical and molecular pathways central to the pathogenesis of childhood adiposity and metabolic disease. Yet the precise roles of genetic and environmental factors and of nutrient balance and energy expenditure in the development and maintenance of childhood obesity remain, surprisingly, obscure, increasing the challenge of defining optimal approaches to prevention and treatment.

Global Prevalence and Trends in Pediatric Obesity

The best estimates of global prevalence and trends in childhood obesity come from the Global Burden of Disease Study 2013 [2]. Data were derived from multi-country screening programs, national health ministry websites and surveys, a systematic literature review, and three large databases (the World Health Organization (WHO) Global Infobase, the International Association for the Study of Obesity Data Portal, and the Global Health Data Exchange).

Between 1980 and 2013, the worldwide prevalence of childhood overweight and obesity is estimated to have risen 47.1% (Fig. 1.2). In developed countries, the combined prevalence of overweight and obesity has increased from ~16.9% in boys and 16.2% in girls in 1980 to 23.8% in boys and 22.6% in girls in 2013. Similar trends, though lower absolute prevalence rates, are noted in low-income, developing countries (from ~8% in 1980 to ~13% in 2013). Rates of obesity in adults have also increased over time in developing as well as developed nations,

As a percentage of the population, childhood obesity is most prevalent in the Pacific Islands and Micronesia (>30%), the Caribbean, the Middle East, and North Africa. In contrast, prevalence rates are low in parts of Southeast Asia and Africa, including Bangladesh, Cambodia, Eritrea, Ethiopia, Laos, Nepal, North Korea, Tanzania, and Togo. Between 1980 and 2013, rates of obesity have risen most dramatically in Egypt, Saudi Arabia, Oman, Honduras, Bahrain, New Zealand, Kuwait, and the United States.

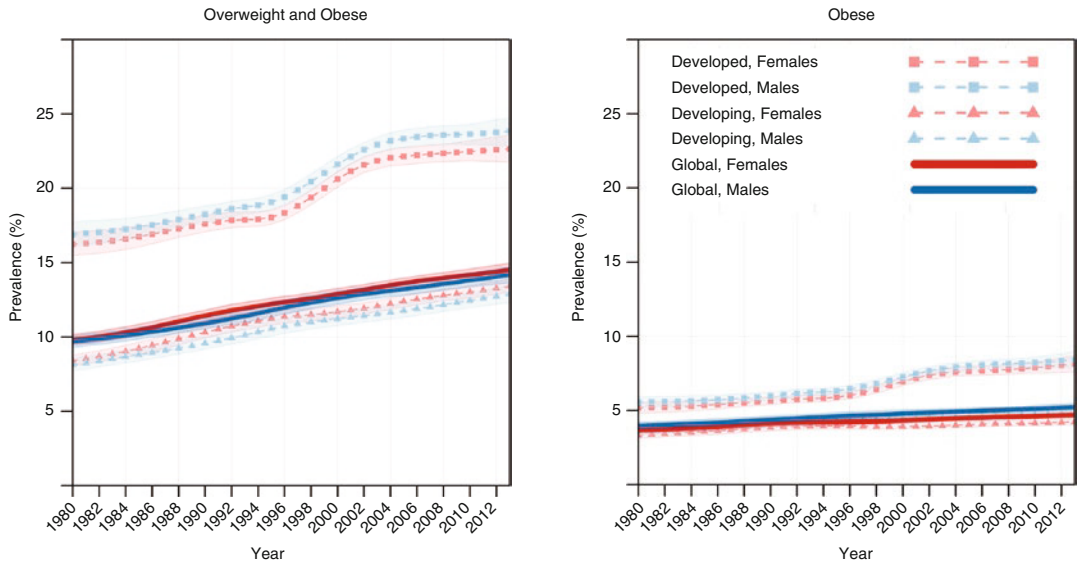

Fig. 1.2 Global prevalence of overweight and obesity in children and adults during 1980–2013. (Used with permission of Elsevier from Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014 Aug 30;384(9945):766–81)

The Relationship Between National Income, Socioeconomic Development, and Childhood Obesity Rates

The emergence of childhood and adult obesity in the developing world is the focus of ISCOLE (the International Study of Childhood Obesity, Lifestyle and the Environment), a cross-sectional analysis [3] of 7341 children (age 9–11 years) in urban and suburban centers throughout the world. Objective measurements of body mass index (BMI) and body fat content were obtained between 2011 and 2013 at sites with diverse levels of income and socioeconomic and educational development.

ISCOLE investigators find that BMIz, % body fat, and rates of childhood obesity correlate *positively* with income in nations with low indices of "human development," as measured by life expectancy at birth, mean years of schooling, expected years of schooling, and gross national income per capita. Conversely, obesity levels correlate *negatively* with income in nations with high levels of "human development" (Fig. 1.3). ISCOLE postulates a transition in the social patterning of obesity, such that people with higher incomes in developing transitional societies adopt lifestyles similar to those in developed "Western" societies. Weight gain under these conditions is valued as an indicator of newly acquired affluence. Rates of obesity gradually increase among those in lower socioeconomic strata, as economic growth, technological advances in food production, and penetration by multinational food corporations reduce the rates of famine and malnutrition while increasing the availability of high-density vegetable oils and simple sugars. In nations with high levels of "human development," people of means can partake of more nutritious (and costly) foods and take advantage of leisure opportunities that

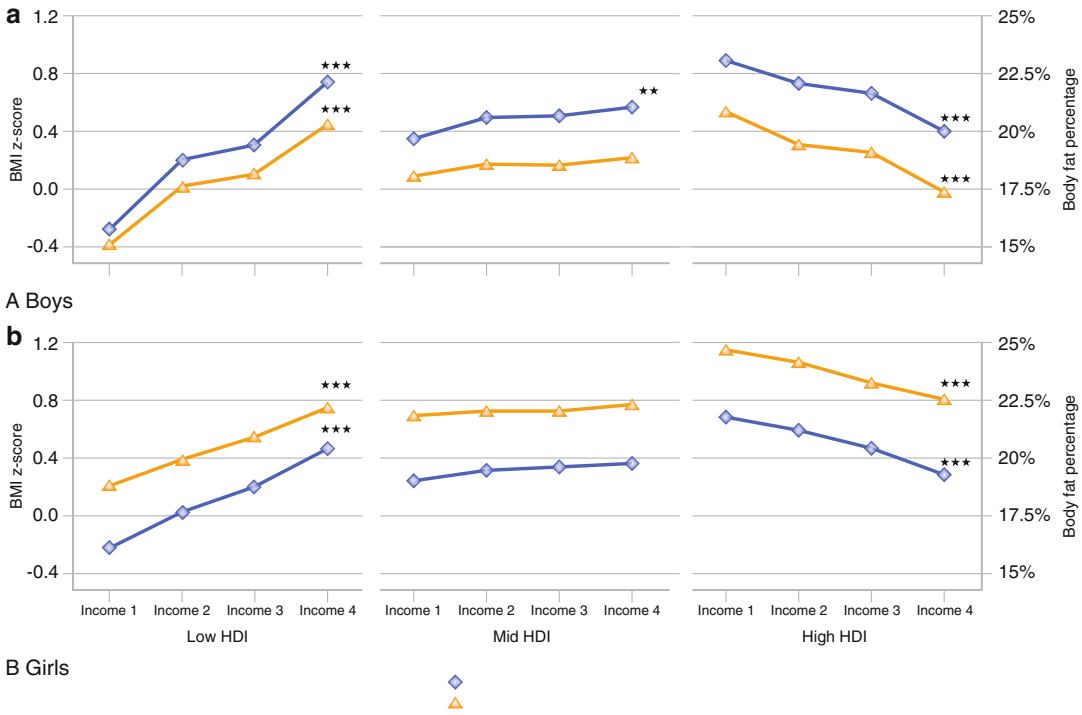

Fig. 1.3 Relationships between national measures of BMIz and % body fat in children and indices of "human development." (Used with permission of Nature Publishing Group from Broyles ST, Denstel KD, Church TS, Chaput JP, Fogelholm M, Hu G, et al., ISCOLE Research Group. The epidemiological transition and the global childhood obesity epidemic. Int J Obes Suppl. 2015 Dec;5(Suppl 2):S3–8)

promote energy expenditure. This serves to reduce the risks of obesity among the more educated and professional classes.

Population Changes in the Relative Severity of Obesity

The acute and long-term risks of obesity depend upon its severity as well as its duration. The severity of obesity can be described as the relative degree to which the body mass index (BMI, equals weight in kg divided by height in square meters) exceeds the 95th percentile for age and gender. Children with *Class I obesity* have BMIs that equal or exceed the 95th percentile for age. In *Class II obesity*, the BMI equals or exceeds 120% of the 95th percentile for age. BMI in *Class III obesity* equals or exceeds 140% of the 95th percentile for age.

A review [4] of National Health and Nutrition Examination Survey (NHANES) data found that the percentage of American children with all classes of obesity increased between 1999 and 2013–2014 (Fig. 1.4). The overall prevalence in rates of *Class II obesity* increased from ~4% of girls and boys in 1999 to 6.8% of girls and 5.8% of boys in 2013–2014. Even higher rates were recorded in adolescents; prevalence rose from 5.2 to 10.2% in teenage girls and from 6.0 to 8.9% in teenage boys.

More severe *Class III obesity rates* increased overall from 0.9 to 2.5% of American girls and from 1.0 to 2.2% of American boys between 1999 and 2013–2014. Among adolescents, the prevalence of Class III obesity increased from 1.7 to 4.9% of girls and from 1.6 to 3.7% of boys.

Although increasing rates of severe obesity were noted in all racial and ethnic groups, the prevalence of Class II and III obesity is highest among black and Hispanic-American children.

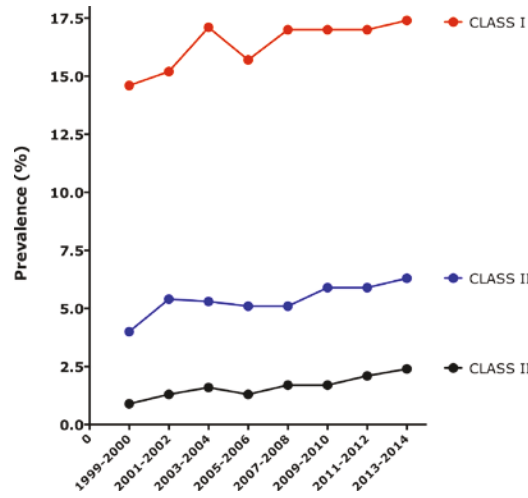

Fig. 1.4 Changes in the percentage of American children with obesity increased between 1999 and 2013–2014. Children with Class I obesity have BMIs that equal or exceed the 95th percentile for age. In Class II obesity the BMI equals or exceeds 120% of the 95th percentile for age. BMI in Class III obesity equals or exceeds 140% of the 95th percentile for age. (Used with permission of John Wiley and Sons from Skinner AC, Perrin EM, Skelton JA. Prevalence of obesity and severe obesity in US children, 1999–2014. Obesity (Silver Spring). 2016 May;24 (5):1116–23)

Table 1.1 Factors that predispose to childhood obesity

1.	Parental overweight or obesity
2.	Ethnic heritage
3.	Excess maternal gestational weight gain
4.	Maternal smoking during pregnancy
5.	Intrauterine exposure to maternal diabetes
6.	High birth weight
7.	Low birth weight with rapid catch-up weight gain (early "adiposity rebound")
8.	Parental education and income (variable depending upon the socioeconomic and cultural milieu)
9.	Formula (as opposed to breast) feeding
10.	Caesarian section delivery

Determinants of Childhood Obesity

Systematic literature reviews and meta-analyses have identified a number of factors associated with the development of childhood, adolescent, and adult obesity [5–10] (Tables 1.1 and 1.2). Among these, the most powerful determinants of future obesity are maternal and paternal BMI, which could reflect shared behaviors and environmental stresses as well as genetic inheritance [(see Chaps. 8 (Pigeyre/Meyre), 9 (Irizarry/Haqq), and 10 (Hinney/Giuranna) on genetic determinants of obesity]. Other major factors that

Table 1.2 Medications that promote weight gain

Atypical (second-generation) antipsychotics
Glucocorticoids
Synthetic progestins
Hypoglycemic agents: insulin, sulfonylureas, thiazolidinediones
Beta-blockers
Antidepressants: tricyclics, paroxetine, trazodone
Antiepileptics: valproate, gabapentin

predict the development of childhood obesity include maternal gestational weight gain, smoking during pregnancy, and birth weight. Conversely, parental education and family income correlate inversely with risks for childhood and adult obesity in the developed world. Members of certain ethnic groups, including African Americans, Hispanic Americans, Native Americans, and Pacific Islanders, are prone to excess weight gain; whether this reflects genetic, environmental, social, and/or economic influences is currently unclear. Prolonged breastfeeding reduces the risks of childhood obesity [10, 11]; this may be related in part to the relatively low protein content of breast milk [12]. Conversely, Caesarian section delivery increased slightly the risk of childhood obesity in some but not all studies [13, 14].

Longitudinal studies of large cohorts in Finland and the United Kingdom testify to the power of these risk factors in predicting future obesity in children. The Northern Finland Birth Cohort [5] followed 4032 children from the 12th week of gestation through 16 years of age. The risk of overweight and obesity at age 7–16 years correlated positively with prepregnancy parental BMI, gestational weight gain, maternal smoking during pregnancy, and birth weight. In contrast, rates of childhood and adolescent overweight and obesity correlated inversely with parental (especially maternal) professional status and number of household members. These findings were validated in parallel studies of smaller cohorts in Veneto, Italy (n = 1503) and Boston, Massachusetts (Project Viva, n = 1032).

Findings similar to those in the Northern Finland Birth Cohort were reported in the Millennium Cohort (UK) Study [6], which analyzed rates of growth and weight gain in 13,513 healthy, singleton term infants from 9 through 37 months of age. In addition to parental BMI, maternal smoking, birth weight (>3.5 kg), and formula feeding, the investigators found that rapid weight gain in infancy (>0.67 SD in weight z during year 1) increased by fourfold the risk of overweight at age 3.

Finally, an analysis [7] of 2119 Finnish children (age 3–18 years) found that parental BMI [odds ratio (OR) 1.57–1.64], birth weight (OR 1.16), and baseline childhood BMI (OR 2.51), blood pressure (OR 1.42), and fasting insulin (OR 1.51) correlated positively with the risk of adult obesity, while family income (OR 0.83) and parental education (OR 0.87) were negative predictors.

Subsequent chapters in this book review in greater detail the roles of maternal determinants (Chap. 11 by Drs. Hollis, Inskip, and Robinson) and early feeding practices (Chap. 15 by Drs. Pesch and Lumeng) in the development of pediatric obesity. It is critical to note that the various risk factors appear to act *in concert* to determine the odds of developing childhood obesity [5]. This is shown in Fig. 1.5, which demonstrates the effects of various factor combinations on childhood obesity risk, and in a calculator that combines various factors to estimate the risk of childhood obesity in the three study cohorts (Finnish, Veneto, and Project Viva). The calculator can be found in Data Set S2 at http://journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0049919#s5.

Intrauterine Growth and the Development of Childhood Obesity

Birth weight has a Janus-like effect on future obesity risk. Excess fetal weight gain in otherwise healthy children predicts obesity more strongly at age 3–13 years than at later stages of life [5–7, 15–19]; on the other hand, fetal overgrowth in infants of diabetic mothers increases the risks of future childhood, adolescent, and

a

Paternal BMI \ Maternal BMI (kg/m²)	20	25	30	35
20	0.13	0.24	0.44	0.79
25	0.32	0.59	1.07	1.93
30	0.79	1.43	2.58	4.61
35	1.93	3.46	6.12	10.62

No gestational smoking
Birth weight = 3 kg
Maternal profession = professional
Number of household members = 5

b

Paternal BMI \ Maternal BMI (kg/m²)	20	25	30	35
20	0.51	0.93	1.69	3.03
25	1.26	2.26	4.05	7.14
30	3.03	5.39	9.41	15.91
35	7.14	12.29	20.34	31.76

No gestational smoking
Birth weight = 3.5 kg
Maternal profession = skilled non manual
Number of household members = 4

c

Paternal BMI \ Maternal BMI (kg/m²)	20	25	30	35
20	3.59	6.36	11.01	18.39
25	8.39	14.31	23.33	35.66
30	18.39	29.11	42.80	57.69
35	35.66	50.25	64.79	77.03

History of gestational smoking
Birth weight = 4 kg
Maternal profession = skilled manual
Number of household members = 3

Fig. 1.5 Risk factors act in concert to determine the odds of developing childhood obesity. (From Morandi A, Meyre D, Lobbens S, Kleinman K, Kaakinen M, Rifas-Shiman SL, et al. Estimation of newborn risk for child or adolescent obesity: lessons from longitudinal birth cohorts. PLoS One. 2012;7(11):e49919. http://journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0049919#s5)

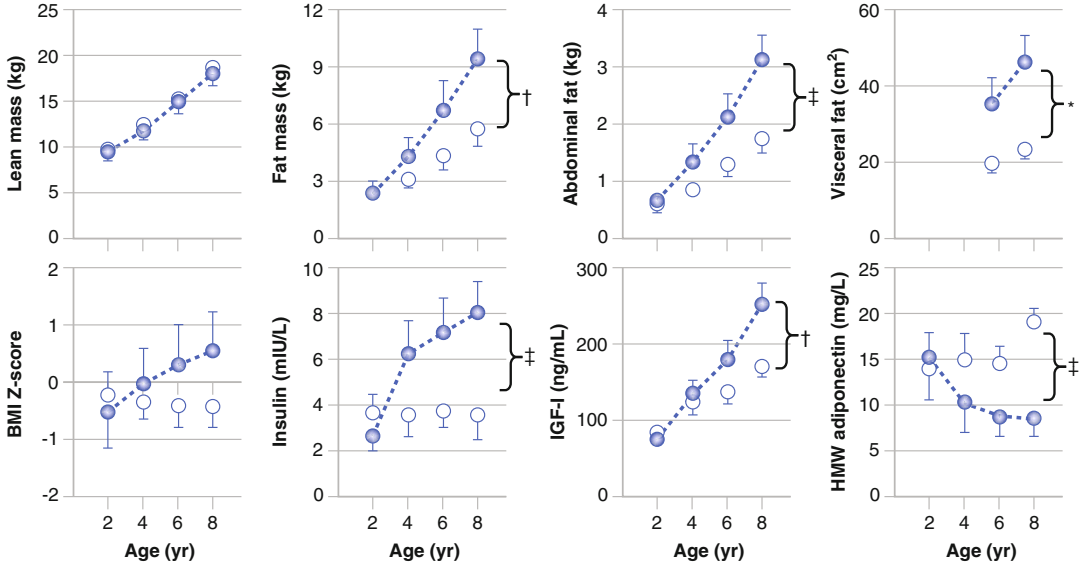

Fig. 1.6 Catch-up weight gain in former small for gestational age (SGA) children is associated with visceral fat deposition, insulin resistance, hyperinsulinemia, and hypoadiponectinemia. (Used with permission of Elsevier from Ibáñez L, Lopez-Bermejo A, Diaz M, de Zegher F. Catch-up growth in girls born small for gestational age precedes childhood progression to high adiposity. Fertil Steril. 2011 Jul;96(1):220–3)

adult obesity [19, 20]. This may reflect a programming effect of fetal hyperinsulinemia on adipogenesis and the propensity to store triglyceride in white adipose tissue. The effects of maternal obesity and gestational diabetes on childhood weight gain are discussed in more detail in Chap. 13 by Dana Dabelea and Katherine Sauder.

Interestingly, low birth weight also increases the risk of future obesity if accompanied by rapid catch-up weight gain during the prepubertal years [15, 16, 21, 22]. As shown in Fig. 1.6, catch-up weight gain in former small for gestational age (SGA) children is associated with visceral fat deposition, insulin resistance, hyperinsulinemia, and hypoadiponectinemia [23]. Similar effects

have been noted in infants and young children recovering from acute and chronic malnutrition [24]. In combination with increasing access to high-density vegetable oils and free sugars [25–27], the propensity of former SGA and malnourished children to deposit fat in excess of lean body mass may explain in part the dramatic increases in rates of obesity and type 2 diabetes (see below) in the developing world. A prime example is India [28], which has high rates of intrauterine growth restriction and childhood malnutrition and an emerging epidemic of adult onset type 2 diabetes. The effects of fetal growth restriction on childhood growth and weight gain are discussed in more detail in Chap. 12 by Ken Ong.

The Adiposity Rebound

Following delivery of a healthy full-term infant, there is an accumulation of body fat (see Appendix Fig. 2) and an increase in BMI calculated as a function of body length (from ~13–14 kg/M2 at birth to ~17.3–18 kg/M2 at 5–9 months of age). The magnitude and age at peak BMI in infancy vary to some extent among ethnic groups [29]; in part this might reflect population differences in maternal nutritional status, birth weight, and infant feeding practices (see Chaps. 11 and 15, by Hollis and colleagues and Pesch and Lumeng, respectively). Genetic determinants also likely play important roles [30]. After peaking in infancy, the BMI normally declines to a nadir at ~5–6 years of age. Thereafter, the BMI "rebounds," rising progressively throughout late childhood and adolescence.

Numerous studies demonstrate that the risk of childhood obesity is higher in those with an earlier and/or exaggerated "adiposity rebound" ([31, 32]; see also Chap. 6 by Dr. Korner and her colleagues). An early rebound is also associated with earlier menarche in girls [33] and with higher risks for obesity, glucose intolerance, and the metabolic syndrome in adulthood [34–36].

As noted previously, the adiposity rebound may in some cases reflect recovery from intrauterine and/or early postnatal malnutrition [31, 37]. In others, an excessive rebound results from dietary indiscretion and/or sedentary behavior (see below). Breastfeeding in infancy *may* delay and reduce the magnitude of the adiposity rebound [12, 31, 38]; some investigators postulate that the high fat/low protein content of breast milk reduces circulating levels of insulin and thereby limits adipogenesis and fat deposition [12, 31, 37].

The Role of Energy Intake in the Development and Maintenance of Childhood Obesity

Many investigators ascribe the rise in childhood obesity rates to increases in the intake of fast-food and sugary beverages. Indeed, cross-sectional studies show that intake of sugar-sweetened beverages and high-fat foods is associated with higher BMIz scores in children [39–43]. However, direct evidence supporting the nutrient hypothesis on a population scale is surprisingly weak, in part because current measures of population-wide caloric intake in children are highly suspect and possibly invalid.

Trends in Population Food Intake and Availability

Most studies of caloric and macronutrient intake in children are based on retrospective *24-hour dietary recalls* performed once or twice in national surveys. The reliability of dietary recalls declines markedly as children enter adolescence; moreover, overweight people are known to underestimate (in some cases dramatically) their intake of calories and foods known to be obesogenic.

This might explain certain paradoxical findings from studies of trends in food intake in American children. Between 1994 and 2010, when the rates of childhood and adolescent obesity rose ~50%, the total energy intake of children as assessed by dietary recall declined 10%, and the relative intake of solid fats and added sugars as a percent of total energy intake fell from 39% to 33% [44–46]. The relative decline

in sugar intake (from 18% to 14%) was greater than that of solid fat (21% to 19%, 44–46). The largest decreases in energy intake were said to have occurred in Mexican American children and other low-income children from families with less educated parents [45], that is, among groups with some of the highest rates of childhood obesity. Moreover, daily per capita food and beverage purchases (as assessed by market bar code analysis) by households have by report declined since 2001 in African American families, whose rates of severe obesity are among the highest recorded in the United States. Other investigators [47] report that energy intake from fast-food restaurants also decreased for American children between 2003 and 2010. Similar observations were recorded in a cross-sectional study [48] in Australia, where an increasing prevalence of childhood obesity was accompanied by a reduction in consumption of sugar and sugar-sweetened beverages.

A different impression is conveyed by analyses [26, 49] of *food balance sheets* provided by the United Nation's Food and Agricultural Organization (FAO). While these do not measure food consumption, they provide estimates of a country's food supply and the availability of nutrients for human consumption when adjusted for imports and exports and for food fed to livestock or used for seed. Review of food balance sheets [26] suggests that worldwide per capita calorie availability (Fig. 1.7) increased 20% between 1961 and 2011, with marked increases in vegetable oils (96%), eggs (71%), fish (59%), meat (55%), and sugars and sweeteners (41%). Modeling of FAO data (49) suggests that increases in food energy supply are sufficient to explain population weight gain, at least in the developed world.

Daily per capita kcal availability in the highest-income countries (3210) is estimated to be 33% higher than that in the lowest-income countries (2454). However, relative calorie availability has increased most dramatically between 1961 and 2011 in low-middle- and upper-middle-income countries, owing to striking increases in vegetable oils, eggs, meat, milk, and sweets. This finding concords with the striking increases in childhood obesity rates in developing countries as people adopt a Westernized lifestyle and diet.

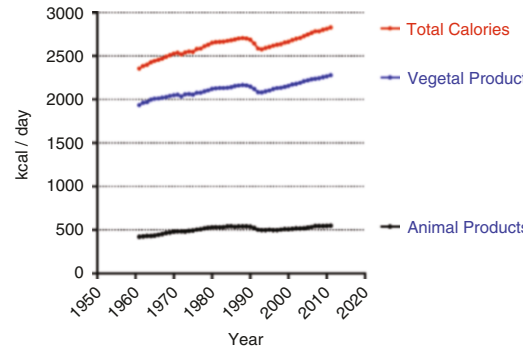

Fig. 1.7 Changes in worldwide per capita calorie availability between 1961 and 2011. (Used with permission of Elsevier from Dave D, Doytch N, Kelly IR. Nutrient intake: A cross-national analysis of trends and economic correlates. Soc Sci Med. 2016 Jun;158:158–67)

Dietary Patterns and the Development of Childhood Obesity

It is possible that the reported reductions in caloric intake in the United States and other developed countries during the past 16 years represent a response to prior weight gain in certain segments of the population. Longitudinal prospective studies of the relationship between food intake and fat deposition are more useful than cross-sectional analyses for identifying determinants of childhood obesity. The best prospective studies have employed an analysis of *dietary patterns* [50, 51] in a large cohort of 6500 children enrolled in the ALSPAC study (UK) at age 5–7 years and followed through age 15 years. Strengths of the study include the use of 3-day food *diaries* before each clinic visit, methodology to identify unreported energy intake, and objective measurements of fat mass by DEXA scan.

The authors identified two predominant dietary patterns. The first (Fig. 1.8) comprised a diet high in energy density, fats, and sugars (cakes, chocolate, processed meats, sugary drinks, whole milk, chips, oils, cheese) and low in fiber, fruits, and vegetables. The second

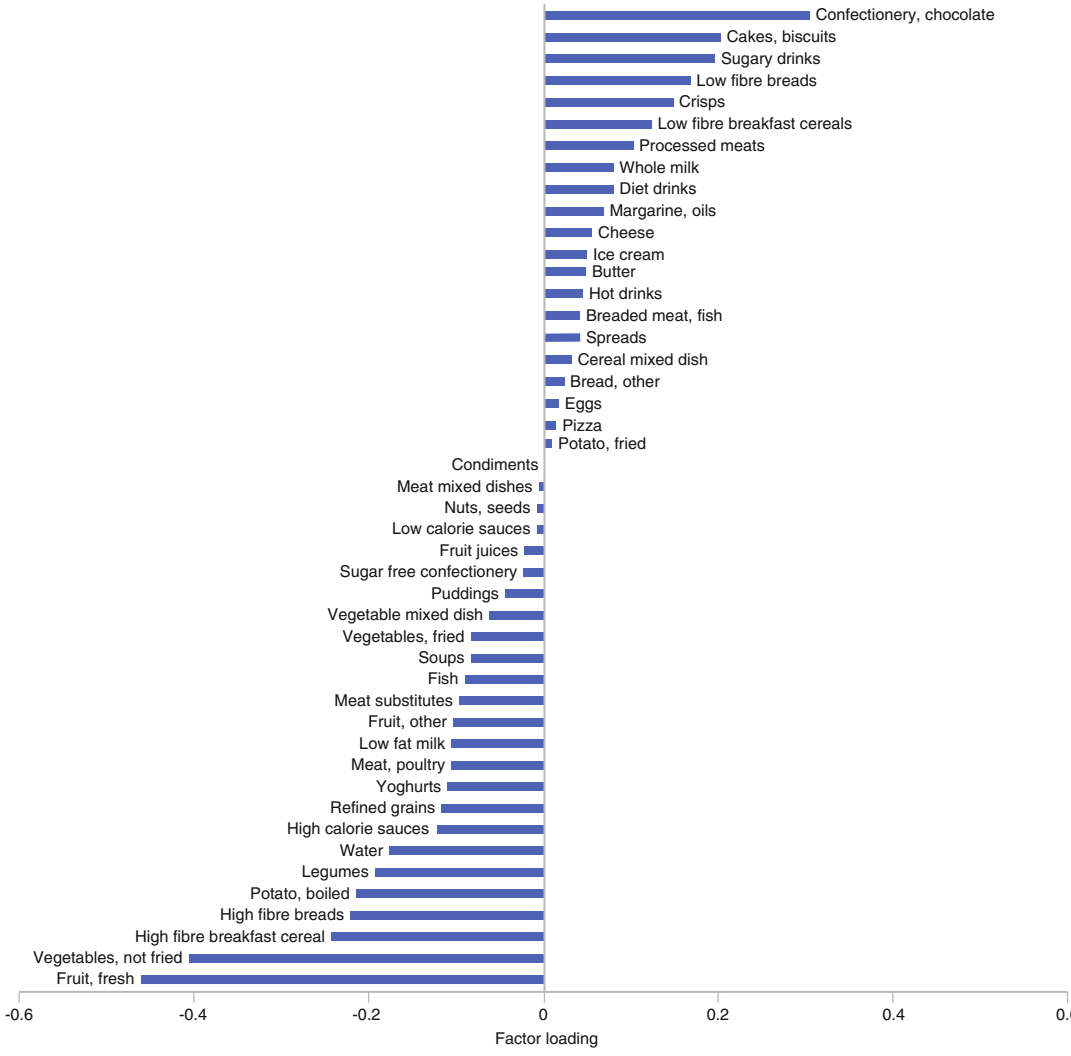

Fig. 1.8 A dietary pattern high in energy density, fats, and sugars (cakes, chocolate, processed meats, sugary drinks, whole milk, chips, oils, cheese) and low in fiber, fruits, and vegetables. (From Ambrosini GL, Johns DJ, Northstone K, Emmett PM, Jebb SA. Free Sugars and Total Fat Are Important Characteristics of a Dietary Pattern Associated with Adiposity across Childhood and Adolescence. J Nutr. 2016; 146: 778–784)

(Fig. 1.9) was high in free sugars but low in fat content, energy density, whole milk, oils, cheese, chips, and eggs. The diet high in energy, fat, and sugar and low in fiber, fruits, and vegetables at age 5–7 year was associated with higher percent body fat and excess adiposity in childhood and adolescence (Fig. 1.10, top). In contrast, the diet high in free sugars but low in fat and energy density did not predict subsequent percent body fat or excess adiposity (Fig. 1.10, bottom). A dietary pattern consisting of high-fat, high-energy foods *without excess sugar* was not identified in this cohort. Nevertheless, these findings suggest that it is the combination of excess fat and sugar, rather than a unique or single macronutrient, which predisposes to childhood obesity. This might explain the increases in childhood obesity in the developing world, where a dramatic rise in childhood and adult obesity rates has been accompanied by striking increases in access to low-cost vegetable oils, animal products, and simple sugars. A detailed analysis of dietary

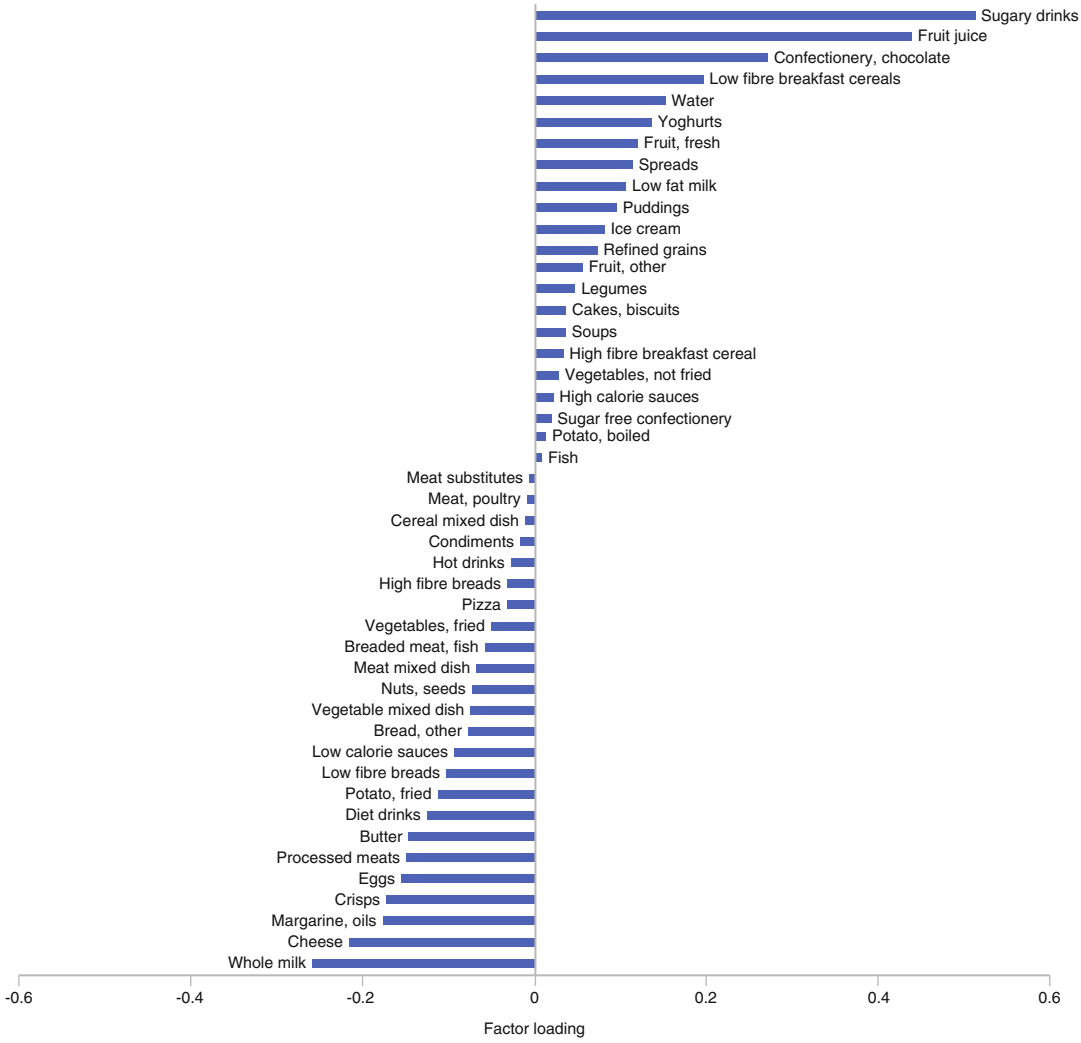

Fig. 1.9 A dietary pattern high in free sugars but low in fat content, energy density, whole milk, oils, cheese, chips, and eggs. (From Ambrosini GL, Johns DJ, Northstone K, Emmett PM, Jebb SA. Free Sugars and Total Fat Are Important Characteristics of a Dietary Pattern Associated with Adiposity across Childhood and Adolescence. J Nutr. 2016; 146: 778–784)

factors and the pathogenesis of childhood obesity is presented in Chap. 16 by Dr. Gow, Ho, Lister, and Garnett.

The majority of studies of macronutrient effects in children have focused on factors that *increase* the risks of obesity and insulin resistance. Small cohort studies in Seventh Day Adventists in the United States and Australia find that children eating plant-based/vegetarian diets have lower rates of obesity than children and adolescents on animal- or meat-based diets [52]. The effects of vegetarianism on childhood weight gain are discussed in more detail in Chap. 17 by Drs. Segovia-Siapco, Jung, and Sabate.

Energy Expenditure and the Development and Maintenance of Childhood Obesity

Technological developments including the widespread use of cell phones and computers, concerns about the safety of outdoor play spaces, and

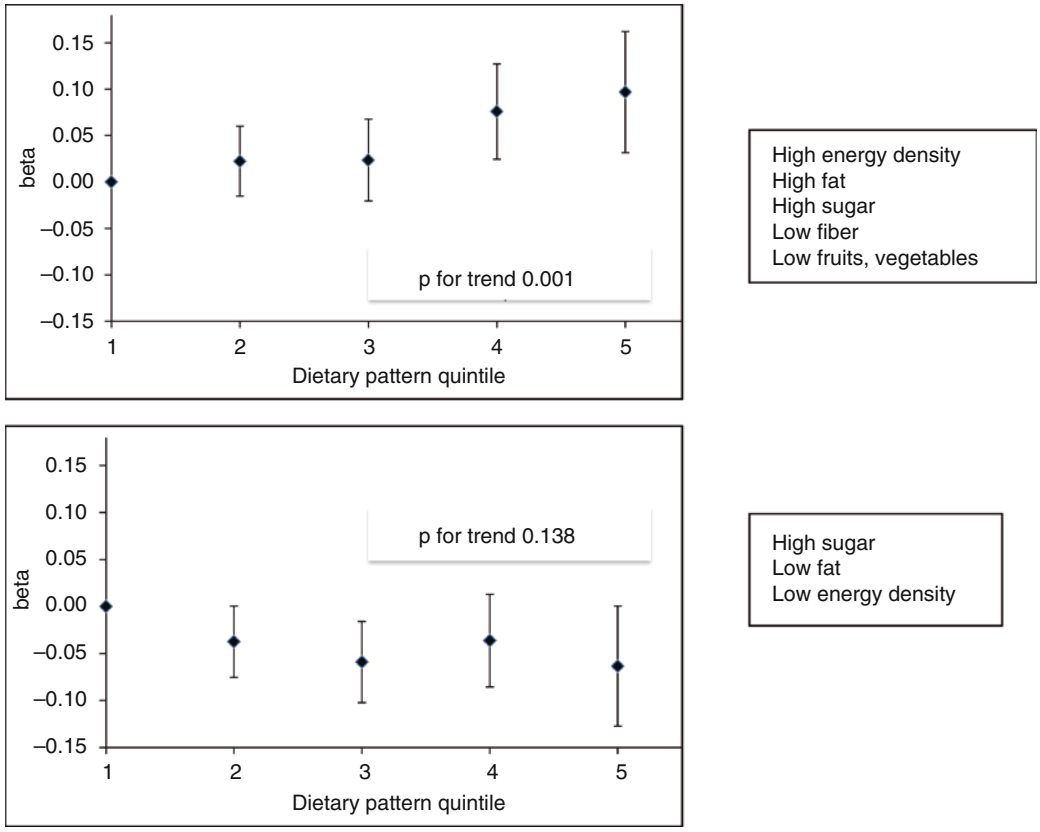

Fig. 1.10 Dietary patterns and adiposity in childhood and adolescence. Relation between quintile of dietary intake and fat mass index (FMI) z score, a measure of fat mass relative to height. Top: a diet high in energy, fat, and sugar and low in fiber, fruits, and vegetables at age 5–7 years was associated with higher percent body fat and excess adiposity in childhood and adolescence. Bottom: the diet high in free sugars but low in fat and energy density did not predict subsequent percent body fat or excess adiposity (From Ambrosini GL, Johns DJ, Northstone K, Emmett PM, Jebb SA. Free Sugars and Total Fat Are Important Characteristics of a Dietary Pattern Associated with Adiposity across Childhood and Adolescence. J Nutr. 2016; 146: 778–784)

the "professionalization" of childhood leisure and athletic activities have prompted many to suggest that the rise of childhood obesity can be traced, at least in part, to reductions in energy expenditure resulting from increases in sedentary behavior and a decline in purposeful physical activity. Indeed, cross-sectional studies demonstrate an inverse correlation between physical activity and childhood BMIz scores.

However, cross-sectional studies may not account for the possibility of reverse causation, that is, that overweight and obese children may be less active than lean subjects. That this is relevant was demonstrated in a longitudinal study [53] of 708 Danish children age 8–11 years. Accelerometer measures of total physical and moderate-vigorous physical activity at baseline did not predict changes in body fat content during a 3–6-month follow-up. On the other hand, baseline body fat content correlated strongly with sedentary time and inversely with energy expended in total physical and moderate-vigorous physical activity. The findings suggest that obese children devote less time and expend less energy through purposeful physical activity; on the other hand, a low level of physical activity at baseline did not predict excess fat deposition. Likewise, a review of six prospective studies in children found no association between baseline energy expenditure and adiposity at follow-up in two

cohorts and a *positive* correlation in one [54]. In a small group (n = 53) of children assessed [55] at age 3 months and at 2, 4, and 6 years of age, total energy expenditure as measured by doubly-labeled water correlated with fat-free mass but not with BMI or percent body fat at age 8.

Physical activity can nevertheless limit or reverse adiposity, to at least some extent. For example, the Avon Longitudinal Study [56] of 4150 British children found that an increase of 15 min of vigorous physical activity per day (assessed by accelerometry), or a 20% increase in total physical activity, at age 12 years was associated with an 5–11% (0.5–1 kg) reduction in fat mass at age 14.

Many of the published studies in children have reported physical activity as a surrogate for energy expenditure. This is problematic, as physical activity (physical work, muscular activity, shivering, fidgeting, and purposeful physical exercise) in most (but certainly not all) people accounts for only 15–30% of total daily energy expenditure [57]; the remainder consists of resting energy expenditure (~55–75%) and the thermic effect of food (~10%). Assessments of childhood obesity and weight loss interventions must therefore include measurements of total as well as physical activity energy expenditure for meaningful interpretation.

Most of the variation in resting metabolic rate is explained by fat-free body mass [57], which is higher in obese than in lean children as well as adults [57, 58]. Total energy expenditure is normal in obese children when expressed per kg lean body mass but low when expressed per kg total body mass (see Chap. 33 by David Thivel and his colleagues). Similar observations have been made in adults [47]. These findings suggest that energy expenditure in skeletal muscle and other organs (such as the liver, heart, brain, kidney, intestinal tract, and, possibly, brown fat) fails to rise adequately, and food intake may fail to decline sufficiently, to prevent or reverse adiposity. In theory, the lack of a compensatory increase in energy expenditure [59] might be related to subtle defects in hypothalamic function or hormone expression and/or innate or acquired deficiencies in mitochondrial metabolism; these in turn could cause reductions (or inadequate increases) in resting energy expenditure, diet-induced thermogenesis, and/or physical activity. Regarding the latter, Chap. 33 by Drs. Thivel and colleagues and Chap. 18 by Drs. Lanningham-Foster and Levine discuss the roles of exercise and nonexercise activity thermogenesis in the pathogenesis of childhood weight gain.

Short-Term Complications of Childhood Obesity

Many of the short-term complications of pediatric obesity are discussed in more detail in subsequent chapters in this book [60, 61]. Here I summarize the pathogenesis of comorbidities in overweight and obese children. At least four overlapping processes are involved.

Insulin Resistance

A key determinant of insulin resistance is the preferential storage of fat in visceral and abdominal regions and redistribution of fat from white adipose tissue (WAT) to extra-adipose tissues such as the liver, skeletal muscle, heart, and pancreas [60] (Fig. 1.11). In obese, insulin-resistant subjects, the redistribution of fat may reflect WAT dysfunction: there is decreased free fatty acid uptake, impaired adipogenesis, exaggerated lipolysis, decreased adiponectin expression, and increased production of leptin and inflammatory cytokines (see also Chap. 6 Antje Korner and her colleagues).

The accumulation of lipids in extra-adipose tissues is associated with resistance to insulin action and changes in tissue metabolism and function [60] (Fig. 1.12). There are increases in hepatic and renal gluconeogenesis (GNG) causing *fasting hyperglycemia*; reductions in skeletal muscle glucose uptake causing *postprandial hyperglycemia*; a paradoxical increase in glucagon secretion, which promotes hepatic GNG and lipolysis; and a reduction in serum osteocalcin, a marker of bone formation and an insulin sensitizer. Resistance to insulin in the brain exacerbates lipolysis and GNG and thereby increases

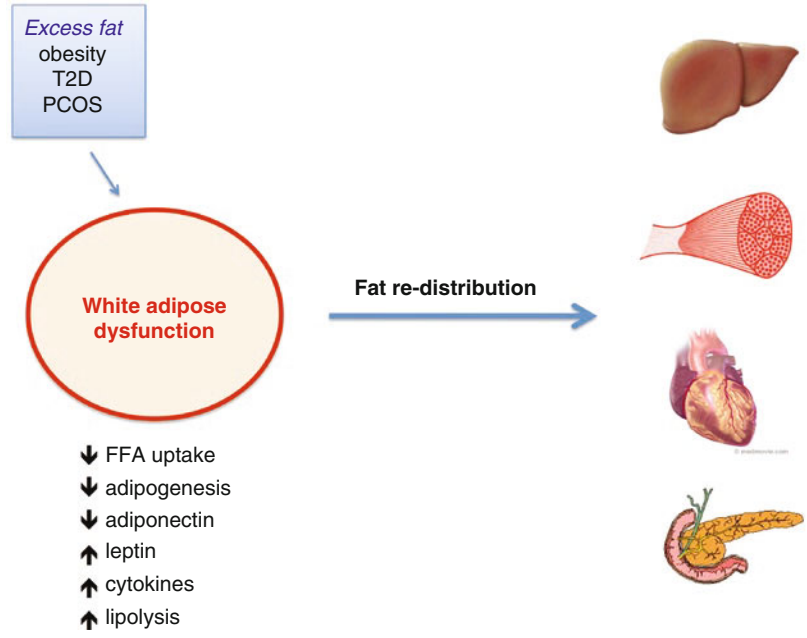

Fig. 1.11 A key determinant of insulin resistance is the preferential storage of fat in visceral and abdominal regions and redistribution of fat from white adipose tissue (WAT) to extra-adipose tissues such as the liver, skeletal muscle, heart, and pancreas (Used with permission of SLACK Incorporated from Freemark M. Predictors of childhood obesity and pathogenesis of comorbidities. Pediatr Ann. 2014 Sep;43(9):357–60)

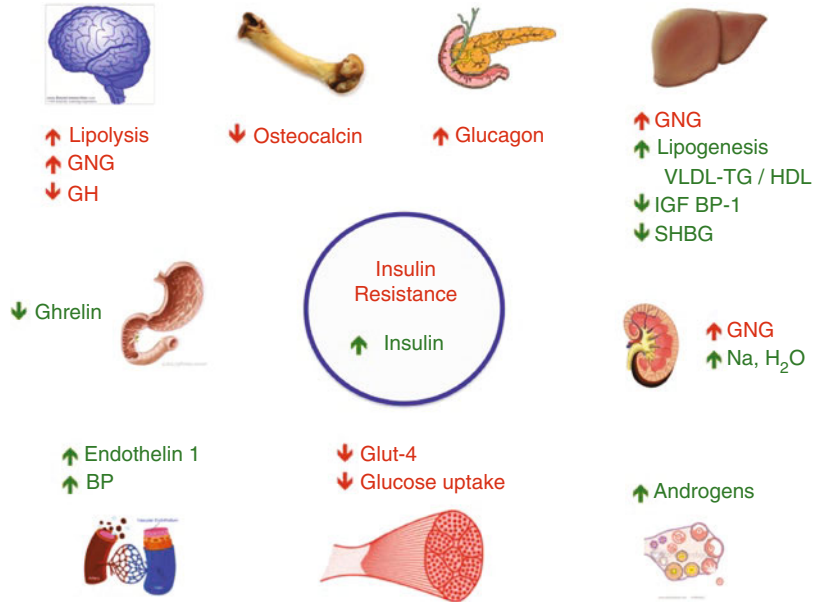

Fig. 1.12 Metabolic complications of insulin resistance (red) and hyperinsulinemia (green). (Used with permission of SLACK Incorporated from Freemark M. Predictors of childhood obesity and pathogenesis of comorbidities. Pediatr Ann. 2014 Sep;43(9):357–60)

free fatty acid and glucose levels, which may explain in part the fall in basal and stimulated levels of growth hormone in obese subjects.

Hyperinsulinemia

It should be noted that insulin resistance in obesity is *tissue and function selective*. Certain tissues become resistant to insulin action, while others remain insulin sensitive. Likewise, certain metabolic processes within a given organ may be resistant to insulin action, while other processes within the same organ retain sensitivity to insulin.

In obesity and other insulin-resistant states, an exaggerated but dysregulated increase in insulin secretion protects against overt metabolic decompensation until beta cell failure ensues.

In addition to promoting the development of acanthosis, hyperinsulinemia has important metabolic consequences [60] (Fig. 1.12). While the liver becomes resistant to insulin suppression of hepatic glucose production (HGP), the hyperinsulinemia of insulin resistance stimulates hepatic lipogenesis. This promotes liver triglyceride storage ("fatty liver"), VLDL production, systemic hypertriglyceridemia, and secondary reductions in high-density lipoprotein. Severe hypertriglyceridemia can cause eruptive xanthomas and pancreatitis. Insulin downregulation of hepatic insulin-like growth factor binding proteins 1 and 2 may increase free insulin-like growth factor 1 (IGF-1) levels, which may sustain or increase linear growth in the face of low GH secretion. Insulin suppression of hepatic sex hormone-binding globulin (SHBG), in combination with upregulation of ovarian thecal androgen production, increases free androgen levels, which may manifest as *precocious adrenarche* and, in teenagers, *polycystic ovary syndrome*. Hyperinsulinemia downregulates secretion of the orexigenic hormone ghrelin, which may limit further weight gain; however, insulin excess increases renal sodium and water retention, vascular endothelin-1 production, and sympathetic nervous system activity, leading to vasoconstriction and hypertension. *Thus, the imposition of hyperinsulinemia on a background of insulin resistance largely explains the clinical phenotype of the metabolic syndrome*.

Chronic Inflammation

Obesity is accompanied by selective tissue accumulation of macrophages; increases in pro-inflammatory cytokines such as leptin, interleukin 6, TNFα, and osteopontin; and a reduction in the anti-inflammatory cytokine adiponectin. Chronic inflammation may impair cellular function and cause cellular damage; a major example is *fatty liver disease*, which can progress to steatohepatitis, cirrhosis, and rarely (in children) hepatic failure (see Chap. 26 by Drs. Della Corte, Mosca, Alterio, Comparcola, Ferretti, and Nobili).

Mass Effects of Excess Fat Deposition

Accumulation of fat in the liver and heart may contribute to *hepatomegaly* and *cardiomegaly*. Accumulation of fat in the neck, palate, and tonsillar/adenoid regions predisposes to *obstructive sleep apnea*, which manifests as excessive snoring, restless sleep, and daytime fatigue. The development of *pseudotumor cerebri* in obese (particularly female) patients may be related to heightened abdominal venous and intrathoracic pressure. Excess weight gain for any reason places severe stress on the bones and joints and can cause orthopedic problems including Blount's disease.

Long-Term Complications of Childhood Obesity

Type 2 Diabetes Mellitus

A central role for childhood obesity in the development of type 2 diabetes has been clearly established by the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) [62] and SEARCH for Diabetes in Youth [63] studies and by the Princeton LRC and Follow-up [64, 65], Bogalusa Heart [66, 67], and Young Finns studies [67–69]. These investigations demonstrate that childhood obesity that persists throughout adolescence increases by 4–28 fold the risk of type 2 diabetes in young adults. A meta-analysis [70] (Fig. 1.13) showed that a 1 SD increase in BMI in childhood (age 7–18 year) predicts a 74% increase in the risk of adult type 2 diabetes. The pathogenesis of insulin resistance and type 2 diabetes in obese adolescents is reviewed in Chaps. 23 and 24 by Drs. Weiss and Hagman and by Drs. Pinhas-Hamiel, Zeitler, and Kelsey.

The rise in obesity rates in children and adolescents no doubt explains, at least in part, the global increase in rates of type 2 diabetes during the past 35 years. As estimated by the NCD Risk Factor Collaboration [71], the worldwide, age-standardized prevalence of diabetes mellitus increased from 4.3% to 9.0% in men and from

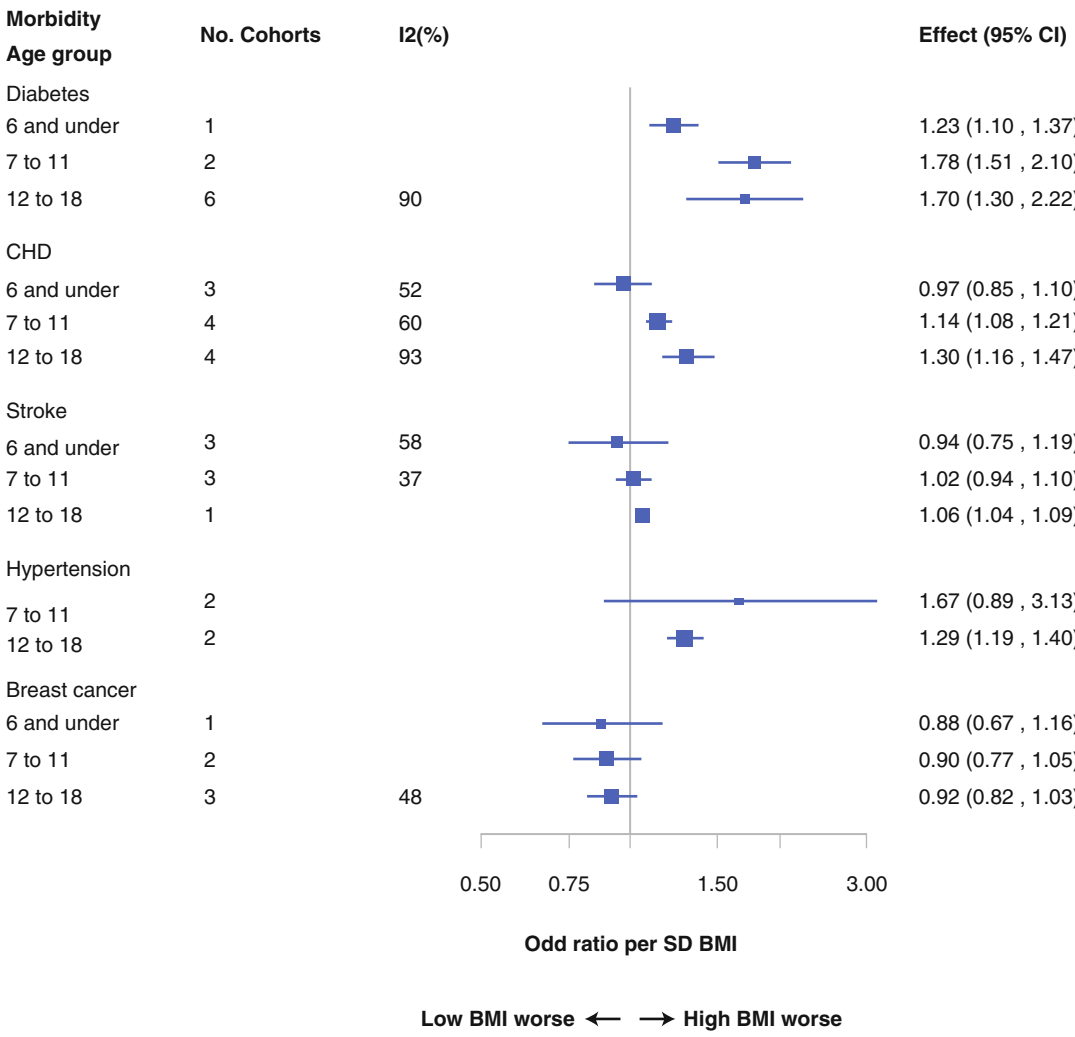

Fig. 1.13 Meta-analysis of the relationship between childhood BMIz and the risks of adults type 2 diabetes mellitus, coronary heart disease (CHD), hypertension, stroke, and breast cancer. (Used with permission of John Wiley and Sons from Llewellyn A, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. Obes Rev. 2016 Jan;17(1):56–67)

5.0% to 7.9% in women between 1980 and 2014. The number of diabetic adults rose from ~180 million in 1980 to ~422 million in 2014; only 40% of the increase in absolute number could be ascribed to population growth and aging. The rise in prevalence of diabetes has been most dramatic in transitioning societies in Asia, North Africa, the Middle East, and Oceania (Fig. 1.14). Approximately one half of all diabetic adults now live in the United States and four countries undergoing rapid changes in social and economic development: China, India, Brazil, and Indonesia. Large numbers are also found in Pakistan, Mexico, and Egypt. As discussed previously, the rise in diabetes in lower- and lower-middle-income countries likely reflects improvements in health care, declining rates of chronic malnutrition, and "Westernization" of patterns of food intake and lifestyle.

Notwithstanding the persistence of type 2 diabetes in most patients who develop the condition in adolescence, an analysis [72] of the combined cohorts from the Bogalusa, Muscatine, and Young Finns studies found that the risk of type 2 diabe-

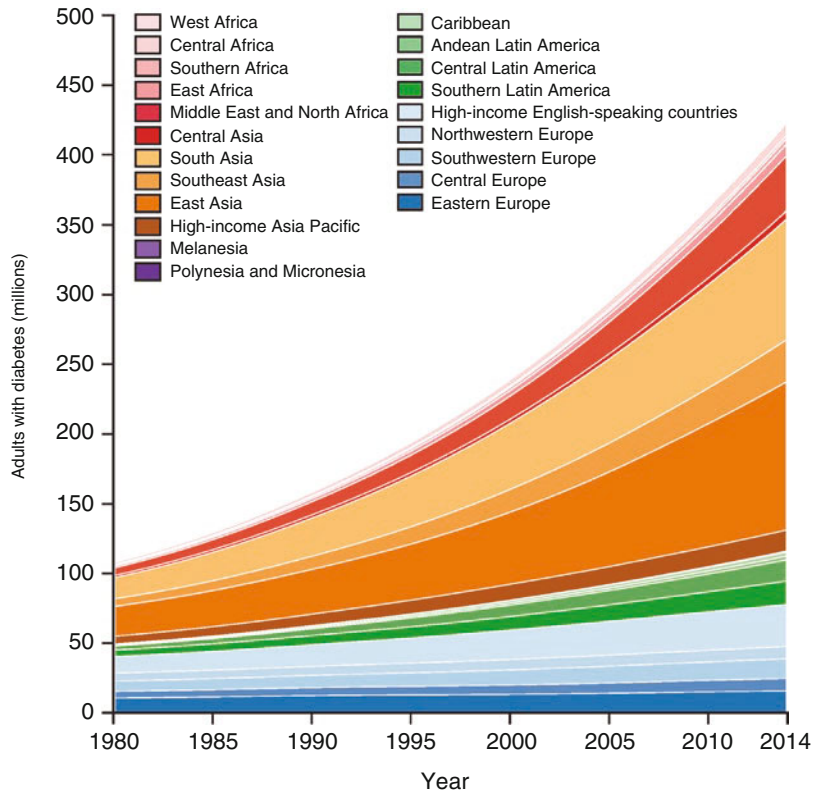

Fig. 1.14 Global increase in rates of type 2 diabetes between 1980 and 2014. (From NCD Risk Factor Collaboration (NCD-RisC. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016 Apr 9;387(10027):1513–30. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)00618-8/fulltext)

tes in people who were overweight or obese as children but not as adults was no higher than the risk of type 2 diabetes in adults who were never overweight. Although most obese adolescents remain obese as young and middle-aged (but not necessarily old) adults [72–74], this encouraging finding suggests that reversal of childhood obesity may prevent subsequent development of type 2 diabetes.

Cardiovascular Disease

Obesity in childhood and adolescence, like obesity in adults, predisposes to hypertension, hyperinsulinemia, and hypertriglyceridemia. The number of small dense LDL particles is increased, and the levels of HDL are low (see Chap. 25 by Brian McCrindle). As shown in the Pathobiological Determinants of Atherosclerosis (PDAY) and the Bogalusa Heart, Muscatine, Princeton Lipid, and Young Finns studies [65, 67, 68, 75–82], obesity and the cardiac risk factors act *in concert*, *synergistically*, to promote atherogenesis and an increase in carotid intimal medial thickness in adolescents and adults. Subsequent chapters provide more detailed discussions of the development of metabolic syndrome (Chap. 29 by Drs. Magnusson, Fraser, and Raitakari) and cardiovascular disease (Chap. 30 by Drs. Shah and Urbina) in pediatric obesity.

A very large (n = 2.3 million), longitudinal (42,297,000 person years of follow-up) study [83] of Israeli adolescents found that obesity at mean age 17.3 years was associated with a 4.9-fold increase in the risk of coronary artery disease and a 4.1-fold increase in cardiovascular deaths by age 47–57 years; this was estimated to account for as much as one-fifth of all cardiovascular deaths and one-fourth of deaths from coronary artery disease.

Lower (but statistically significant) risks of future acute coronary events (10% increase for every 1 unit increase in BMIz) were noted in a study of 7–13-year-old Danish children [84]. A meta-analysis [70] (Fig. 1.13) showed that a 1 SD

increase in BMI in childhood and adolescence (age 7–18 years) predicts a 14–30% increase in the risk of adult coronary heart disease. The risk increases with the age of assessment of BMI.

Adjustment for adult BMI in a subgroup of the Israeli cohort (n = 37,674) did not attenuate the risk of cardiovascular deaths associated with adolescent obesity [85]. In contrast, the association of carotid intimal thickening with childhood obesity was abolished after adjustment for adult obesity in the Bogalusa, Muscatine, and Young Finns studies [72]. Relative differences in the effects of childhood and adult obesity on cardiovascular outcomes might be explained in part by differences in the ages of assessment at baseline (Israeli study participants averaged 17.3 years of age; other study subjects were 3–18 years) and/or differences in duration of follow-up (Israeli 30–40 years, others mean 23 years).

The critical role of pubertal weight gain was recently demonstrated in a study of Swedish men [86]. Cardiovascular mortality was increased in adult men who gained excess weight during adolescence; those who were obese in childhood but not in adolescence were not at higher risk.

Hypertension and Renal Disease

Systolic hypertension is a common complication of obesity and predisposes to ventricular hypertrophy, carotid artery intima-media thickening, endothelial dysfunction, proteinuria, renal scarring, and stroke [87]. Even in the absence of hypertension, obesity may cause focal glomerulosclerosis; however, the combination of obesity and hypertension creates a vicious cycle that may progress to renal failure. The renal complications of obesity are discussed in more detail in Chap. 27 by Drs. Hunley, Albaugh, and Kon.

Malignancies

Relative to lean adults, obese adults have increased risks for a variety of malignancies including esophageal adenocarcinoma, endometrial carcinoma, and cancers of the liver, stomach, kidney, gall bladder, pancreas, and colon. Mechanisms thought to promote carcinogenesis in adult obesity include hyperinsulinemia, hypoadiponectinemia, abnormalities in sex steroid balance, and increases in the levels of free/bioavailable IGF-1, leptin, and pro-inflammatory cytokines.

Reports of the relationship between childhood obesity and adult malignancy are limited, but a meta-analysis [70] showed that a 1 SD increase in BMI in childhood is associated with ~20% increases in rates of adult colon and kidney cancer and a 10–30% increase in the rates of adult liver cancer (Fig. 1.15). The latter may reflect the association between childhood obesity and steatohepatitis; concurrent type 2 diabetes increases markedly the risk of liver cancer in subjects with fatty liver disease.

The Human Costs of Childhood Obesity

Obesity can exact an emotional toll on the child and his/her family as obese children are often subject to *social ostracism*, bullying, self-criticism, and negative self-image. *Depressive symptoms* are more common in obese than in lean children, but the relationship may be bidirectional; obesity may lead to feelings of sadness, frustration, and hopelessness, while depression and its treatment with certain psychotropic (and other) drugs may cause disordered eating and excessive weight gain (Table 1.2). Successful treatment of obesity may improve self-image and social interactions and increase overall quality of life.

Cognitive function in obese children may be variably impaired; whether this reflects chronic emotional distress, social isolation, recurrent school absence, or intrinsic neurological dysfunction is currently unclear. It is interesting that *academic achievement* correlates inversely with obesity rates (and social class) in higher-income countries but positively with obesity rates in lower-income, transitional nations [88]. Possible effects of obesity on behavior and cognitive function are discussed in Chap. 31 by Drs. Eichen, Appleton-Knapp, and Boutelle.

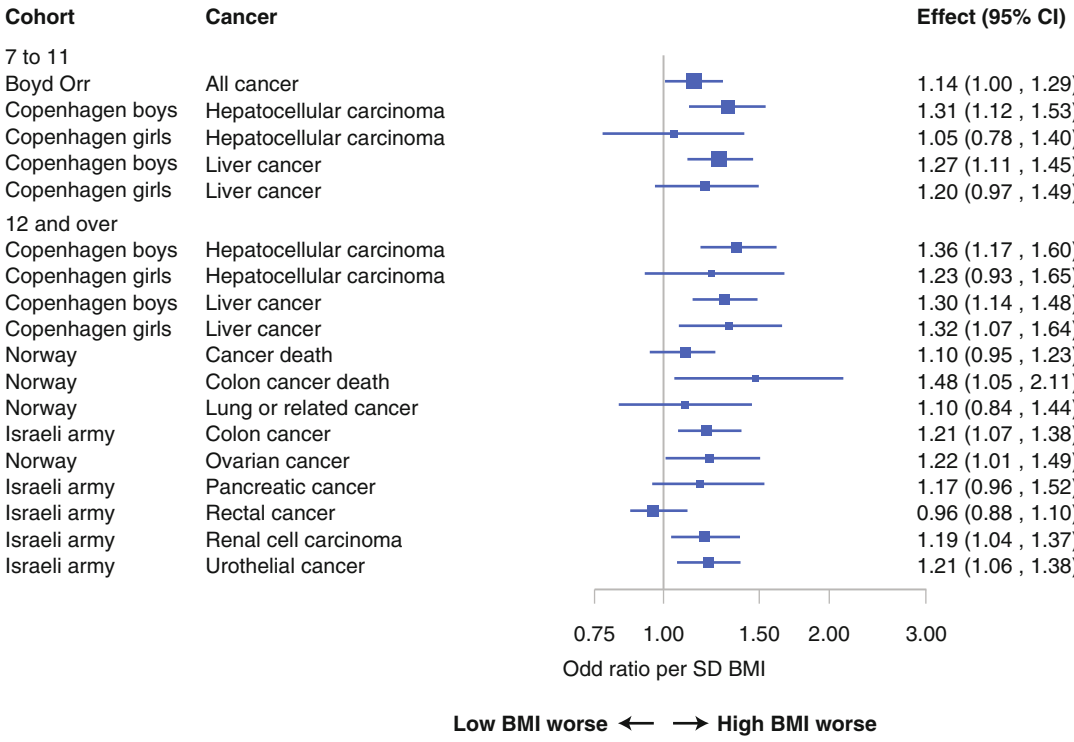

Fig. 1.15 Meta-analysis of the relationship between childhood BMIz and the risk of malignancies in adulthood. (Used with permission of John Wiley and Sons from Llewellyn A, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. Obes Rev. 2016 Jan;17(1):56–67)

Finally, the families of obese children and the society at large confront staggering financial costs that threaten the viability of local, regional, and national health-care systems. Even accounting for an increase in early mortality in obese adults, the *excess direct medical costs* required for caring for an obese child throughout his/her lifetime currently approximate $13,000 in the United States [89]. This represents an enormous financial burden for a society in which 15–20% of children are obese. Direct lifetime medical costs are actually eclipsed by *indirect costs* of childhood and adult obesity, which include lack of educational achievement, disability and job absence (of the caretaker as well as the child), and loss of human productivity [89, 90].

For all these reasons, a better understanding of childhood obesity and its comorbidities, and new approaches to prevention and treatment, are urgently required. It is those objectives that the editor hopes to achieve through publication of this book.

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Part II

Hormonal and Metabolic Control of Appetite, Fat Deposition, and Energy Expenditure

2 Central Control of Energy Metabolism and Hypothalamic Obesity

Belma Haliloglu and Abdullah Bereket

Hypothalamic Regulation of Energy Storage and Expenditure

The hypothalamus is the primary center controlling energy intake, expenditure, and storage. The mission of energy balance is executed via afferent and efferent signals. Afferent signals received from peripheral tissues including white adipose, pancreas, liver, and the gastrointestinal tract are processed and interpreted in the hypothalamus. Signals originating in the hypothalamus are delivered to organs and tissues via efferent signals. Earlier studies identified the ventromedial hypothalamus (VMH) and the lateral hypothalamic area (LHA) as the satiety and feeding centers of the brain, respectively. However, recent investigations have increased our understanding of hypothalamic structure and function and now identify major areas for energy regulation in the paraventricular nuclei (PVN) and arcuate nucleus (ARC) as well as VMH and LHA (Fig. 2.1) [1, 2].

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The ARC consists of two groups of neurons: the orexigenic neurons that secrete agouti-related protein (AgRP) and neuropeptide Y (NPY) and the anorexigenic neurons that secrete proopiomelanocortin (POMC) and cocaine-amphetamine-related transcript (CART). AgRP/NPY and POMC/CART neurons function as sensors of peripheral tissues, responding to nutrient, neuronal, and hormonal signals including glucose, amino acids, short-chain fatty acids, adipocytokines (such as leptin), ghrelin, insulin, and the gastrointestinal hormones [3, 4].

POMC is cleaved by prohormone convertases (PC1/PC3, PC2) and processed via tissue-specific posttranslational modification. In the hypothalamus, POMC cleavage generates a variety of peptides including ACTH, melanocyte-stimulating hormone (MSH), beta-lipotropin, endorphins, and corticotropin-like intermediate lobe peptide (CLIP) [4]. α-MSH binds as an agonist to melanocortin receptors 3 and 4 (MC3R/MC4R) in PVN neurons and inhibits food intake. Conversely, AgRP promotes food intake by antagonizing MC3R/MC4R signaling and inhibits energy expenditure. NPY also stimulates food intake via binding to Y receptors in the PVN [4, 5].

Peripheral hormones and cytokines, including leptin, ghrelin, insulin, and glucagon-like peptide 1 (GLP-1), play central roles in this system. Ghrelin stimulates appetite and food intake by activating NPY neurons in the ARC and mimics

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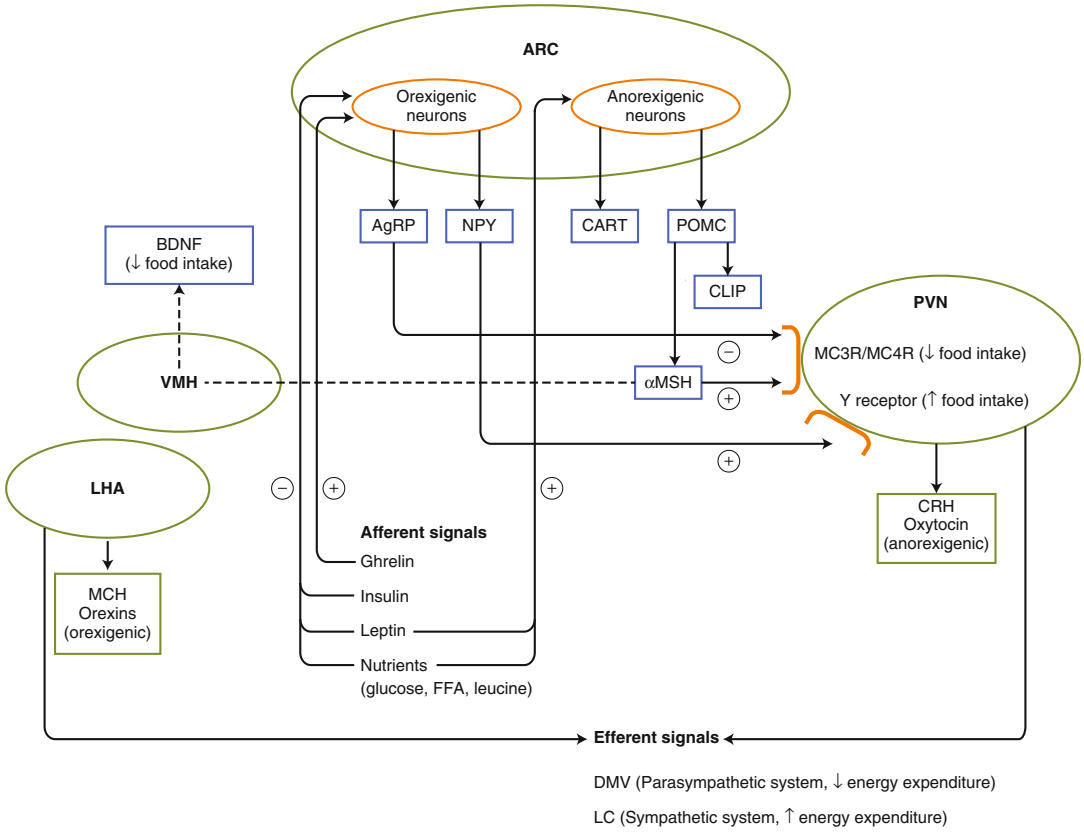

Fig. 2.1 A simplified scheme of regulation of energy homeostasis by the hypothalamus. *ARC* arcuate nucleus, *PVN* paraventricular nucleus, *VMH* ventromedial hypothalamus, *LHA* lateral hypothalamic area, *AgRP* agouti-related peptide, *NPY* neuropeptide *Y*, *CART* cocaine-amphetamine-related transcript, *POMC* proopiomelanocortin, *CLIP* corticotropin-like intermediate lobe peptide, *α-MSH* alpha-melanocyte-stimulating hormone, *BDNF* brain-derived neurotrophic factor, *MCH* melanin-concentrating hormone, *CRH* corticotropin-releasing hormone, *DMV* dorsal motor nucleus of the vagus, *LC* locus coeruleus

the effect of NPY in the PVN [5]. In contrast, insulin (administered centrally) and leptin suppress the expression of AgRP and NPY [6]. At the same time, leptin stimulates the expression of POMC and CART and thereby limits the drive to feed [2].

Although insulin and leptin receptors are localized in a variety of brain areas, the ARC is adapted for sensing of additional hormone and nutrient signals by virtue of its having a relatively permeable blood-brain barrier [6]. The ARC responds to glucose, oleic acid, leucine, and GLP-1, which is derived from proglucagon in the L cells of the ileum and colon. GLP-1 reduces food intake through both peripheral (vagal) and central mechanisms (see also Chap. 3 on GI Hormones and the Control of Food Intake and Energy Metabolism). In addition to mediating the anorexic effect of GLP-1, the ARC GLP-1 receptor also binds oxyntomodulin (OXM), another anorexigenic peptide derived from proglucagon. Peptide YY (PYY, peptide tyrosine-tyrosine), which is also released from intestinal L cells, decreases food intake through its interaction with NPY receptors in the ARC [6].

While the ARC is the key area for the regulation of energy homeostasis, the VMH, PVN, and LHA have important functions as well. The VMH contains neurons sensitive to glucose and other feeding-related stimuli. The VMH also responds to melanocortins, which reduce

food intake in part through induction of brain-derived neurotrophic factor (BDNF) [1, 2]. Intracerebroventricular injection of BDNF inhibits feeding and reduces mesenteric fat mass in Goto-Kakizaki rats [7]. The PVN has an anorexigenic action that is effected via secretion of CRH and oxytocin and expresses both MC3R/MC4R and Y receptors [2]. Conversely, the LHA has an orexigenic effect and secretes anabolic peptides such as melanin-concentrating hormone and orexins [3, 8]. Orexins are induced by fasting and promote arousal, feeding behavior, brown adipogenesis, lipogenesis, emotional memory, and autonomic nervous system activity [9].

The activity of the autonomic nervous system is integrated with hypothalamic signaling to modulate energy balance. The PVN and LHA send impulses to the dorsal motor nucleus of the vagus (DMV) and the locus coeruleus (LC) for control of the parasympathetic (PNS) and sympathetic nervous systems (SNS), respectively. While anorexigenic signals activate the SNS via the LC and increase energy expenditure, orexigenic signals send projections to the DMV and promote energy deposition [10]. Gastrointestinal satiety hormones (including cholecystokinin, GLP-1, and PYY) that are secreted in response to dietary lipid or protein can activate receptors on local sensory nerves in the duodenum and signal to the hypothalamus via the vagus nerve [6] (see Chap. 3).

Genetic defects in the peptides, enzymes, or receptors in these pathways, or damage to their neural circuits, can lead to hypothalamic obesity (HyOb, Table 2.1) (see a more detailed discussion in Chap. 8 on Monogenic Obesity and Chap. 9 on Syndromic Obesity).

Pathophysiologic and Metabolic Features of Hypothalamic Obesity

Biochemical features of HyOb include hyperleptinemia, hyperinsulinemia, sympathetic nervous system (SNS) dysregulation, enhanced white adipose 11β-hydroxysteroid dehydrogenase-1 (11β-HSD1) activity, and impaired melatonin signaling.

Table 2.1 Etiology of hypothalamic obesity

Structural causes	Functional causes
— *Brain tumors*	— *Genetic causes*
Craniopharyngioma	Leptin (LEP)
Glioma	Leptin receptor (LEPR)
Germinoma	MC4R
Ependymoma	POMC
Meningioma	CART
Hamartoma	Prohormone convertase-1
Pinealoma	TrkB, NTRK2
Endothelioma	BDNF
Colloid cysts	SIM-1
Pituitary macroadenoma	SH2B1
Leukemia	KSR2
Langerhans cell histiocytosis	TUB
Teratoma	
Metastasis	
	— *Syndromes*
— *Inflammatory*	Prader-Willi syndrome
Sarcoidosis	Bardet-Biedl syndrome
Tuberculosis	ROHHAD
Arachnoiditis	
Encephalitis	— *Psychotropic drugs*
Histiocytosis X	(Antidepressants, mood stabilizers, antipsychotics)
— *Neurosurgery*	
— *Cranial radiotherapy*	

Hyperleptinemia

Leptin levels rise in "exogenous" obesity in proportion to white adipose tissue mass. In response to progressive weight gain, the transport of leptin into the CSF plateaus, and there is partial inhibition of central leptin signaling; in combination, these blunt the anorectic effect of leptin in severe obesity. Patients with hypothalamic damage or genetic defects in leptin or the leptin receptor have even greater impairment in leptin action; this promotes food-seeking behavior and limits energy expenditure, leading to massive weight gain and fat deposition [3]. Except in patients with leptin gene mutations, the levels of leptin in children with HyOb are higher than in BMI-matched patients with common exogenous obesity [11].

Hyperinsulinemia

The hypothalamus controls pancreatic insulin release via α-MSH activation of the sympathetic system and vagal stimulation [10, 12]. Damage to the hypothalamus is associated with hyperinsulinemia, weight gain, and glucose intolerance [13]. Conversely, insulin acts centrally to suppress food intake and weight gain [10, 14]. The hyperinsulinemia of HyOb results from defects in α-MSH signaling, vagal hyperactivity, and loss of central insulin signaling [10]. Although some studies showed similar fasting insulin levels in HyOb and BMI-matched obese patients [11, 15], the insulin secretory response to glucose is exaggerated in children with HyOb and is generally higher than expected for their BMIs (Table 2.2) [11, 13].

Hyperinsulinemia promotes lipogenesis and inhibits lipolysis and may thereby induce, or exacerbate, weight gain in children with HyOb. It has been proposed that hyperinsulinemia (and weight gain) may maintain linear growth in GH-deficient children following hypothalamic surgery, the so-called growth without growth hormone [16].

Dysregulation of Autonomic Nervous System Activity

Experimental and clinical studies establish strong and reciprocal links between autonomic nervous system activity and HyOb. Lesions of the VMH and LHA in experimental animals cause HyOb via increased parasympathetic tone, decreased sympathetic activity, reduced thermogenesis, and decreased mobilization of fatty acids [12]. Likewise, post-op craniopharyngioma patients with obesity had lower urinary catecholamine metabolites (homovanillic acid, HVA, and vanillylmandelic acid, VMA), lower morning heart rates, and lower activity scores; those with highest BMI had the lowest urinary HVA and VMA [17]. ARC neurons expressing CART likely play a role in regulation of autonomic activity: central

Table 2.2 Metabolic features of hypothalamic obese (HyOb), hypothalamic nonobese (HyNOb), and simple obese (Ob) children

	HyOb	HyNOb	Ob	*p*
n	23	16	22	
Gender (M/F)	11/12	5/11	10/12	NS
Age (years)	10.3 (8–14.6)	11.4 (8.9–14.1)	10.8 (8.9–12.8)	NS
BMI-SDS	2.0 (1.5–2.1)	0.18 (−0.5–0.56)	2.1 (1.8–2.3)	<0.001 (HyNOb vs. HyOb, Ob)
Leptin (ng/mL)	89.2 (40.7–143.6)	25.3 (13.3–53.3)	66 (48–90)	<0.05 (HyNOb vs. HyOb, Ob)
Leptin/BMI	4.0 (1.6–5.2)	1.5 (0.8–3.1)	2.5 (1.8–3.5)	<0.05 (HyOb vs. HyNOb, Ob)
sOb-R (ng/mL)	46.3 (36.1–53.5)	44 (36.9–59.8)	40.3 (34.1–51.8)	NS
Leptin/sOb-R (FLI)	2.0 (0.8–3.5)	0.6 (0.3–1.2)	1.5 (1–2.3)	<0.05 (HyNOb vs. HyOb, Ob)
Resistin (ng/mL)	2.6 (1.9–3.1)	2.8 (1.7–3.4)	3.0 (2.2–3.5)	NS
Fasting glucose (mmol/L)	4.3 (3.7–4.6)	4.4 (4–4.9)	5 (4.7–5.3)	<0.05 (Ob vs. HyOb, HyNOb)
120 min glucose in OGTT (mmol/L)	6.1 (5.1–6.5)	5.8 (4.8–6.1)	6.0 (5.6–6.9)	NS
Fasting insulin (mU/L)	16 (9–23)	10 (6.6–16)	28 (19–39)	<0.05 (Ob vs. HyOb, HyNOb)
120 min insulin in OGTT (mU/L)	58.5 (42–70)	33 (12–49.5)	78 (51–92)	<0.05 (Ob vs. HyNOb)
% change of insulin during OGTT	259 (162–411.5)	152 (50–327.5)	161 (79.5–221.5)	<0.05 (Ob vs. HyOb)
HOMA-IR	2.8 (2–4.3)	1.8 (1.2–3)	6.5 (3.9–8.5)	<0.05 (Ob vs. HyOb, HyNOb)

sOb-R (soluble leptin receptor) and FLI (free leptin index)

Used with permission of Springer Science from Guran T, Turan S, Bereket A et al. The role of leptin, soluble leptin receptor, resistin, and insulin secretory dynamics in the pathogenesis of hypothalamic obesity in children. Eur J Pediatr 2009; 168: 1043–1048

administration of CART increases uncoupling protein levels and thermogenesis in brown adipose tissue via the sympathetic nervous system (SNS) [18].

Melatonin Dysregulation

Through release of norepinephrine, the SNS controls the release of melatonin from the pineal gland. In one study HyOb patients had lower morning and nighttime salivary melatonin levels, which were related inversely to BMI [19]. In animal studies, melatonin administration has been shown to decrease adiposity, leptin levels, and body weight and to reduce insulin secretion via pancreatic melatonin receptors (MT1 and MT2) [20, 21]. Spontaneous physical activity and core body temperature are increased and the relative weight of intra-abdominal fat is reduced. Thus decreases in melatonin secretion may contribute to, or exacerbate, the hyperinsulinemia and weight gain of patients with HyOb.

11β-Hydroxysteroid Dehydrogenase-1 (11β-HSD1)

After extensive suprasellar operations for resection of hypothalamic tumors, some patients develop Cushing-like morbid obesity, while they receive replacement doses of glucocorticoids. It was hypothesized that target tissue conversion of inactive 11-ketosteroids to active 11β-OH glucocorticoids might explain the obesity of some patients with hypothalamic lesions. 11β-HSD1 catalyzes the transformation of inactive cortisone to active cortisol in white adipose tissue, liver, and skeletal muscle. Overexpression of 11β-HSD1 in white adipose tissue is accompanied by abdominal adiposity and features of the metabolic syndrome. Tiosano and colleagues studied ten patients with hypothalamic obesity and secondary adrenal insufficiency and six control Addisonian patients while they were on glucocorticoid replacement therapy. They found increased 24 h urine-free cortisol to cortisone ratio in HyOb patients after a single oral dose of 12 mg/m^2 hydrocortisone acetate, with a positive correlation between urine cortisol/cortisone and the ratio of visceral fat to subcutaneous fat [22]. The authors proposed that a deficiency of hypothalamic messengers after surgical injury enhances glucocorticoid activity in visceral white adipose via upregulation of 11β-HSD1 activity. The exact mechanism by which hypothalamic obesity upregulates visceral 11β-HSD1 activity is not well understood. However, ACTH, CRH, and α2-adrenergic stimulation diminish 11β-HSD1 activity in human adipocyte cultures, whereas β2-adrenergic stimulation and inflammatory cytokines (such as TNFα and IL-1β) upregulate 11β-HSD-1 activity [23].

Etiology of Hypothalamic Obesity

The causes of HyOb may be classified in two broad categories. Damage causing disruption of hypothalamic pathways can be *structural*, as seen in hypothalamic tumors prior to, and more commonly after, neurosurgery, inflammatory disorders, radiotherapy, or trauma. Alternatively, it can represent a *genetic or syndromic disorder* such as rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome or the Prader-Willi syndrome (Table 2.1).

Craniopharyngioma (CF)

The most common cause of HyOb is acquired structural hypothalamic damage; among its causes, the best known and most extensively studied is craniopharyngioma. The diagnosis of craniopharyngioma in children is often delayed, so the major manifestations are visual impairment (62–84%) and neuroendocrine deficits (52–87%) [24]. Detailed assessment of the initial MRI can delineate the extent of hypothalamic involvement and predict the likelihood of subsequent HyOb (see below). The prevalence of HyOb has been reported to be as high as 55% after surgical treatment of craniopharyngioma [24, 25]. Suprachiasmatic lesions are associated with even

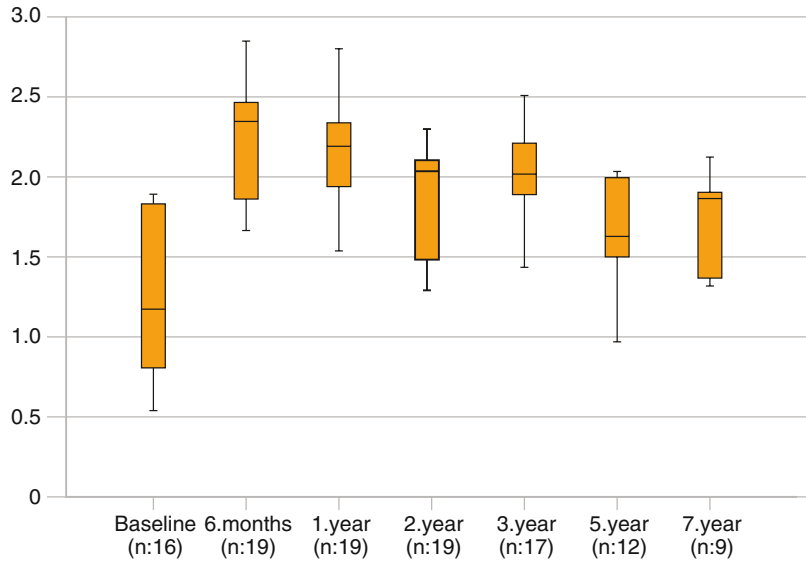

Fig. 2.2 Mean BMI-SDS during 7 years of follow-up in patients with hypothalamic obesity. The boxes represent interquartile range (25–75%) (Used with permission of John Wiley and Sons from Haliloglu B, Atay Z, Guran T, Abali S, Bas S, Turan S, Bereket A. Risk factors for mortality caused by hypothalamic obesity in children with hypothalamic tumours. Pediatric Obesity 2016 11(5):383–8)

higher morbidity rates; surgical removal of tumors beyond the mammillary bodies places the child at very high risk of HyOb [26].

HyOb is associated with rapid weight gain during the first 6 months after surgery; this is commonly followed . by stabilization of weight [25, 27] (Fig. 2.2). Factors predicting the development of HyOb include age <5–6 year at diagnosis, tumor histology (craniopharyngioma, optic glioma), hypothalamic tumor involvement, radiotherapy (>51 Gy), third ventricle hydrocephalus, and the presence of hypothalamic endocrinopathy [25, 27, 28] (Table 2.3). Weight gain often persists or progresses despite hormone replacement therapy.

Table 2.3 Predictive factors for the development of HyOb

Predictive factors for the development of HyOb
— Hypothalamic involvement
— Young age (<5–6 years) at diagnosis
— Histology of tumor
— Radiotherapy (>51 Gy)
— Presence of hypothalamic endocrinopathology
— Hydrocephalus requiring ventriculoperitoneal shunt

Acute Lymphoblastic Leukemia (ALL)

Although obesity is a common complication of childhood ALL, with a prevalence ranging from 9 to 48%, HyOb is not common [29]. Factors contributing to obesity in ALL include sedentary behavior, radiotherapy-induced hypothalamic damage, chemotherapy, growth hormone deficiency, and corticosteroid therapy [14, 29]. Cranial irradiation and intrathecal chemotherapy can cause hypothalamic damage, leading to hormonal deficiencies and hypothalamic dysregulation of food intake. Increases in fat deposition usually emerge during the first year of therapy and often persist during subsequent years. Female gender and ≥20 Gy cranial radiation therapy seem to be risk factors for BMI ≥ 30 in several studies [29].

Monogenic and Syndromic Forms of HyOb

A variety of mutations in genes controlling appetite, energy expenditure, and weight gain can cause early-onset obesity in children. *These are described in detail in Chap. 8 on Monogenic Obesity by David Meyre and Marie Pigeyre*. Likewise, a number of genetic syndromes associated with hypothalamic dysfunction cause early- or late-onset childhood obesity; these are discussed in Chap. 9 on Syndromic Obesity by Krystal Irizarry and Andrea Haqq. In Table 2.4

Table 2.4 Genetic causes of HyOb and clinical features

Gene	Function	Phenotype
LEP[a]	Anorexigenic effect	Severe obesity, hyperphagia, hypogonadism, normal height until puberty but short stature after puberty
LEPR[b]	Leptin signaling	Severe obesity, hyperphagia, hypogonadism hypothyroidism, growth retardation (low IGF1, IGFBP3)
MC4R[c]	α-MSH signaling	Severe obesity, increased linear growth, hyperphagia, severe hyperinsulinemia
POMC[d]	Precursor of α-MSH	Early-onset obesity, red hair, central adrenal insufficiency
CART[e]	Anorexigenic effect	Childhood and adult obesity in heterozygotes
PCSK1[f]	Cleaving of POMC to α-MSH	Obesity, central adrenal insufficiency, hypogonadism, impaired glucose tolerance, postprandial hypoglycemia, severe malabsorptive neonatal diarrhea
TrkB and NTRK2[g]	TrkB is the receptor for BDNF, NTRK2 codes a subunit for TrkB	Obesity, hypotonia, developmental delay, impaired short-term memory and decreased nociception
BDNF[h]	Regulation of MC4R signaling	Haploinsufficiency of BDNF detected in WAGRO syndrome
SIM-1[i]	Formation of PVN	Obesity, hyperphagia, developmental delay
SH2B1[j]	Modulation of tyrosine kinases or JAK-associated cytokine receptors	Early-onset obesity, hyperphagia, disproportionate insulin resistance, reduced final height, behavioral abnormalities
KSR2[k]	Intracellular protein involved in multiple signaling pathways	Hyperphagia, obesity, low heart rate, reduced basal metabolic rate, severe insulin resistance
TUB[l]	Control in insulin and leptin signaling and action in vivo hypothalamic nuclei	Obesity, retinal dystrophy
ch15q11–13 (PWS)[m]	Lack of paternally imprinted genes on ch15q11–13	Hyperphagia, severe obesity, short stature, hypogonadism hypotonia, hyperghrelinemia
Several genes[n] (BBS)[o]	Cilia function, intracellular protein trafficking, hypothalamic leptin receptor signaling	Obesity, retinitis pigmentosa, polydactyly, hypogonadism
Unknown (ROHHAD)[p]		Rapid-onset obesity, hypothalamic dysfunction, hypoventilation, autonomic dysfunction, and neural tumor

[a]Doche ME, Bochukova EG, Su HW, Pearce LR, Keogh JM, Henning E, et al. Human SH2B1 mutations are associated with maladaptive behaviors and obesity. J Clin Invest. 2012; 122(11): 4732–6

[b]Pearce LR, Atanassova N, Banton MC, Bottomley B, van der Klaauw AA, Revelli JP, et al. KSR2 mutations are associated with obesity, insulin resistance, and impaired cellular fuel oxidation. Cell. 2013; 155(3): 765–77

[c]Borman AD, Pearce LR, Mackay DS, Nagel-Wolfrum K, Davidson AE, Henderson R, et al. A homozygous mutation in the TUB gene associated with retinal dystrophy and obesity. Hum Mutat. 2014; 35(2): 289–93

[d]Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M. Recommendations for the diagnosis and management of Prader-Willi syndrome. J Clin Endocrinol Metab 2008; 93: 4183–4197

[e]Seo S, Guo DF, Bugge K, Morgan DA, Rahmouni K, Sheffield VC. Requirement of Bardet-Biedl syndrome proteins for leptin receptor signaling. Hum Mol Genet 2009; 18: 1323–1331

[f]Patwari PP, Wolfe LF. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation: review and update. Curr Opin Pediatr 2014; 26(3): 487–92

[g]Farooqi IS. Monogenic human obesity. Front Horm Res 2008; 36: 1–11

[h]Manzardo AM, Johnson L, Miller JL, Driscoll DJ, Butler MG. Higher plasma orexin A levels in children with Prader-Willi syndrome compared with healthy unrelated sibling controls. Am J Med Genet A. 2016 Aug;170(7):2097–102

[i]Goldstone AP, Patterson M, Kalingag N et al. Fasting and post-prandial hyperghrelinemia in Prader-Willi syndrome is partially explained by hypoinsulinemia, and is not due to peptide YY 3–36 deficiency or seen in hypothalamic obesity due to craniopharyngioma. J Clin Endocrinol Metab 2005; 90: 2681–2690

[j]Dhondt K, Verloo P, Verhelst H, Van Coster R, Overeem S. Hypocretin-1 deficiency in a girl with ROHHAD syndrome. Pediatrics. 2013; 132(2): e788–92

[k]Jacobson LA, Rane S, McReynolds LJ, Steppan DA, Chen AR, Paz-Priel I. Improved Behavior and Neuropsychological Function in Children With ROHHAD After High-Dose Cyclophosphamide. Pediatrics. 2016 Jul;138(1)

[l]Roth CL, Eslamy H, Werny D, Elfers C, Shaffer ML, Pihoker C, Ojemann J, Dobyns WB. Semiquantitative analysis of hypothalamic damage on MRI predicts risk for hypothalamic obesity. Obesity (Silver Spring). 2015 Jun;23(5):1226–33

Table 2.4 (continued)

[m]Geffner M, Lundberg M, Koltowska-Häggström M, Abs R, Verhelst J, Erfurth EM et al. Changes in height, weight, and body mass index in children with craniopharyngioma after three years of growth hormone therapy: analysis of KIGS (Pfizer International Growth Database). J Clin Endocrinol Metab 2004 Nov; 89(10): 5435–5440

[n]At least 20 BBS genes have been defined and all acts in primary cilia functioning

[o]Srinivasan S, Ogle GD, Garnett SP, Briody JN, Lee JW, Cowell CT. Features of the metabolic syndrome after childhood craniopharyngioma. J Clin Endocrinol Metab 2004; 89: 81–86

[p]Müller HL, Handwerker G, Gebhardt U, et al. Melatonin treatment in obese patients with childhood craniopharyngioma and increased daytime sleepiness. Cancer Causes Control 2006; 17: 583–589

we provide a list of genetic and syndromic causes of obesity associated with hypothalamic dysfunction.

Clinical Features

Accelerated weight gain and severe obesity are the most striking features of HyOb; they are caused by hyperphagia, reduced basal metabolic rate (BMR), and decreased physical activity. The accumulation of fat is usually very rapid; following surgery for craniopharyngioma, there is often a dramatic and progressive increment in BMI during the first 6 months. This is typically followed by a stabilization period with no reduction in BMI [25, 27].

Children with craniopharyngioma have greater risks for metabolic syndrome due to increased abdominal adiposity, higher fasting triglycerides, and lower HDL compared with healthy age-, sex-, BMI-, and pubertal stage-matched controls [30]. Nonalcoholic fatty liver disease (NAFLD) develops in about 50% of patients; the use of stimulants (such as modafinil) for treatment of daytime sleepiness may exacerbate hepatic dysfunction [31].

Interestingly, HyOb may exist in the absence of hyperphagia. Studies comparing children with craniopharyngioma and BMI-matched controls found no differences in eating behavior or the frequency of eating disorders [26]. It should be noted, however, that these studies were conducted months or years after surgical treatment. It is possible that initial weight gain is driven by hyperphagia resulting from hypothalamic damage and high-dose glucocorticoid therapy. Subsequently, obesity may be maintained by a reduction in energy expenditure (BMR and physical activity).

Indeed, physical activity is reduced to a far greater degree in hypothalamic obese patients than in simple obese patients and age-matched controls [3, 24]. It is exacerbated by concomitant visual or neurological problems, increased daytime sleepiness, and disturbances of circadian rhythms. The hypothalamic disturbance in sleep regulation results in low nocturnal and early morning melatonin levels. Based on this information, melatonin administration in children with craniopharyngioma has been suggested to improve physical activity and daytime sleepiness [32]. However, long-term studies are needed to evaluate the effect of the hormone in controlling BMI.

Patients with hypothalamic obesity often have sleep-disordered breathing (SDB), which may be associated with decreased melatonin production, disruption of circadian rhythms, and endocrine dysfunction [19] (see Chap. 28 on Sleep-Disordered Breathing and Sleep Duration in Child Obesity by Drs. Van Eyck and Verhulst). In one study 46% of children with central nervous system neoplasms involving the hypothalamus or thalamus had SDB [33]. Excessive daytime sleepiness and SDB are also common in Prader-Willi syndrome. Thus, routine polysomnography should be considered in children with hypothalamic obesity. Central stimulating agents (dextroamphetamine, methylphenidate) could be beneficial in these patients [34].

Risk Factors and Prevention for HyOb in Craniopharyngioma

As the currently available options are not very successful in treatment of HyOb, determination of risk factors and prevention of obesity are of prime importance. The first 6 postoperative months are crucial for preventing HyOb in

patients undergoing brain tumor surgery (Fig. 2.2). Factors predicting the development of HyOb in children with brain tumors are listed in Table 2.3. Hypothalamic involvement and hence, disturbance in energy balance contribute to the development of severe obesity and might explain why 12–19% of patients with craniopharyngioma develop obesity even before diagnosis. MRI findings at diagnosis can also provide postoperative risk assessment: patients who develop HyOb frequently have lesions involving the third ventricular floor, mammillary bodies, and anterior, medial, and most importantly posterior hypothalamus (Fig. 2.3a–d) [35] The development of

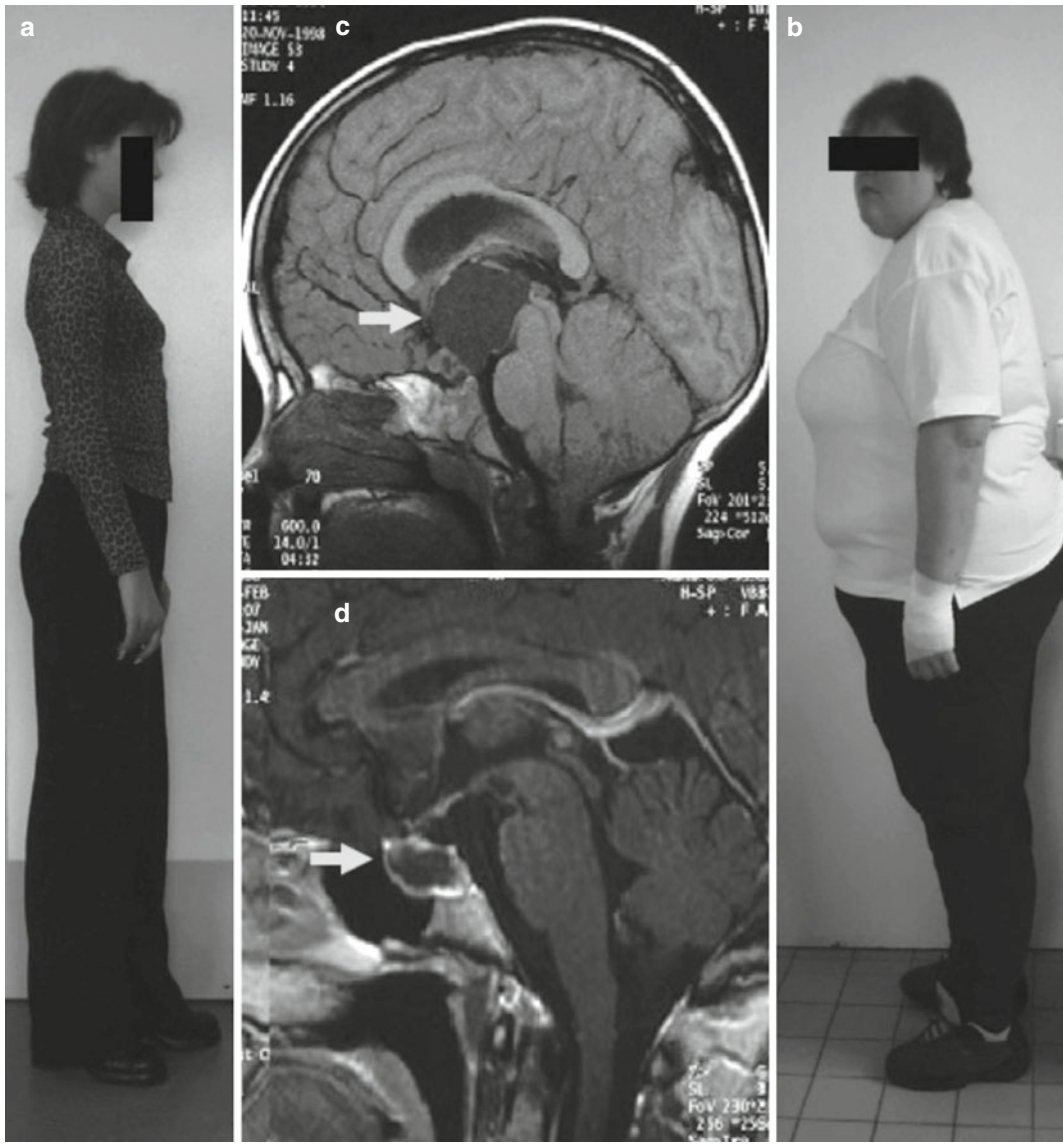

Fig. 2.3 (**a**–**d**) Development of obesity and localization of craniopharyngioma. Postoperatively, both patients had panhypopituitarism. The patient seen in (**a**) had a small tumor revealed by magnetic resonance imaging (MRI) (**d**), which was removed transsphenoidally. Postoperatively, the patient continued to have normal eating behavior, and her weight developed normally (body mass index [BMI]: +1.0 standard deviation [SD]). The patient whose preoperative MRI (**b**) showed a large tumor extending to the suprasellar region and infiltrating the hypothalamus went on to develop an eating disorder and, consequently, obesity (BMI, +14.0 SD) (**c**) (Used with permission of Springer Science from Müller HL et al. Kraniopharyngeom im Kindes- und Jugendalter. Monatsschr Kinderheilkd 2003; 151: 1056–1063)

Table 2.5 Fasting insulin, fasting glucose, resistin, and leptin levels in relation to hypothalamic involvement in HyOb and HyNOb patients

	HyOb			HyNOb		
	With hypothalamic involvement ($n = 17$)	Without hypothalamic involvement ($n = 6$)	p	With hypothalamic involvement ($n = 4$)	Without hypothalamic involvement ($n = 12$)	p
Fasting insulin (mU/L)	16.7 (9.1–24)	13.8 (9.6–16)	0.34	15.1 (10.3–20.2)	9.3 (6.1–13)	0.21
Fasting glucose (mmol/L)	4.3 (3.7–4.4)	4.3 (4–4.7)	0.98	4.4 (4.1–5.3)	4.3 (4–4.7)	0.30
Resistin (ng/mL)	2.8 (2.2–3.1)	1.9 (1.6–2.9)	0.21	2.2 (1.7–2.7)	3 (1.7–3.8)	0.24
Leptin (ng/mL)	119 (73–155)	35.2 (23–67)	0.02	75.7 (25.5–91.6)	17.7 (13–43.5)	0.01

Used with permission of Springer Science from Guran T, Turan S, Bereket A et al. The role of leptin, soluble leptin receptor, resistin, and insulin secretory dynamics in the pathogenesis of hypothalamic obesity in children. Eur J Pediatr 2009; 168: 1043–1048

central diabetes insipidus may serve as a marker of hypothalamic damage or dysfunction. Children who have hypothalamic tumor involvement have higher leptin levels than those without hypothalamic involvement (Table 2.5). Younger age at diagnosis is a risk factor unrelated to hypothalamic involvement; some authors argue that it is related to ongoing brain growth and myelinization until 4 years of age [28]. The dose of radiation (>51 Gy) is important for development of HyOb in older as well as younger children; it may be associated with cognitive dysfunction, fatigue, and attention deficits [28].

Multiple hormone deficiencies are common in craniopharyngioma, with frequencies ranging from 40 to 87% [24]. GH deficiency, hypothyroidism, hypogonadism, and hyperprolactinemia may contribute to weight gain in some patients (see Chap. 19 by Dr. Freemark on the Pathogenesis of Weight Gain in Endocrine and Metabolic Disorders). High-dose glucocorticoid treatment in the immediate postoperative period can exacerbate hyperphagia, but chronic replacement of hydrocortisone at physiologic replacement doses (5–8 mg/m^2/day) should not promote excess weight gain. As noted above, a recent study found diabetes insipidus to be an endocrine marker for HyOb risk [28, 35]. This may reflect disruption of the hypothalamic pituitary stalk and/or more severe hypothalamic damage or dysfunction. GH treatment of children with HyOb may reduce BMI in some cases. However, one study found that GH treatment had only a slight beneficial effect on the rate of gain in body weight [36].

Imaging studies indicate that the degree of obesity correlates with the degree and extent of hypothalamic damage. Reducing hypothalamic damage is therefore a major objective of neurosurgery. For unfavorably localized tumors, limited resection should be performed to preserve neural and vascular integrity and to avoid further damage to hypothalamic and optic structures [26]. Although there is no consensus about the optimal and standard therapeutic approach for pediatric craniopharyngioma, current strategies favor subtotal resection combined with postoperative adjuvant focal radiotherapy [24, 26]. Elowe-Gruau and colleagues found that this approach reduced the frequency of severe obesity and was associated with similar local recurrence rates when compared with complete resection [37]. Mallucci and colleagues suggested that comorbidities could be reduced in appropriate cases by drainage of tumor cysts followed by surgical resection [38]. In light of these findings, it seems that hypothalamus-sparing surgery combined with focal radiotherapy may limit the prevalence and severity of postoperative HyOb.

Mortality in Hypothalamic Obesity

As a well-known cause of HyOb, craniopharyngioma has the highest mortality rate in cases of tumors in the sellar region. The standardized mortality ratio in childhood-onset craniopharyngioma is 17 (95% Cl 6.3–37), which is higher

than observed in both adult-onset craniopharyngioma and other childhood central nervous system malignancies [39]. Increases in BMI-SDS >1 SDS after 6 months of tumor therapy are associated with higher mortality rates [27].

The causes of mortality in adults with HyOb include hypothalamic insufficiency (ACTH and ADH deficiencies), cardiovascular disease, myocardial infarction, type 2 diabetes mellitus, cerebrovascular disease, and sleep apnea [39]. In children, obstructive sleep apnea and central sleep apnea seem to be the predominant causes of death [27]. However, decreased sympathetic nervous system activity and increased parasympathetic nervous system activity play important roles: cardiac arrhythmias and severe sleep-disordered breathing (SDB) may increase the risk of sudden death [27]. The treatment of SDB requires a multidisciplinary approach involving a pediatric sleep physician, pediatric endocrinologist, exercise physiologist, and otolaryngologist. An evaluation for SDB via polysomnography should be performed during the early stages of HyOb, and noninvasive ventilation begun in those affected as soon as possible.

Treatment

We now have a greater understanding of the pathways regulating appetite and satiety and the mechanisms of HyOb development, yet there is still no curative therapy for HyOb. As in simple "exogenous" obesity, the first-line treatment is lifestyle modification. HyOb is often unresponsive to diet and exercise, but patients should be encouraged to adopt a healthy diet and to maintain regular physical activity to the extent possible. A multidisciplinary approach involving the parents and school may assist the child in controlling weight gain. Rakhshani and colleagues compared a comprehensive care clinic (CCC) model, which includes medical, behavioral, dietary, and exercise support and with a standard care model in post-op children with brain tumors. They found that percent weight gain, percent of ideal body weight, and increment in BMI were lower in the CCC model; children also reported improved quality of life, physical functioning, and school performance [40].

Pharmacological Treatment

Patients with HyOb have impaired sympathoadrenal activation, so treatment with sympathomimetic agents has been recommended to decrease weight gain. The use of dextroamphetamine in five children with HyOb following surgery for craniopharyngioma reduced the rate of weight gain and stabilized BMI during a 24-month treatment protocol. Caloric intake did not change during treatment, but spontaneous physical activity increased significantly [34]. Another study showed similar effects, with weight stabilization and improvements in daytime wakefulness observed in 12 hypothalamic obese children treated with dextroamphetamine [41]. Additionally, caffeine and ephedrine administration in three children with HyOb resulted in weight loss in two of them [42]. Larger studies of efficacy are needed before suggesting dextroamphetamine for HyOb treatment. Moreover, chronic sympathomimetic therapy can increase heart rate and blood pressure and may thereby increase long-term cardiovascular risk.

Parasympathetic hyperactivity causes hyperinsulinemia, which has a critical role in weight gain associated with hypothalamic disease. Hence, inhibition of insulin secretion with somatostatin analogs was attempted as a means for treating HyOb. In a double-blind, randomized controlled study, octreotide caused significant reduction in weight gain in children with HyOb due to brain tumors or radiotherapy [43]. However, a larger multinational study with octreotide-LAR in 60 patients with HyOb was terminated because of ineffectiveness in reducing BMI [44]. In addition, serious side effects including gallstones, abdominal discomfort, and flatulence were reported in these studies [43, 44]. A pilot study treating adolescents with HyOb with a combination of diazoxide (which inhibits insulin secretion) and metformin showed reductions in weight gain and BMI [45]. However, a follow-up placebo-controlled investigation found that

diazoxide alone had no effect on weight gain after 2 months of treatment [46].

Decreased sympathetic nervous system activation and a possible reduction in type 2 deiodinase activity in HyOb [47] have stimulated interest in clinical trials using triiodothyronine (T3). In three patients, significant weight loss was reported with no symptoms of hyperthyroidism [47]. Inhibitors of 11β-HSD1 are potential therapeutic agents, but their use has not yet been explored.

A possible alternative approach could entail the use of analogs of glucagon-like peptide-1 (GLP-1). GLP-1 reduces food intake and body weight via direct effects in arcuate nucleus [6]. In a recent study, the GLP-1 analog liraglutide 3.0 mg caused loss of more than 10% of body weight in one-third of 3731 obese adults; however, adverse events (nausea, vomiting, diarrhea) were common, and gallbladder disease and/or pancreatitis occurred in 6.2% of the patients [48]. Zoicas and coworkers used a GLP-1 analog in nine (eight exenatide, one liraglutide) adult patients with HyOb; eight also had T2DM. Although one patient withdrew quickly because of intolerable nausea and vomiting, there was substantial weight loss in the remaining eight patients (−13.1 ± 5.1 kg (range −9 to −22). Insulin resistance and HbA1c levels also improved [49]. Substantial and sustained weight loss with exenatide or liraglutide was observed in other cases of HyOb (one patient was 17 years old), with no severe side effects [50, 51]. Additional trials seem warranted.

Although an effect of melatonin on weight gain in humans with HyOb has not yet been demonstrated, studies in rats observed that administration of a melatonin agonist (NEU-P11) or a MT1/MT2 receptor agonist (ramelteon) decreased body weight and increased insulin sensitivity in rats [52, 53]. These studies suggest potential new options for treatment of HyOb.

Finally, a recent study showed that a pharmacologic agonist (setmelanotide) for the melanocortin 4 receptor (MCR4) reversed hyperphagia and caused impressive weight loss (51 kg after 42 weeks and 20.5 kg after 12 weeks) in two patients with mutations in POMC [54]. Whether or not MCR4 agonists would reduce body weight in patients with postsurgical HyOb is currently unclear.

Surgical Treatment

Bariatric surgery has proved effective in the treatment of patients with severe obesity and comorbidities. The number of adolescent patients who have undergone bariatric surgery is increasing, and the outcomes thus far are comparable or better than those seen in adults [55, 56].

As recommended by the ASMBS (American Society for Metabolic and Bariatric Surgery) pediatric guidelines in 2012, the selection criteria for bariatric procedures in adolescents should include a BMI ≥35 kg/m^2 with major comorbidities (type 2 diabetes mellitus, moderate to severe sleep apnea, pseudotumor cerebri, or severe nonalcoholic steatohepatitis) or a BMI ≥40 kg/m^2 with other comorbidities (hypertension, insulin resistance, glucose intolerance, substantially impaired quality of life or activities of daily living, dyslipidemia, and mild sleep apnea) [55]. Furthermore, the teenager should have completed or nearly completed skeletal and sexual developmental (95% of linear growth or Tanner IV). Nevertheless, the severity of the weight gain in HyOb places even a young teenager at risk of life-threatening complications that may outweigh the theoretical risk of growth impairment following surgery [56].

There is as yet no randomized controlled study of bariatric surgery in adolescents with postsurgical HyOb and very limited experience with surgical procedures in the prepubertal period. On the other hand, a recent study demonstrated significant weight loss in 24 children (4.9–18 years, mean age 10.7) with Prader-Willi syndrome who underwent laparoscopic sleeve gastrectomy. Patients lost 14.7% (n = 22) and 10.7% (n = 7) of body weight by the first and fifth annual visits, respectively; 95% of comorbidities remitted or improved with no postoperative complications [57]. A meta-analysis of the effects of bariatric surgery in postsurgical adolescents and adults with craniopharyngioma found net weight loss of

6.1% after 12 months ($n = 6$) in the group receiving adjustable gastric bands, 20.2% ($n = 6$) in the group undergoing Roux-en-Y gastric bypass, 19.6% ($n = 8$) in the patients subjected to vertical sleeve gastrectomy, and 24.8% in the single patient undergoing biliopancreatic diversion. Long-term studies are needed to define appropriate selection criteria and the optimal procedure(s) for bariatric surgery in HyOb [58].

Conclusion

Hypothalamic obesity (HyOb) is a complex neuroendocrine disorder caused by damage to the hypothalamus, which results in disruption of energy regulation. This devastating problem can have profound effects on morbidity and mortality. Conventional lifestyle modification usually fails, and there is at present no curative pharmacologic treatment. Although several agents have been used to treat HyOb, the results are inconclusive and generally unsatisfactory. Thus, the clinician should be alert and vigilant in patients at risk for development of HyOb; prevention and management of HyOb should begin before neurosurgery and should provide an intensive and comprehensive multidisciplinary approach when weight gain begins.

Editor's Comments and Questions

1. Hypothalamic obesity is an intractable problem resulting from defects in α-MSH signaling, central resistance to the actions of leptin and insulin, vagal hyperactivity, glucocorticoid therapy, and reductions in resting and physical activity energy expenditure. Untreated GH deficiency, central hypothyroidism, hypogonadism, and hyperprolactinemia may exacerbate weight gain in postsurgical patients.

   Once established, severe adiposity is difficult or impossible to reverse without bariatric surgery. Ideally this might be avoided if excess weight gain could be prevented. I generally warn families from the outset about the risks for hypothalamic obesity and suggest that they begin to limit the child's intake of sugary drinks, fast foods, and starches even *before* tumor resection. I also consider pharmacologic intervention *prior to* obvious weight gain in those at high risk, as defined by the size and locale of the lesion, the surgical outcome, and the feeding behavior in the postoperative period. For that purpose I have used metformin, with variable (and somewhat limited) success. I do not begin pharmacotherapy prior to hospital discharge and strongly encourage ongoing compliance with dietary restriction. What are your thoughts about this approach?

2. While initial responses to GLP-1 analogs are promising, their use may be problematic in perioperative patients treated with high-dose glucocorticoids, which can exacerbate gastritis and potentiate the risks of pancreatitis[a]. The initial response to setmelanotide was dramatic in two adults with POMC mutations[b]. In theory, postsurgical patients with hypothalamic obesity would fail to respond to MCR4 agonists because of structural damage to α-MSH-responsive centers. However, there might be gradations of hypothalamic damage and dysfunction among children undergoing hypothalamic surgery, such that some response to agonist might be retained in some patients. This possibility awaits formal investigation; nevertheless, do you agree with the general concept?

Authors' Responses

1. We completely agree with you. From the beginning, families should be informed about the risk of development of HyOb and the changing of eating

habits before operation. Also, frequent visits after hospital discharge are necessary especially for the first year. For prophylactic pharmacotherapy, we think that we need controlled studies for recommendation of this kind of treatment.

2. Yes. We agree with the general concept. Although GLP-1 analogs seem to be a good option for HyOb patients, their side effects cannot be ignored. So they might be used in selected patients who are not in the perioperative period and are stable in terms of hormone replacement. We also think that setmelanotide deserves a trial.

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3 Gastrointestinal Hormones and the Control of Food Intake and Energy Metabolism

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Introduction

The gastrointestinal (GI) tract is the largest endocrine organ in the body, and regulatory factors released from the gut into the circulation play essential roles in motility, digestion, and metabolism. Work over the last several decades has also identified GI peptides that contribute to the control of satiety, food intake, and energy balance. A wide range of preclinical and clinical research now implicates the gut as a nutrient sensor as well as portal of entry, and both endocrine and neural signals connect the GI tract to regions of the central nervous system (CNS) that regulate eating and metabolism [1, 2].

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The epithelium of both the small bowel and colon contains specialized cells that produce hormones. These enteroendocrine (EE) cells are derived from stem cell precursors in the intestinal crypts and turn over (are sloughed and renewed) every 3–60 days. EE cells comprise only 1–2% of mucosal cells but given the large surface area of the intestine constitute a substantial mass of endocrine tissue. Initial characterization of EE cells suggested specific types that produced a major single product, e.g., G-cells producing gastrin, S-cells secretin, I-cells cholecystokinin (CCK), K-cells glucose-dependent insulinotropic polypeptide (GIP), X/A-cells ghrelin, and L-cells glucagon-like peptide 1 (GLP-1) and peptide tyrosine-tyrosine or peptide YY (PYY). However, recent evidence suggests that EE cells express the genes for several peptides and probably have some plasticity to respond to changing environmental cues by modifying their products. There is a distinct geographic distribution of the cell types, with G-cells and X/A-cells located primarily in the mucosa of the stomach; I-, S-, and K-cells in the upper intestine; and L-cells in the distal small bowel and colon.

While the term "enteroendocrine" emphasizes hormonal products, an equally accurate depiction of these cells is as nutrient sensors. Most intestinal EE cells have direct contact with digesting nutrients and other luminal contents, and these products are the principle stimuli for hormone release. Glucose, fatty acids, peptides, and amino

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acids all activate specific EE cells to differing extents, through either absorption or interaction with specific receptors on the cell surface. Some EE cells express the same receptors as taste buds in the tongue, and parallels have been drawn between gustatory and enteroendocrine signaling [3]. In addition, recent evidence suggests that factors produced by intestinal microbes can also stimulate the release of gut hormones [4].

While the discovery of secretin more than 100 years ago was the first direct evidence for an endocrine mechanism of action, recent findings attest to important connections between EE cells and neurons [5]. The mucosa of the GI tract is richly innervated with connections to the extensive enteric nervous system. In addition, external sensory afferents carried by the vagus and spinal nerves also provide gut-brain communication. Finally, it is clear that autonomic fibers provide efferent signals from the CNS that regulate GI function. Thus, many of the gut hormones, such as ghrelin, CCK, and GLP-1, are also likely neurotransmitters.

The widespread increase in bariatric surgery as a treatment for obesity has intensified interest in GI endocrinology because several of the gut hormones are implicated in the response to treatment. In particular, secretion of the L-cell products GLP-1 and PYY, which promote satiety, is greatly amplified after surgery, while ghrelin, which stimulates appetite, is reduced in many patients [6]. Moreover, circulating concentrations of bile acids, which have endocrine actions, are increased after surgery and may mediate some of the salutary effects on weight and metabolism [7, 8]. The associations between GI hormones and the clinical benefits of bariatric surgery have enhanced interest in developing various hormonal compounds as therapeutics.

Overview of Gastrointestinal Hormone Physiology

The gastrointestinal hormones rise and fall in relation to meals and the types of nutrients consumed (Table 3.1 and Fig. 3.1). Additional factors, including circulating and neural regulators, body weight, and GI pathology, also affect gastrointestinal hormone secretion. Although these patterns are well characterized in adults, studies in children are limited. While we have included pediatric information when available, the majority of data presented below was collected in adults.

Control of GI Hormone Release by Food Intake

Ghrelin is a 28-amino acid peptide secreted mainly by the X/A-like cells of the stomach but also by the small intestine and epsilon cells of the pancreas [9–11]. Ghrelin exists as two isoforms: acyl and desacyl ghrelin, with desacyl

Table 3.1 Physiology of gastrointestinal hormones important to food intake

Hormone	Primary location of release	Pattern of release	Nutrients effects	Half-life
Ghrelin	X/A-like cells stomach	Peaks *preprandially*, falls 30–60 min after eating	Proteins: best suppress, followed by carbohydrates	9–11 min
GLP-1	L-cells ileum, colon	Secreted *postprandially* in a biphasic pattern: early phase occurs 10–15 min after eating	Carbohydrates and fat: best stimulate release	1–2 min
CCK	I-cells duodenum, jejunum	Rises *postprandially* within 15 min of eating, falls over 3–5 h	Fat and protein: best stimulate release	1–2 min
PYY	L-cells terminal ileum, colon, rectum	Rises *postprandially* within 30 min of eating, peaks 1–2 h after eating, falls over 6 h	Fat: best stimulates release	15 min
FGF19	Ileum enterocytes	Rises *postprandially* 90–180 min after eating	Proportionate to bile acid levels	Biphasic, dose-dependent

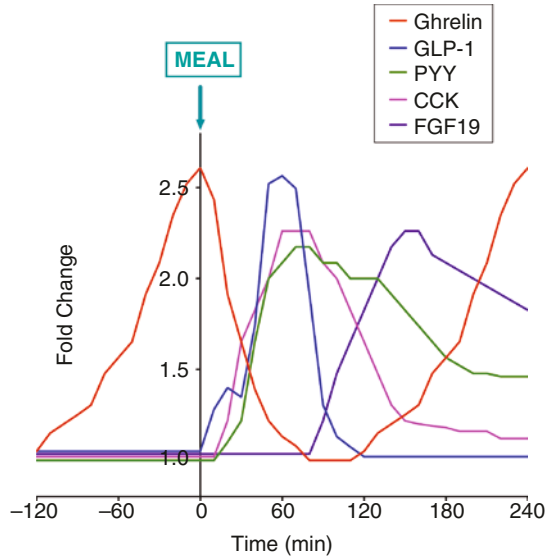

Fig. 3.1 Schematic depicting the responses of gastrointestinal hormones to a meal. Ghrelin rises preprandially, peaking just before a meal and then falls quickly afterward. The other gastrointestinal hormones (GLP-1, PYY, CCK, and FGF19) peak postprandially. Factors including subject characteristics (weight status, insulin resistance, medication exposure, diseases) and meal composition influence the maximum level each hormone reaches and the time to nadir. This figure is meant to serve as a stylized depiction of the changes of gastrointestinal hormones in response to food intake, recognizing that these responses can be quite variable

ghrelin being more prevalent in the circulation [12]. Conversion to acyl ghrelin is catalyzed by the enzyme ghrelin O-acyltransferase (GOAT); acylation allows ghrelin to bind to its only known receptor, the growth hormone secretagogue receptor 1a (GHSR1a) [9, 13]. Although some studies suggest that desacyl ghrelin may promote glucose-stimulated insulin secretion and have cardiovascular protective properties, no receptor has been identified, and its significance in humans is unclear [14–16]. Thus, the focus of most research, and the following discussion, is on acyl ghrelin.

Acyl ghrelin rises before meals and falls 30–60 min after eating, with levels varying two–threefold between the fasting and fed states [12, 17, 18]. Concentrations of ghrelin are maximally suppressed by meals high in protein or carbohydrates, although levels rebound 1–2 h after high carbohydrate consumption in adults and prepubertal children [18, 19]. The half-life of acyl ghrelin is approximately 9–11 min, with deacylation by esterases and clearance by the liver contributing to elimination [20]. In a study of premature infants, ghrelin levels decreased postprandially soon after birth and at 15 days of life, suggesting that this pattern is established early in development [21]. In general, baseline ghrelin levels appear to increase in the first 2 years of life, with a subsequent decline to adult levels during puberty [22–24].

Coincident with the fall in ghrelin levels after feeding, there are significant increases in a variety of other GI peptides including GLP-1, CCK, PYY, and FGF19.

Glucagon-like peptide 1 (*GLP-1*) is a 30-amino acid product of the proglucagon gene that is synthesized and released by intestinal L-cells primarily in the lower jejunum, ileum, and colon [25, 26]. Nutrient ingestion is the primary stimulus for GLP-1 secretion. In many studies, GLP-1 release follows a biphasic pattern, with an early pulse of peptide detected within 10–15 min of a meal followed by a longer secondary phase [27]. Circulating concentrations of GLP-1 rise two–threefold after a meal, are proportional to meal size, and depend on nutrient composition, with fat and carbohydrate

causing greater prandial increases than protein [28]. The half-life of GLP-1 in the circulation is quite short, only 1–2 min, as the hormone is rapidly degraded by the enzyme dipeptidyl peptidase (DPP-IV) [29].

GLP-1 levels rise postprandially in preterm and term neonates as well as older children and adults [30]. However, fasting and fed GLP-1 levels are higher in neonates than adults, possibly due to decreased clearance [30]. As GLP-1 promotes replication of pancreatic beta cells, it has been suggested that elevated GLP-1 levels may be important for the substantial increase in pancreatic beta cell mass in infancy [30]. Interestingly, baseline GLP-1 levels at 4 months of age are higher in formula-fed small-for-gestational-age (SGA) infants than in breastfed SGA and appropriate-for-gestational-age infants [31]. This finding may have implications for food intake and weight gain later in life, but additional studies are needed to confirm this hypothesis.

Cholecystokinin (*CCK*) is produced by I-cells of the duodenum and jejunum and exists as multiple molecular forms derived from procholecystokinin [32]. CCK-8 and CCK-33 are thought to have the greatest effect on appetite and food intake [33, 34].

Levels of CCK rise approximately 15 min after meal initiation and gradually fall over the next several hours [35]. Release is primarily stimulated by protein and fat consumption [36]. CCK is degraded by aminopeptidases and its half-life is 1–2 min [37]. Breastfed neonates appear to have biphasic CCK release with an initial peak immediately after breastfeeding and a second rise 30–60 min later [38]. A study in premature infants showed increased postprandial CCK levels on day 1 of life, but this was not replicated in infants 3–4 days old [39]. Baseline CCK levels also appear to be elevated in infants compared to adults [38].

Peptide YY (*PYY*) exists in two major isoforms, $PYY_{1–36}$ and N-terminally truncated $PYY_{3–36}$, which forms following cleavage of $PYY_{1–36}$ by the enzyme DPP-IV [40]. PYY is secreted by intestinal L-cells with production increasing distally between the terminal ileum and the rectum [41]. The bulk of research suggests that only the $PYY_{3–36}$ isoform affects food intake and weight [42]; a definitive physiologic role for $PYY_{1–36}$ has not been demonstrated.

PYY rises within 30 min of eating, peaking 60–120 min postprandially, with maximal release in response to fat in adults and protein in children [19, 37, 43]. Levels then fall slowly over a period of hours [43]. PYY has a 15-min half-life, longer than the previously discussed gastrointestinal hormones, and its elimination occurs via degradation by peptidases [44]. Baseline PYY levels are higher in preterm and term infants than in older children and adults but similarly rise in response to feeding [45, 46].

Fibroblast growth factors (*FGF*) *19 and 21* are members of the FGF family that is comprised of 22 members and 7 subfamilies [47]. The FGF19 subfamily includes FGF19, FGF21, and FGF23. FGF19 activates mainly FGF receptor 4 (FGFR4), whereas FGF21 and FGF23 signal predominantly via FGFR1c and FGFR2c [48]. FGF19 is secreted by the intestines during feeding and negatively regulates bile acid synthesis and secretion, whereas FGF21 is produced in the liver during fasting and plays an important role in the regulation of glucose and lipid metabolism [49].

FGF19 is a product of the FGF19 gene on chromosome 11q13.1, which codes for a 216-amino acid protein [50]. Much of the current understanding of FGF19 physiology comes from rodent studies of FGF15, the mouse ortholog of the human protein. FGF19 is produced by enterocytes of the ileum and released in response to binding of reabsorbed bile acids to the farnesoid X receptor (FXR) [51, 52]. Once released into the circulation, FGF19 binds selectively to FGFR4, which is a tyrosine kinase surface receptor highly expressed in hepatocytes. Binding of FGF19 to FGFR4 activates the receptor and causes suppression of hepatic CYP7a1 transcription [50, 52]. The CYP7a1 gene codes for cholesterol 7a-hydroxylase, the rate-limiting step of bile acid synthesis, and as such FGF19 has an enteroendocrine role as a regulator of bile acid synthesis. Human studies have shown that FGF19 levels peak 1.5–3 h after a meal in a pattern that follows the increased intra-intestinal flow of bile acids [53].

FGF19 levels also play an important role in hepatic nutrient handling. When FGF19 levels are elevated, hepatic glycogen stores are increased, a process that is also regulated by insulin [51]. FGF19 also inhibits hepatic gluconeogenesis and stimulates hepatic protein synthesis [51, 54, 55]. These actions suggest that FGF19 mimics the actions of insulin at least in the liver but in a time-delayed fashion compared to the earlier postprandial rise of insulin. However, in contrast to insulin, FGF19 decreases hepatic lipogenesis and hepatosteatosis in the setting of a high-fat diet [56]. In rats, FGF19 suppresses the hypothalamic-pituitary-adrenal axis, an effect that has been connected with its inhibitory effect on hepatic glucose production [55]. While central nervous system actions have not been established in humans, this finding adds further support to an endocrine function of FGF19 [55].

The human *FGF21* gene was first identified in the liver [57], where it is predominantly expressed; lesser amounts are expressed in the adipose tissue, skeletal muscle, heart, kidney, and testes. Metabolic, cellular, nutritional, and environmental stresses such as fasting or starvation, endoplasmic reticulum stress, oxidative stress, obesity, and cold exposure can all upregulate FGF21 expression, suggesting an adaptive role to maintain homeostasis [49]. One of the main targets of FGF21 is white adipose tissue (WAT) where FGF21 regulates aspects of the fasting response and stimulates glucose uptake [52, 58]. FGF21 mediates its function via the transmembrane receptor β-klotho, a FGFR co-receptor with high expression in the liver, fat, and the central nervous system. Recent studies have demonstrated that FGF21 treatment leads to increased brown adipose tissue (BAT), increased UCP1 expression, and decreased body weight [59, 60] (see also Chap. 7 on Brown Adipose Tissue and Body Weight Regulation).

Effects of the GI Hormones on Food Intake, Weight Gain, and Energy Expenditure

The physiologic variations in gastrointestinal hormone levels suggest that they may modulate feeding behavior. Experimental manipulation has delineated a clear role in hunger or satiation for some of these hormones, while data for others remain mixed (Table 3.2). Very few of these studies have focused on children or adolescents. In this section, we discuss evidence from basic and clinical research that gastrointestinal hormones may regulate energy balance.

Ghrelin is the only known orexigenic gastrointestinal hormone. In rodents, exogenous ghrelin promotes hyperphagia and weight gain [61] and increases adiposity independent of food intake through decreased fat utilization [62]. Not surprisingly, antagonism of the GHSR and inhibition of GOAT induce weight loss in mice [63, 64]. However, KO models yield variable results in terms of food intake and obesity. Ghrelin KO mice have normal body weights and feeding behaviors [65], while GOAT KO mice have decreased food intake and mesenteric adipose stores on high-fat, high-sucrose diets [66]. GOAT KO mice also have slightly increased energy expenditure, with a trend toward increased locomotor activity [66].

In humans, exogenous ghrelin increases food intake at a buffet meal in both lean and obese individuals [67]. Participants report increased

Table 3.2 Role of gastrointestinal hormones in appetite, weight gain, and energy expenditure and mechanism of action

Hormone	Effect on appetite	Effect on weight	Effect on energy expenditure	Proposed location/mechanism of action
Ghrelin	↑↑↑	↑? **(mixed)**	**?**	Hypothalamus and limbic system
GLP-1	↓↓↓	↓↓	**?**	Hypothalamus, limbic system, and possibly vagal afferents
CCK	↓**?**	↓**?**	**?**	Vagal afferents, decreased gastric emptying
PYY	↓↓**?**	↓**?**	↑**?**	Hypothalamus +/− limbic system
FGF19	?	↓	↑	Hypothalamus

"hunger" and decreased "satiation" scores after receiving ghrelin [67], and no compensatory under-eating occurs following the infusion [61]. Interestingly, ghrelin positively correlates with fat mass percentage at 3 months of age, a finding suggestive, but not definitive, of a role in energy balance in early life [23]. Several naturally occurring GHSR mutations have been described in humans [68]. Although these mutations cause loss of function or have no obvious effect on function, some have been phenotypically associated with short stature and, surprisingly, obesity [68].

In rodents and humans, *GLP-1* reduces food intake in a dose-dependent manner [69, 70]. This effect likely explains the weight reduction observed in diabetic patients treated with GLP-1 receptor agonists. GLP-1 infusions reduce composite appetite scores while increasing the sensation of fullness [71, 72], and GLP-1 agonists cause a significant BMI reduction in obese individuals, including adolescents [73–75]. Consistent with these effects, central administration of a GLP-1 antagonist in rodents results in hyperphagia and weight gain, mostly due to increased fat mass [76].

The effect of GLP-1 on energy expenditure is less clear as some human studies show no changes [77, 78], while another found that a GLP-1 agonist slightly reduced energy expenditure [72]. In the latter study, however, there was a nonsignificant trend toward increased fat oxidation in treated subjects [72]. Similar to ghrelin, several single nucleotide polymorphisms (SNPs) have been identified in the human GLP-1R, but their roles in disease states including obesity have not yet been elucidated [79].

The effect of *CCK* on appetite and weight gain is also unclear. In rats, exogenous CCK decreases food intake in a dose-dependent fashion [80]. However, this effect appears to be short-lived. When given chronically over 7 days, CCK has no effect on body weight or food intake [81]. Findings also vary by animal model. Rats lacking a CCK1R are hyperphagic and develop obesity early in life due to excess food intake [82]. CCKR antagonism in rats also increases food intake [83]. In contrast, CCK1R KO mice do not have increased energy consumption and maintain a normal body weight [84].

CCK infusions have a dose-dependent suppressive effect on energy intake in obese and normal-weight humans [85–87], but data on appetite are mixed. One study showed decreased preprandial hunger and increased fullness with CCK infusion [88], while others found no effect on appetite, hunger, or fullness ratings [85, 87]. Similarly, CCKR blockade with loxiglumide had variable outcomes, with no effect on hunger, fullness scores, or food intake in one study [89] and slightly increased caloric intake and hunger sensation in another [90]. Interestingly, CCK-related polymorphisms have been associated with higher percent body fat and propensity to large meal sizes [91, 92].

In rodents, exogenous *PYY* decreases food intake and weight gain [93]. Data from PYY KO mice are conflicting, with some studies finding hyperphagia, increased food intake, and increased fat mass [94] and others showing no difference between the KO and WT mice [95]. PYY overexpression has no effect on body weight in mice fed a normal diet but reduces adiposity in mice fed a high-fat diet, possibly by increasing thermogenesis [96].

In both obese and normal-weight humans, PYY infusions decrease hunger scores, buffet meal consumption, and 24-h cumulative food intake [97]. PYY may also affect energy expenditure in humans, as higher levels of fasting and postprandial PYY are associated with a lower respiratory quotient [98] and exogenous PYY results in a trend toward increased energy expenditure [99]. Several PYY-related polymorphisms may contribute to obesity and other traits associated with metabolic syndrome [100, 101]. One specific variant is associated with childhood, but not adult, obesity [102].

A physiologic role for *FGF19* in the control of food intake has not yet been elucidated. It appears that the type of diet may have a significant impact on how acute changes in FGF19 affect food intake. In mice fed a high-fat diet, acute administration of FGF19 did not change food intake in one study; however, another study showed a 25% reduction in food intake in chow-fed mice and a 20% reduction in food intake in high-fat-fed mice [103, 104]. This effect is likely

mediated by binding of FGF19 to FGFR4 receptors in the hypothalamus [104]. Accordingly, CNS-specific FGFR4 inhibition increases food intake [103, 104].

FGF19 has had more pronounced effects on metabolic rate and body weight. Transgenic mice expressing FGF19 had significant weight loss despite high-fat diet. They also had increased metabolic rate with lower respiratory quotient [103, 105]. Weight loss was accompanied by a compensatory increase in food intake [105]. Studies with acute injections of FGF19 showed similar increases in metabolic rate but only after 5 days of treatment, implicating changes in gene expression rather than direct endocrine hormone action. Several mechanisms have been proposed as the cause of this increased metabolic rate, including increased BAT thermogenesis, increased hepatic lipid oxidation, and increased hepatic leptin receptor expression [103]. How these findings translate to humans given exogenous FGF19 has not yet been addressed.

Like FGF19**,** *FGF21* is thought to be an important regulator of whole-body energy expenditure and metabolism. Evidence is accumulating that FGF21 is involved in the regulation of BAT and browning of WAT (see Chap. 7 on Brown Adipose Tissue and Body Weight Regulation). Upon cold exposure or beta-adrenergic stimulation, FGF21 expression from BAT increases [106, 107], and FGF21 KO mice display an impaired response to cold exposure [108]. Pharmacological FGF21 treatment or overexpression of FGF21 gene increases expression of thermogenesis genes in BAT [108, 109]. Interestingly, the effect on weight loss persists when FGF21 is administered to UCP1 KO mice, suggesting that it is independent of BAT [60]. In view of the metabolic benefits of FGF21, efforts have been adopted to enhance the action of FGF21 with FGFR1/β-Klotho agonist and to develop FGF21 agonists. The first proof of concept clinical study was performed using daily subcutaneous injection of FGF21 analogue LY2405319 in obese subjects with type 2 diabetes [110]. LY2405319 caused significant improvement in dyslipidemia and showed favorable effects on body weight, fasting insulin, and adiponectin but had no significant effect on glucose lowering. These results indicate that FGF21 is bioactive in humans and that FGF21-based therapy may exert favorable effects on metabolic function.

Mechanisms by Which GI Hormones Promote Hunger or Satiation

GI hormones may promote hunger or satiety through actions on the central nervous system and/or the gastrointestinal tract itself (Table 3.2, Fig. 3.2). Within the central nervous system, the hypothalamus, which contains neurons expressing orexigenic and anorexigenic peptides, is critical to food intake and energy balance (see also Chap. 2 on Central Control of Energy Metabolism and Hypothalamic Obesity). Although the ability of GI hormones to cross the blood-brain barrier is controversial, there is evidence that certain hormones access the arcuate nucleus as well as the limbic system. For other hormones, action on gastrointestinal vagal afferents provides signals to the brainstem, which in turn can influence or potentiate the effects of gastric acid secretion, gastric distention, and/or gastric emptying. These complicated feedback loops are only beginning to be understood, with much of the data coming from animal models. Recently, however, functional MRI (fMRI) has enhanced our understanding of this complex system.

The orexigenic properties of *ghrelin* appear to be primarily mediated centrally. The ghrelin receptor is expressed in a variety of brain tissues including the arcuate nucleus of the hypothalamus [111, 112], and ghrelin has been shown to access the arcuate nucleus through the fenestrated capillaries of the median eminence [113]. Intracerebroventricular administration of ghrelin increases the expression of the orexigenic peptides neuropeptide Y (NPY) and agouti-related peptide (AgRP) and stimulates food intake in rats [114]. In vitro studies have also shown inhibition of POMC neurons by ghrelin [115].

In addition to the hypothalamus, the ghrelin receptor is found in the mesolimbic pathway [116, 117], suggesting that ghrelin may also be

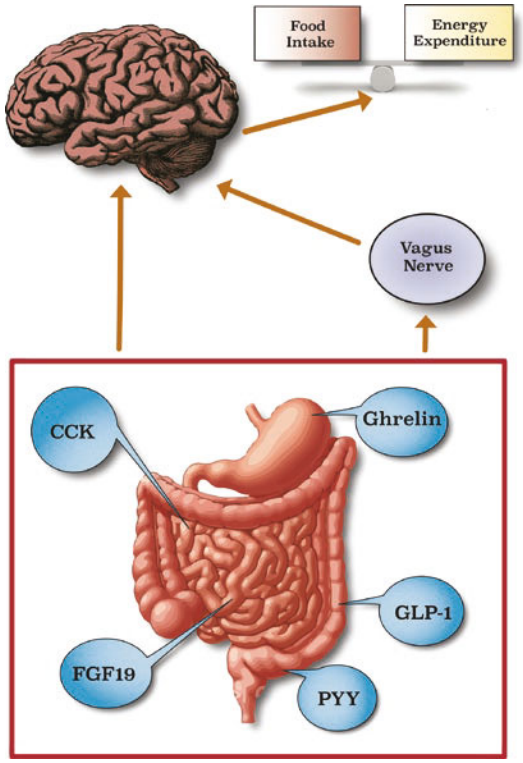

Fig. 3.2 Major gastrointestinal hormones thought to affect energy balance through food intake and/or energy expenditure. GI hormones may act directly on the CNS, specifically the hypothalamus, which regulates appetite and food intake, or indirectly, with vagal afferents serving as an intermediary between the gastrointestinal tract and brain. Direct action on the hypothalamus is likely for ghrelin, GLP-1, PYY, and possibly FGF19. Ghrelin, GLP-1, and PYY may also act on the limbic system, which is important to the hedonic aspects of food. Conversely, CCK acts primarily through vagal afferents, which may also play a role in the actions of GLP-1. Many of these pathways, and particularly the importance of interactions with other hormones within and outside of the gastrointestinal tract, remain unclear with limited data currently

involved in the motivational and reward aspects of food. Multiple rodent studies have shown that ghrelin injected into the limbic system's ventral tegmental area (VTA) increases food intake [116, 118] as well as incentive motivation for sucrose [119, 120], chocolate [121], and a high-fat diet [122]. Furthermore, peripheral ghrelin injections increase neuronal signaling on) fMRI in the amygdala and orbitofrontal cortex of healthy volunteers [123]. Ghrelin also increases gastric acid secretion and gastric motility; however, it is unclear how much these effects contribute to the orexigenic properties of ghrelin.

GLP-1 is produced by neurons in the nucleus tractus solitarius [124] as well as intestinal L-cells. Thus, pathways of GLP-1 action must consider both centrally and peripherally derived peptide. The GLP-1 receptor is found in the hypothalamus, including the arcuate nucleus and paraventricular nucleus, medulla, and parietal cortex [125, 126], and most of the effects of GLP-1 on food intake appear to be centrally mediated. Accordingly, rats have lower food intake following intracerebroventricular, but not intraperitoneal, injections of GLP-1 [127]. Similarly, food intake is reduced in GLP-1-treated rats despite vagotomy [128]; moreover, body weight and energy balance remained unchanged in rats after knockdown of GLP-1 receptors in vagal afferent nerves, despite increased rates of gastric emptying [129]. However, vagal afferent signaling may still account for some of the effects of GLP-1 on satiation. While GLP-1 can cross the blood-brain barrier [130], the short half-life of the peptide suggests that the hormone may act preferentially in the gastrointestinal tract under physiologic conditions. This might not be the case in humans and rodents treated with inhibitors of DPP-IV.

GLP-1 signaling may also be involved in food reward. fMRI studies show that the GLP-1 agonist liraglutide decreases activation of the parietal cortex to highly desirable food images (125). In mice, GLP-1 also decreases mesolimbic dopamine signaling, which was associated with decreased intake of high-fat foods [131].

Although the role of *CCK* in appetite control and weight gain is not entirely clear, the peptide does slow gastric emptying [132] and may signal satiation through this mechanism. CCK stimulates gastric and duodenal vagal afferent activity in rats [133, 134], and vagotomy decreases the satiety effect of CCK [135]. These gastrointestinal vagal afferents project onto the nucleus tractus solitarius, which subsequently signals the hypothalamus. Demonstrating the importance of this hindbrain pathway, rat midbrain transection

blocks CCK from potentiating the effects of leptin on food intake [136]. CCK has also been found in the hypothalamus and limbic system of rats [137], but its direct effects in these areas are not well explored.

While *PYY* prolongs gastric emptying and intestinal transit in healthy humans [138], its effects on appetite seem to be mediated centrally in the hypothalamus [139, 140]. PYY has been shown to cross the blood-brain barrier in mice, likely through transmembrane diffusion [141]. Once there, it binds to the Y2 receptor in the arcuate nucleus, where it appears to exert some of its effects on appetite by decreasing NPY activity [93, 142]. As with ghrelin and GLP-1, fMRI has yielded additional information on the effects of PYY in humans, with increased activity in the hypothalamus and limbic system during PYY infusion [143]. This finding suggests a potential role of PYY in the hedonic aspects of food. PYY also increases vagal afferent signaling [144], similar to CCK, but the contribution of these vagal afferents to the satiety effects of PYY is debated due to conflicting data in mice and rats following vagotomies [144, 145].

FGF19 has been shown to decrease food intake acutely in rodents after intracerebroventricular injections, and FGFR4 gene expression has been found at multiple sites in the CNS, including the hypothalamus, anterior pituitary, and medial habenular nucleus near the pineal stalk [104, 146, 147]. These findings suggest that this system is involved in hunger or satiation. The transport of FGF19 across the blood-brain barrier is limited [148]. There is evidence that FGF19 may exert its effect in the arcuate nucleus, which as a circumventricular organ with an incomplete blood-brain barrier has access to circulating hormones. Peripheral and central injections of FGF19 activated ERK1/ERK2 signaling in the arcuate nucleus in one study; this decreased activity of orexigenic AgRP/NPY neurons [149]. There are no known human mutations in the FGF19 or FGFR4 genes that have been linked to any metabolic process. One study in young women with anorexia nervosa found that FGF19 levels were not statistically different from controls [150].

Effect of Obesity, Insulin Resistance and Type 2 Diabetes, Bariatric Surgery, and Other Weight Loss on GI Hormone Levels and Physiology

Just as GI hormones can affect appetite and weight gain, so too can obesity affect GI hormone levels (Table 3.3). The timing of these effects is currently unclear: for example, how quickly do GI hormone profiles become disturbed in early life and can parental obesity result in GI hormone abnormalities in infancy? As described below, weight loss does not necessarily restore normal patterns of GI hormone secretion, which if disrupted may predispose individuals to regain lost weight.

Since *ghrelin* stimulates appetite and promotes a positive energy balance, one might expect ghrelin levels to be elevated in obesity. However, ghrelin is chronically low in obese individuals, including children and adolescents, and postprandial suppression is blunted [151–154]. Children and adults with Prader-Willi syndrome are exceptions, as they have elevated fasting ghrelin levels despite obesity [155, 156] (see Chap. 9 on Syndromic Obesity). Fasting total ghrelin levels are reduced in adolescents with insulin resistance and type 2 diabetes [153, 157, 158]. The correlation of acyl ghrelin with insulin resistance in children is less clear and requires further investigation [153, 157].

The response of ghrelin to bariatric surgery varies with the type of procedure (see also Chap. 38 on Bariatric Surgery in Adolescents). Sleeve gastrectomy and Roux-en-Y gastric bypass (RYGB) tend to suppress ghrelin secretion, while gastric banding procedures result in increased

Table 3.3 Effect of obesity on gastrointestinal hormone levels

Hormone	Disruption in obesity compared to normal-weight individuals
Ghrelin	↓Baseline levels and postprandial suppression
GLP-1	↓Postprandial levels
CCK	**?**
PYY	↓Postprandial levels
FGF19	↓Fasting levels

fasting ghrelin levels [159–161]. Increased fasting ghrelin is also seen with nonsurgical weight loss [161]. Rodent studies suggest that when bariatric surgery leads to decreased ghrelin secretion, there is a compensatory increase in hypothalamic expression of the ghrelin receptor (GHS-R1a) [159]. Interestingly, humans who maintained weight loss after RYGB surgery suppressed postprandial ghrelin secretion more robustly than those who regained weight after the procedure [162]. Further research will determine the overall impact of ghrelin on bariatric surgery outcomes.

Some, but not all, studies suggest that GLP-1 secretion and signaling are reduced in obese adults and adolescents [163–167]. Studies of the effects of diet-induced weight loss have been mixed, with one showing a decrease in fasting and postprandial GLP-1 levels [168] and another showing a moderate rise [169]. Changes in GLP-1 secretion in diabetes had been controversial, with small studies showing both increased and decreased GLP-1 secretion compared to nondiabetic controls. However, a recent meta-analysis does not confirm a deficiency of GLP-1 in type 2 diabetes [170].

Of the GI hormones, GLP-1 has the most dramatic response to bariatric surgery (see also Chap. 38 on Bariatric Surgery in Adolescents). RYGB increases postprandial GLP-1 levels 10–20-fold within 1 week of surgery, and this response persists for several years [171, 172]. Small intestinal biopsies taken at time of surgery and 10 months after RYGB demonstrate increased density of GLP-1-positive L-cells and increased expression of preproglucagon [173]. Individuals with successful weight loss maintenance after RYGB had a larger GLP-1 response to meal ingestion compared to those who regained weight [162].

Data on *CCK* and obesity are variable, with one study in women showing decreased CCK levels in obesity, another showing no difference between lean and obese women, and a third showing increased CCK levels in obesity [174–176]. These discrepancies may be due to small study samples and assay variability. In response to diet-induced weight loss, plasma CCK concentrations decrease [177, 178]. While earlier studies suggested no significant effect of bariatric surgery on postprandial CCK [172], more recent studies have shown increases within 1 week after surgery that persisted at 1 year postoperatively [171, 172, 179]. Moreover, the rise in CCK levels is more pronounced with sleeve gastrectomy than with RYGB [171]. As with GLP-1, small intestinal biopsies taken at time of RYGB and 10 months later show increased density of CCK-positive cells [173].

PYY levels are lower in obese adolescents and adults and are not affected by weight loss [97, 180]. Individuals with type 2 diabetes have elevated fasting PYY levels similar to postprandial levels in healthy lean adults but show a blunted response to a fat load or mixed meal [181, 182]. RYGB results in lower fasting and higher postprandial PYY levels within a week of surgery, which persists for at least a year [171, 172]. This postprandial response is more dramatic in individuals with good weight loss maintenance following surgery [162]. Similar to GLP-1 and CCK, RYGB increases the density of PYY-positive cells in the small intestine [173]. In diabetic rats, RYGB restores normal insulin secretion and islet morphology, benefits that are reversed after PYY neutralization. Furthermore, treating islets from diabetic rats that did not undergo surgery with PYY in vitro replicates the changes seen with RYGB surgery in regard to insulin secretion and islet morphology [183]. These studies suggest that improved glycemic control following bariatric surgery may be directly linked to restoring normal PYY levels.

In human studies, obesity is associated with decreased levels of *FGF19* compared to healthy, lean controls, and there is a negative correlation between BMI and FGF19 levels [184, 185]. Studies have not shown a significant difference in FGF19 levels between obese subjects with varying degrees of impaired glucose tolerance [184–186]. FGF19 levels did not improve with weight loss secondary to lifestyle modification or gastric banding, but did increase with weight loss following sleeve gastrectomy and RYGB

[184, 185, 187, 188]. The rise in FGF19 was detected 4 days postoperatively and was sustained at 6 weeks in individuals that had undergone RYGB [188]. Following RYGB, individuals who eventually had remission of type 2 diabetes had elevated FGF19 levels compared to those who did not have remission [189]. Circulating levels of FGF21 have been reported to be 20–50% higher in patients with obesity or type 2 diabetes than in healthy subjects [51–54], while patients with type 1 diabetes have lower levels of FGF21 [53].

In an effort to elucidate the mechanism behind the rapid resolution of diabetes in the majority of individuals undergoing weight loss surgeries with anatomic diversions, *bile acids* have been an area of great interest [190]. Following RYGB, fasting and postprandial bile acid concentrations are significantly increased [188, 191]. By stimulating TGR5 receptors on L-cells and FXR in ileal enterocytes, bile acids promote GLP-1, PYY, and FGF19 secretion and likely contribute to an improved metabolic profile [192].

Summary and Conclusions

While the history of GI endocrinology goes back at least 100 years, great progress has been made in understanding this system in the last two decades. The gut endocrine system acts to transmit information from the exterior environment, i.e., substances traversing the lumen, to mediate a range of interior physiology. Signals provided by nutrients are central in this process, and it is now apparent that signaling molecules from the GI tract play important roles in feeding behavior. What is less clear is the role of these factors to cause and respond to metabolic disease. However, with the expansion of methodology to study gastrointestinal function, it seems likely that new physiologic and pathophysiologic roles for GI hormones will be uncovered. Moreover, it is apparent from the development of novel diabetes drugs based on GLP-1 that the gut holds promising targets for novel treatments for obesity.

Editor's Comments

The *adaptive response to weight gain* includes an increase in insulin, which maintains glucose tolerance in the face of insulin resistance; a rise in leptin and a fall in ghrelin, which attenuate food intake; and an increase in T3, which promotes energy expenditure and thereby limits further weight gain. Interestingly there is no adaptive rise in the levels of the anorectic peptide GLP-1 unless the patient undergoes bariatric surgery. GLP-1 receptor agonists may have important metabolic benefits in obese subjects given that they promote glucose-dependent insulin secretion, decrease glucagon, and postprandial lipid concentrations, reduce blood pressure through natriuresis and vasodilatation, and exert anti-inflammatory and antiatherogenic effects[a]. At higher doses, the GLP-1 agonists also reduce body weight in obese adults[b], albeit with potentially dangerous side effects[b,c]. The potential use of GLP-1 agonists in childhood obesity is discussed in Chap. 35 on the "Role of Pharmacotherapy in Treatment of Pediatrics Obesity and Its Co-Morbidities" by Drs. Kelly and Fox.

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The Gut Microbiome and Control of Weight Gain

4

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Introduction

Recognized as one of the most serious global health issues in our society, the prevalence of overweight and obesity in preschool children has increased over the last two decades to 6.7% in 2010 [1]. Obese children are more likely to be obese in adulthood and are at greater risk of adverse health outcomes in adult life and premature mortality [2]. The etiology of obesity is complex and involves lifestyle factors that are challenging to modify. Attention has therefore turned to preventative strategies and the identification of modifiable prenatal and early-life exposures associated with overweight risk in childhood.

Over the last decade, novel evidence from animal and human studies has identified associations between our intestinal bacteria (collectively known as our gut microbiota) and host metabolism and obesity [3–5]. Infancy is a critical period in the development of the commensal gut bacteria, with a gradual increase in colonization with the *Bacteroidetes* phylum from the time of birth. Initial colonization, especially with members of this phylum, is influenced by a number of early-life exposures including birth mode, infant nutrition, and antibiotic use [6, 7]. The introduction and wider use of next-generation sequencing techniques and metabolomic technologies have increased our ability to study gut microbiota, their metabolic functions, and associations with overweight.

This chapter summarizes current evidence on the link between infant gut microbiota and weight in children and discusses early-life interventions that impact its composition and may reduce future adiposity.

Link Between Gut Dysbiosis and Overweight

Obesity has been associated with alterations in the composition of intestinal bacteria, commonly known as gut dysbiosis. However, discrepancies exist in the nature and directionality of these shifts, some of which can be attributed to study design and microbial profiling methods. While experimental rodent models have provided important evidence regarding the link between gut microbiota and obesity, differences exist between animal model and human study design in microbiome research. These are comprehensively reviewed by Nguyen and colleagues [8] and only highlighted here. To start, there are dissimilarities in morphology between the human and murine gastrointestinal tracts. Unlike humans, in whom microbial fermentation of nondigestible dietary fiber takes place primarily in the proximal large colon, rodents

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have a well-developed cecum where fermentation occurs [8]. Lactobacilli comprise up to 25% of the murine gut microbiota, whereas in the human gut, they are mainly allochthonous (transient) members obtained from our diet [9]. In both humans and mice, the *Firmicutes* and *Bacteroidetes* dominate the intestine [10]. Yet, 85% of the bacterial taxa in cecal microbiota of mice represent genera that have not been detected in humans.

With major technological advancements in genomic sequencing over the last decade, our understanding of the human gut microbiome is rapidly and constantly expanding. Targeted qPCR (quantitative polymerase chain reaction) and culture methods, and even older molecular profiling methods (e.g., FISH cytometry), are being replaced with high-throughput genomic sequencing of whole microbial communities. This transition poses challenges for comparative evaluation across studies and synthesis of findings into theories of understanding. For example, targeted microbe studies make it difficult to assess if certain species are key obesogenic microbes or simply indicators of other aberrations in microbial taxa that have a greater influence on weight gain. On the other hand, genomic sequencing rarely is able to identify microbes at the species level. The reader is encouraged to peruse a user-friendly overview of current profiling methods in microbiome research by Tyler and colleagues [11].

Bacteroidetes and *Firmicutes*

The first evidence for an obesogenic gut microbiota profile implicated the phyla *Bacteroidete*s and *Firmicutes*. Ley and colleagues reported that obese, leptin-deficient *ob/ob* mice possessed reduced abundance of *Bacteroidetes* in their fecal samples and higher proportions of *Firmicutes* relative to their lean counterparts [10]. This higher ratio of *Firmicutes* to *Bacteroidetes* was later confirmed by Turnbaugh and coworkers in a study in a high-fat-diet-induced obese model [4, 12]. The high-fat diet intervention was associated with a bloom in a single clade of the *Firmicutes* phylum, *Mollicutes* [12], later reclassified as *Erysipelotrichaceae* [13]. In humanized gnotobiotic mice fed a high-fat diet to induce obesity, higher proportions of *Firmicutes* and *Erysipelotrichi* and a lower abundance of *Bacteroidetes* were found in stool samples [14]. Consistent with animal models, initial small-scale sequencing or qPCR studies in humans reported fewer microbiota in the *Bacteroidetes* phylum and a predominance of *Firmicutes* in the gut of obese versus normal-weight adults. In the study by Ley and coworkers, the abundance of *Bacteroidetes* increased with weight loss on a fat- or carbohydrate-restricted low-calorie diet [15].

The results of subsequent clinical investigations have been variably consistent with this paradigm. A systematic review and meta-analysis by Angelakis and coworkers [16] reported both lower and higher abundance of *Bacteroidetes* and a predominance of the *Firmicutes* phylum in the gut microbiota of obese/overweight adults. Likewise, Zhang and colleagues demonstrated that *Firmicutes* were dominant in obese adults compared to those who had undergone gastric bypass surgery; however, the *Prevotellaceae*, a family belonging to *Bacteroidetes*, were significantly enriched in obese subjects [17]. Conversely, Schwiertz and colleagues showed a reversal of the *Firmicutes* to *Bacteroidetes* ratios in obese individuals compared to lean controls; levels of the genus *Bacteroides* were higher, whereas numbers of clostridial clusters IV and XIVa, belonging to *Firmicutes*, were reduced in overweight or obesity [18]. Still others have not detected differences in genus *Bacteroides* between obese and lean subjects at baseline or after 8 weeks of a carbohydrate-restricted diet [19]. In this trial, statistical reduction was attained in the proportion of *Roseburia* and *Eubacterium*, members of the *Firmicutes* phylum, present in stool with successive decreases in total carbohydrate, starch, and non-starch polysaccharide intake.

The composition of gut bacterial species varies greatly between individuals [20], but microbial profiles are more similar among family members. Hence, monozygotic or dizygotic twins discordant for obesity provide an attractive model for studying associations between gut microbiota and obesity [21]. Using the twin design, Turnbaugh and colleagues observed low abundance of *Bacteroidetes* and *Actinobacteria* in obese individuals compared to their lean twins, but no significant differences in proportions of *Firmicutes* [5].

Lactobacillus and Bifidobacteria

The Waldram group found that genus *Bifidobacterium* was significantly less abundant in obese Zucker *fa/fa* rats compared to nonobese rats, in conjunction with significantly higher levels of the *Clostridium* cluster XIVa and *Lactobacillus* group [22]. Cani and colleagues also observed a reduction in *Bifidobacterium* and *Bacteroides* levels in mice fed a high-fat diet but less *Clostridium* cluster XIVa [23]. In the systematic review by Angelakis and coworkers [16], human 16S rRNA gene sequencing studies also reported lower concentrations of bifidobacteria but higher levels of lactobacilli in the gut microbiota of obese and overweight adults compared to lean individuals. Later studies by Million and colleagues found that some species of *Lactobacillus* (*L. reuteri*) were associated with obesity, while certain *Bifidobacterium* species were negatively correlated with body mass index (BMI) [24]. As further summarized by Koleva and colleagues [25], some *Lactobacillus* species promote weight gain to varying degrees (*L. ingluviei* > *L. fermentum* > *L. acidophilus*), while other species or strains cause weight loss (*L. plantarum*, *L. gasseri*) and are being tested for their effectiveness in overweight reduction.

Oscillospira and Akkermansia

Based on 16S rRNA gene surveys of the human microbiome, Konikoff and Gophna noted the association of an unculturable bacterium called *Oscillospira* with leanness or lower BMI in both infants and adults [26]. This association was supported by an elegant animal study comparing the microbiota response to fasting across five different vertebrate hosts, in which the abundance of *Oscillospira* increased after prolonged fasting in most animals [27]. Recently, Davis and colleagues reported an increase to the relative abundance of *Oscillospira* during weaning, especially after transition from breast milk to cow's milk [28]. It is unclear if the increase in *Oscillospora* is a consequence or a mediator of weight loss during caloric restriction. Another microbial species that inversely correlates with body weight in pregnant women and children is *Akkermansia muciniphila*; it is a well-known mucin-degrading bacterium that resides in the mucous layer of the gastrointestinal tract [29, 30].

Mechanisms in Microbially Induced Obesity

We are beginning to appreciate that human gut microbiota can contribute to obesity development in several ways. The majority of microbiota reside in the large intestine, where they produce short-chain fatty acids (SCFAs) from undigested carbohydrates, namely, dietary fiber and resistant starch, and to a limited extent from proteins. Elevated SCFA levels have been found in the colon of overweight adults and the serum of obese children [31, 32]. Total SCFAs are higher when *Firmicutes* microbes are prominent in adult stool and in children, especially for acetate, when the *Firmicutes* to *Bacteroidetes* abundance ratio is higher. The elevation of SCFAs is thought to result from excess production since SCFA absorption is not reduced in overweight versus lean individuals [32]. Once absorbed, SCFAs are used as energy for colonocytes or transported to various tissues such as the liver, where they are utilized in lipogenesis or gluconeogenesis. Excess fecal SCFA production by *Firmicutes* species in lean individuals has been equated with increased energy harvest and reduction in nutrient absorption. This caloric loss in stool is not evident in obese adult individuals, indicating enhanced energy extraction by gut microbiota in the overweight state [33].

Excess SCFA concentrations can stimulate colonic release of anorectic hormones, such as peptide tyrosine-tyrosine (PYY) and glucagon-like peptide (GLP)-1 [34]. These hormones also reduce colonic motility, which may enhance nutrient absorption and counter appetite suppression effects. As summarized in Table 4.1, other proposed mechanisms for gut microbiota involve intestinal permeability, systemic inflammation, and promotion of vagally mediated insulin and ghrelin secretion. No singular mechanism has been adequately studied in human adults or children, and many questions remain, most notably whether differences in gut microbiota and SCFA

Table 4.1 Mechanisms in microbially induced obesity

Research evidence	Study design/model
Biological pathway: gut microbiota influence energy harvest/storage via *pathways which break down dietary fiber into SCFA*	
*Germ-free mice have less total body fat than conventionally raised mice [3] *Conventionalization of germ-free mice leads to (a) 60% increase in total body fat and lower insulin sensitivity [3, 35], (b) increased ability of the host to extract energy from indigestible complex plant polysaccharides in the diet [3], and (c) higher ability of the host to regulate energy storage as triglycerides [35] *Transplanting microbiota from an obese twin to the nonobese twin mouse causes gains in total body and fat mass; obesity-associated metabolic phenotypes are also transmitted [36]	Germ-free mice; conventionalized (microbiota introduced through intestinal contents) germ-free mice; fecal transplantation in twin mice discordant for obesity
*In the leptin-deficient obesity model, bomb calorimetry shows that obese mice have less energy in their cecum than lean mice. The cecal contents of obese mice have a higher *Firmicutes* to *Bacteroidetes* ratio, are enriched with genes for enzymes that utilize nondigestible dietary carbohydrates to produce short-chain fatty acids (SCFAs), and have elevated concentrations of the SCFAs, butyrate and acetate [4]	Leptin-deficient obesity in mice
*When lean adults are fed a high calorie diet, a greater percent of ingested calories is found in their stool and thus not absorbed. The caloric content of stool is negatively correlated with a higher abundance of *Firmicutes* microbiota and a reduction in the *Bacteroidetes* [33]. Caloric loss is not evident in obese adults with comparable gut transit times to lean adults, suggesting that energy extraction by gut microbiota might be enhanced in overweight versus normal-weight individuals	Diet intervention in obese and lean adults
*Overweight children have much lower fecal concentrations of intermediate metabolites such as lactate yet higher levels of butyrate, a by-product of lactate-utilizing microbiota [37]. Their metabolite profile suggests exhaustive substrate utilization by obese gut microbiota. Rate of carbohydrate fermentation by gut microbiota has been found to be higher in obese vs. lean children and adolescents [31]	SCFA levels in obese and normal-weight children
Biological pathway: gut microbial SCFA metabolites influence nutrient intake, absorption, and utilization via *appetite hormones and colonic motility*	
*High-fat feeding alters the microbiome of rats, increasing the ratio of *Firmicutes* to *Bacteroidetes*. Changes in the microbiome lead to increases in production and turnover of acetate, which acts centrally to promote vagal activity, glucose-stimulated insulin secretion, hyperghrelinemia, and weight gain [38] *In both rodents and humans, direct colonic administration of the SCFA acetate increases blood levels of two gut hormones, glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) [34, 39, 40]. Primarily produced by enteroendocrine cells in the large intestine, these satiety (or anorectic) hormones diminish appetite [41]; lower PYY levels have been observed in overweight versus normal weight *Ileal/colonic infusions of acetate or a SCFA mixture into pigs/rats have also reduced gastric/colonic motility [39, 42]; the former has been attributed to concurrent PYY release *SCFA dose and site of action may be important. In van der Beek et al.'s study, distal colonic acetate infusions of adults, but not proximal colonic infusions, increased plasma PYY and fat oxidation [40]. In their human supplementation trial, Rahat-Rozenbloom et al. observed raised serum SCFA but not GLP-1 or PYY concentrations after a standard lunch and prior ingestion of dietary fiber [43]	Microbial acetate promotes weight gain in high-fat-fed rats SCFA or dietary intervention in humans and animal models
Biological pathway: gut microbiota influence intestinal permeability and systemic inflammation	
*Feeding mice a high-fat diet, Cani and coworkers observed elevated plasma LPS (lipopolysaccharide component of the cell wall of Gram-negative bacteria), weight gain, and insulin resistance [23]. The proportion of an LPS-containing microbiota also increased in the gut *This hypothesis is centered on the translocation of bacterial lipopolysaccharides (i.e., LPS) from the intestinal lumen to the circulation, which initiates systemic inflammation via activation of Toll-like receptors on macrophages [23, 44]	Diet-induced obesity in mice

in obese versus lean individuals are a cause or consequence of the obese state and if mechanistic insights from animal models can be extrapolated to humans. Finally, individual SCFAs may differ in their obesogenic potential or pathway. Comprehensive reviews of potential pathways for overweight that involve microbial metabolites can be found in review papers by Philip Gerard [44], Kumari and Kozyrskyj [45], and Rosenbaum and colleagues [46].

Origins of Gut Dysbiosis in the Development of Child Overweight

Gut microbial compositional differences with overweight are already evident in childhood. In Karlsson's case-control study of 4–5-year-old children, members of the *Enterobacteriaceae* family were overrepresented in fecal samples of overweight versus normal-weight children [29]. Cross-sectional studies by Bervoets and colleagues and Xu and colleagues have found higher *Firmicutes* to *Bacteroidetes* ratios in overweight versus normal-weight children [47, 48]. Bervoets and colleagues also reported *Bacteroides fragilis* to be more prevalent in gut microbiota of children with a higher BMI; however, other *Bacteroides* species such as *B. vulgatus* were less abundant, and lactobacilli were more prevalent in overweight children. In the Bervoets study, fecal concentrations of lactobacilli in children correlated with a serum marker of inflammation (C-reactive protein).

Normal Transitions in Gut Microbiota Development

It is likely that obesity-related changes in gut microbiota in children have their origins in infancy, at a time when the gut microbiome is established. Seeding of our gut microbiota begins at birth, and in some infants, it occurs in utero [49]. First colonizers, facultative anaerobes, lay the foundation for subsequent colonization by anaerobes of the *Actinobacteria* and *Bacteroidetes* phyla. New evidence from the GUSTO cohort shows that the higher initial presence of *Enterobacteriaceae* soon after birth predicts higher abundance of bifidobacteria in later infancy [50]. Throughout the first year of life, microbial diversity increases, converging toward the microbiota of the adult. Mode of delivery, infant diet, and maternal or infant antibiotic treatment are the main determinants of microbial colonization and development in infancy [6, 7]. The development of the gut microbiome during infancy plays a crucial role in the maturation of immunologic and metabolic pathways [51].

Abnormal Transitions that Precede Overweight

Indeed, compelling evidence supports the concept that shifts in the complex microbial system that occur early in life confer an increased risk for developing obesity. Indirect evidence for this thesis originates from studies of antibiotic use in infancy. Data from two large birth cohorts in Denmark and the UK found modest increases in risk for overweight at age 7 years and 38 months, respectively, with antibiotic treatment before 6 months of life [52, 53]. In a prescription database-linkage study, Azad and coworkers reported significantly greater odds of child overweight at age 9–12 years with exposure to antibiotics by age 1 but in male children only [54]. Their study also found an association between infant antibiotic treatment and central adiposity (measured by waist circumference), thought to be a better predictor of cardiovascular outcomes than BMI-based measures. A similar sex-specific effect of infant antibiotic treatment and BMI was reported from the International Study of Asthma and Allergies in Childhood [55].

To date, six epidemiological studies have published evidence on associations between infant gut microbiota and infant weight gain or later child overweight (Table 4.2). Two are nested case-control studies of children, matched according to birth mode, gestational age, birth weight, probiotic intervention group, breastfeeding duration, antibiotic use, and atopic disease status and

Table 4.2 Associations between gut microbial community and child overweight status

Authors and year of publication	Study design (location)	Participants (exclusion criteria)	Microbiota profiling time point and method	Overweight assessment	Main significant findings associated with overweight	Confounding variables considered in design/ analysis
Goffredo et al. 2016 [31]	Prospective cross-sectional study (US)	84 children and adolescents (use of medication known to affect liver function or alter glucose, lipid metabolism)	16S rRNA sequencing and qPCR	Body fat (total, visceral, sub cutaneous, hepatic) by fast magnetic resonance imaging, BMI	↑ *Firmicutes*-to-*Bacteroidetes* ratio ↑ Relative abundance of *Actinobacteria* and ↓ *Bacteroidetes* ↑ *Actinomyces*, *Bifidobacterium*, *Streptococcus*, *Blautia* ↓ *Odoribacter*, *Oscillospira*, *Bacteroides*, *Faecalibacterium*	Analysis adjusted for age, ethnicity, and gender
Dogra et al. 2015 [50]	Prospective general cohort (Singapore GUSTO cohort)	75 infants	Day 3, week 3, 3 months, and 6 months 16S rRNA sequencing	Subscapular skinfold thickness (mm) at 18 months	↑ *Streptococcus* abundances at month 6 Reaching more "mature" microbiota profile (high in *Bifidobacterium* and *Collinsella* and low in *Enterobacteriaceae*) later associated with ↓ skinfold thickness at 18 months	Analysis adjusted for gestational age and delivery mode
Scheepers et al. 2015 [56]	Prospective general and anthroposophic cohort (Dutch KOALA cohort)	909 infants (preterm birth before 37 weeks' gestation, twins, the presence of congenital abnormalities relating to growth, use of antibiotics before fecal collection)	1 month qPCR: bifidobacteria, *Bacteroides fragilis*, *Clostridium difficile*, *Escherichia coli*, lactobacilli, and total bacterial counts	Age- and gender-standardized BMI z-scores from parent's reported weight and height at 7 time points between ages 1 and 10 years	Positive *B. fragilis* colonization (*only* in children with low-fiber intake at age 4 years in conventional subcohort) ↑ *B. fragilis* counts in conventional high-fiber diet subcohort ↓ *B. fragilis* counts in low-fiber subcohort and alternative subcohort	Analysis controlled for gender, place and mode of delivery, birth weight, age at collection of fecal sample, maternal smoking during pregnancy, type of infant feeding in the first month, duration of breastfeeding, maternal education, and total bacterial counts

Bervoets et al. 2013 [47]	Prospective cross-sectional (Belgium)	26 overweight or obese and 27 normal-weight children	6–16 years qPCR: bacterial species belonging to the genera *Bacteroides*, *Bifidobacterium*, *Clostridium*, *Staphylococcus*, and *Lactobacillus*	Age- and gender-standardized BMI at age 6–16 years	↑ *Firmicutes*-to-*Bacteroidetes* ratio ↓ *B. vulgatus* ↑ *Lactobacillus* spp.	Age- and gender-standardized BMI
White et al. 2013 [57]	Prospective general cohort (Norwegian NOMIC cohort)	218 infants (preterm (GA < 253 days), term infants born via cesarean section, and term infants born vaginally but exposed to antibiotics before day 4 were excluded from the analysis)	4, 10, 30, 120 days BLAST: *Enterococcus* spp., *Lactobacillus* spp., *Lactobacillus paracasei/casei*, *Staphylococcus* spp., *Streptococcus* spp., *Clostridium* spp., *Lachnospiraceae* spp., *Veillonella* spp., *Pseudomonas* spp., *Escherichia coli*, *Enterobacteriaceae* other than *E.coli*, *Gammaproteobacteria*, *Varibaculum* spp., *Bifidobacterium longum*, *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium* spp., *Bacteroides fragilis*, *Bacteroides* spp.	Difference in weight-for-age z-score from birth to 6 months from parent's reported weight	Negative *Bacteroides* spp. colonization at day 30 (males only)	Analysis controlled for antibiotic use after day 4, sex, use of milk substitutes, maternal smoking, and parity
Karlsson et al. 2012 [29]	Nested case-control (Sweden)	20 overweight or obese and 20 normal-weight children	4–5 years qPCR: *Lactobacillus*, *Bifidobacterium*, *Enterobacteriaceae*, *Akkermansia muciniphila*-like bacteria, *Desulfovibrio*, and *Bacteroides fragilis*	Age- and gender-standardized BMI at age 4–5 years	↑ *Enterobacteriaceae* ↓ *Desulfovibrio* ↓ *Akkermansia muciniphila*-like bacteria	Age- and gender-standardized BMI
Xu et al. 2012 [48]	Case-control (China)	85 overweight/obese and 91 normal weight (antibiotic administration within 2 weeks of fecal sample, stress, gastrointestinal disorder, polio vaccination within 1 month)	7–13 years qPCR: *Bacteroidetes*, *Firmicutes*	Age- and gender-standardized BMI	↑ *Firmicutes*-to-*Bacteroidetes* ratio ↓ *Bacteroidetes*	Age- and gender-standardized BMI

(continued)

Table 4.2 (continued)

Authors and year of publication	Study design (location)	Participants (exclusion criteria)	Microbiota profiling time point and method	Overweight assessment	Main significant findings associated with overweight	Confounding variables considered in design/ analysis
Luoto et al. 2011 [58]	Nested matched case- control (Finland)	15 overweight or obese and 15 normal-weight children with family history of atopic disease	3 months FISH: *Bacteroides-Prevotella* group, *Bifidobacterium* genus, *Clostridium histolyticum* group, *Lactobacillus-Lactococcus-Enterococcus* group, and total counts	BMI at 10 years from parent's reported weight and height	↓ Bifidobacteria numbers (NS)	Matched for sex, gestational age, BMI at birth, mode of delivery, probiotic intervention, and duration of breastfeeding
Vael et al. 2011 [59]	Prospective general cohort (Belgium)	138 infants (preterm birth, delivery by cesarean section)	3, 26, and 52 weeks Cultures: *Bacteroides fragilis*, *Bifidobacterium*, *Lactobacillus*, *Enterococci*, *Enterobacteriaceae*, *Clostridium*, *Staphylococcus*	BMI at 12, 18, 24, 30, and 36 months from parent's reported weight and height	↑ *B. fragilis* concentration at 3 and 26 weeks ↓ *Staphylococcus* concentration at 3 and 52 weeks ↓ *Staphylococcus/B. fragilis* ratio at 3 weeks	Analysis controlled for maternal BMI, formula or breastfeeding, antibiotic use in infancy, SES, maternal smoking status, birth weight
Kalliomaki et al. 2008 [60]	Nested matched case- control (Finland)	25 overweight or obese and 24 normal-weight children with family history of atopic disease	6 and 12 months FISH/FISH-FCM: *Bacteroides-Prevotella* group, *Bifidobacterium* genus, *Clostridium histolyticum* group, *Lactobacillus-Lactococcus-Enterococcus* group, and total counts qPCR: *Bifidobacterium* genus, *Bifidobacterium adolescentis*, *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Bacteroides fragilis*, *Staphylococcus aureas*	BMI at 7 years from parent's reported weight and height	↓ Bifidobacterial numbers ↑ *S. aureus* numbers	Infants matched for gestational age, BMI at birth, mode of delivery, probiotic intervention, duration of breastfeeding, antibiotics in infancy, and frequency of atopic diseases and sensitization at 7 years of age

BLAST basic local alignment search tool, *BMI* body mass index, *FISH-FCM* fluorescent in situ hybridization coupled with flow cytometry, *qPCR* quantitative polymerase chain reaction, *NS* nonsignificant, *SES* socioeconomic status

selected from a prospective follow-up of high-risk (for allergy) infants [58, 60] randomized to pre- and postnatal probiotic supplementation [61]. Using FISH flow cytometry and qPCR methods, Kalliomaki and coworkers reported lower bifidobacterial numbers and higher counts of *Staphylococcus aureus* in fecal samples obtained at 6–12 months after birth in 7-year-old children classified as overweight versus normal weight [60]. At 6 months of age, there was a trend for lower counts of lactobacilli but higher counts of *B. fragilis* in the children who became overweight. In a follow-up study at age 10, Luoto and coworkers found that fecal bifidobacteria also tended to be lower in number in 3-month-old infants who developed overweight compared to those who did not [58].

In a general population cohort of vaginally delivered full-term infants, higher *B. fragilis* in gut microbiota at age 3–26 weeks and lower staphylococcal concentrations (as measured by culture) were correlated with a higher BMI z-score in preschool children between 1 and 3 years of age [59]. Analyses were adjusted for known risk factors of childhood overweight, including maternal BMI and smoking status, birth weight, breastfeeding status, and infant use of antibiotics. On the other hand, a prospective follow-up of full-term infants, delivered vaginally and not exposed to antibiotics, found early detection of *Bacteroides* species (as per DNA cloning methods) in fecal samples at 1 month of age to be associated with a reduced growth trajectory over the first 6 months of life [57]. This was observed in male infants only; the presence of *Staphylococcus* species at day 4 was associated with expected growth in both males and females. Findings were independent of maternal BMI and other pregnancy complications, fetal growth, birth weight, and breastfeeding status.

Additional evidence for a relationship between gut microbial composition and infant weight gain comes from the large prospective KOALA Dutch birth cohort study [56] of offspring from women following a conventional or anthroposophic (alternative) lifestyle (based on dietary habits, child-rearing practices, vaccination schemes, and/or use of antibiotics). All results were adjusted for several confounding factors, including prepregnancy overweight, birth mode, breastfeeding duration, and caloric intake at age 4. In the conventional cohort, newborn fecal colonization with *B. fragilis* at 1 month postpartum was associated with a higher BMI z-score until age 10 but only among children with a low-fiber intake at age 4. Among newborns who were colonized with this microbe, *B. fragilis* counts were positively correlated with BMI z-score in children eating a high-fiber diet in the conventional cohort and were negatively correlated with future BMI in the low-fiber and anthroposophic cohorts. Newborn colonization with *C. difficile* at 1 month in the conventional cohort was associated with lower BMI z-score at 8 ½ years of age. The *C. difficile* finding will be discussed further in the context of breastfeeding and weaning in the next section.

Another recent prospective cohort study from Singapore (GUSTO) reported on microbiota acquisition from birth to 6 months of age in relation to delivery mode and gestational age, as well as associations with later adiposity [50]. This study found that infants who acquired a profile high in *Bifidobacterium* and *Collinsella* (of the *Actinobacteria*) and low in *Enterobacteriaceae* at 6 months versus earlier (from 3 days to 3 months after birth) had lower adiposity, as measured by subscapular skinfold thickness, at 18 months of age. A linear association between *Streptococcus* abundance at month 6 and changes in subscapular skinfold thickness from birth to 18 months was also observed. Both findings were independent of gestational age and delivery mode.

In sum, there is a relative dearth of prospective studies testing the association between gut microbiota in infancy or childhood and subsequent overweight. Studies by Vael and coworkers, Bervoets and coworkers, and Scheepers and coworkers, as well as other human adult investigations, point to a role for *Bacteroides* spp. in weight control in early life [15, 47, 56, 59, 62]. Gut lactobacilli, bifidobacteria, staphylococci, streptococci, and enterobacteria may also be important for regulating growth in infants and young children. It is also likely that growth is sensitive to perturbations in diet or other environ-

mental factors during critical windows of microbiota development. For example, Vael and coworkers and White and coworkers reported stronger correlations between infant growth and *B. fragilis* counts at <26 weeks but not later during infancy [57, 59].

Breast Milk Intervention to Alter Gut Microbiota and Prevent Obesity

Since the gut microbial community is strongly implicated in weight control, manipulating this "organ system" has the potential to prevent or treat obesity. Intervening during infancy offers new therapeutic possibilities. As exciting as this intervention appears, fecal transplantation has been primarily tested in animal models and in humans, only in adults with *C. difficile* diarrhea [63]. Hence, we have focused our discussion on the manipulation of gut microbiota by human milk, a natural modifier of gut microbial composition. For a full review on the effectiveness of probiotics and prebiotics in reducing excessive weight gain in children, see Koleva and coworkers [25].

Breast Milk Feeding

Uniquely adapted to infants to provide complete nutrition during the first 6 months of life, human milk has been associated with a number of health benefits, including reduced risk of later overweight [64]. Human milk contains a large proportion of bioactive compounds important in the stimulation of the immune system and intestinal microbiota [65, 66]. Human milk oligosaccharides (HMO) represent the third largest component of human milk [67]. They are complex sugars that resist digestion by the stomach and reach the small intestine and colon intact where they are metabolized by selective intestinal microbiota, increasing their numbers and function within the gut [68]. HMO metabolism leads to the production of short-chain fatty acids (SCFAs), which reduce the pH of the intestinal lumen, alter microbial composition, and inhibit pathogen growth [69]. As discussed in Table 4.1, SCFA may contribute to dietary energy harvest, modulate host adiposity, and alter gene expression of host satiety hormones.

In addition to providing substrates for microbial metabolism, there is evidence from several studies demonstrating the presence of live bacteria in human milk [70]. Summarized by McGuire and McGuire, the large diversity and richness of the human milk microbiome include, but is not limited to, *Bifidobacterium*, *Lactobacillus*, *Staphylococcus*, and *Streptococcus* [70]. The presence of bacteria in human milk was thought to be a result of contamination from maternal skin. However, this has been disputed by studies which show that orally administered probiotics given to lactating women can be detected in human milk [71, 72] and knowledge that certain milk genera, such as bifidobacteria, are strict anaerobes.

Accordingly, differences in early gut microbiota between breastfed and formula-fed infants have been observed in several studies. Using targeted qPCR techniques, Penders and colleagues found exclusively formula-fed infants at 1 month of age to be colonized with *E. coli*, *C. difficile*, *Bacteroides*, and lactobacilli to a greater extent than breastfed infants [7]. With 16S rRNA gene sequencing and targeted qPCR, Azad and colleagues characterized the gut microbiota of non-breastfed infants as having higher species richness at 3 months, with overrepresentation of genus *Akkermansia* and *C. difficile* [6]. Of note, 20–60% of breastfed infants were colonized with *C. difficile*. In a large sample from the same Canadian cohort, breastfeeding exclusively at 3 months was inversely associated with *Bacteroidetes* and *Clostridiales*, including *Veillonellaceae*, *Lachnospiraceae*, and *Ruminococcaceae* [73]. Breastfeeding also increases levels of fecal immunoglobulin A (IgA) in infants at 3 months of age in a dose-dependent manner [74].

Weaning off breast milk has been reported to have a greater impact on infant gut microbial composition than other early-life exposures [75]. In the systematic review by Vail and colleagues, ten observational studies found an inverse associ-

ation between age at weaning and infant growth, but reverse causation was a likely explanation in four studies [76]. The introduction of cow's milk, even in small quantities while breastfeeding [28], has been associated with dramatic increases in the abundance of genera *Bacteroides* and *Oscillospira* and the disappearance of *C. difficile* colonization [28].

Breastfeeding and Maternal Prepregnancy Overweight, Pregnancy Weight Gain, Birth Mode, and Probiotic Use

Human milk is not uniform and can differ significantly between mothers [77], including the presence of specific microbial taxa [70]. While some of this variation may be a function of methodological issues, recent studies have shown that certain maternal factors, including weight status, birth mode, and probiotic use, can influence the composition of human milk and infant gut microbiota. Herein, we address a number of commonly asked questions about the relationships among breastfeeding, the microbiome, and childhood weight gain.

Is Overweight in a Breastfeeding Mother Associated with Changes in Infant Gut Microbiota?

Strong evidence exists that maternal pregnancy overweight is a risk factor for overweight in offspring [78] and that breastfeeding can lower this risk [64]. Pregnancy overweight has also been associated with changes in both breast milk and infant gut microbiota. Characterizing breast milk microbiota [79], Cabrera-Rubio and colleagues observed higher quantities of genus *Staphylococcus* and less *Bifidobacterium* in human milk of obese compared to normal-weight Finnish mothers over the first 6 months of breastfeeding. *Lactobacillus* was dominant in the colostrum (first breast milk) and in mature breast milk at 6 months. Excessive pregnancy weight gain was associated with similar compositional patterns of breast milk. However, the gut microbiota of their infants was more likely to be colonized with *C. difficile* at 6 months of age and to have lower total bifidobacterial counts. In a larger sample of infants from the same cohort ($n = 42$), who were exclusively breastfed for 3–4 months on average [80], prepregnancy overweight was associated with lower counts of genus *Bacteroides* in the infant gut at 1 month, but not at 6 months of age. Instead, at this later age, prepregnancy overweight was associated with a greater likelihood of gut colonization with *C. difficile* and *Akkermansia muciniphila* and higher counts of staphylococci, but lower concentrations of bifidobacteria.

As shown in the Santacruz and colleagues' study of Spanish women, maternal microbial influences on offspring weight are already evident at birth [30]. High birth weight following prepregnancy overweight or excessive weight gain during pregnancy was associated with a maternal fecal microbiota enriched with *E. coli* and depleted in lactobacilli. In a Finnish cohort, Cabrera-Rubio and colleagues detected fewer bifidobacteria in third-trimester fecal microbiota of women with prepregnancy overweight [79]. Maternal pregnancy weight influences may be reinforced by the microbial composition of breast milk soon after birth, which becomes enriched with staphylococci when levels of bifidobacteria are low, independent of gestational age and delivery mode [81].

Alongside modifications to milk microbiota in overweight women seen for the first 6 months of breastfeeding, dysbiosis of the gut microbiome is observed in their infants. Gut dysbiosis soon after birth is likely the product of cesarean delivery, common with overweight mothers. Early *C. difficile* colonization of the infant gut following pregnancy overweight could simply be an indicator that the infant is being breastfed since *C. difficile* levels drop abruptly after weaning to cow's milk [28]. Gut microbial changes which emerge later in infancy, such as reductions in the counts of bifidobacteria or staphylococci, may indeed, be promoted by breast milk composition in overweight mothers. There is also the possibility that these changes to gut microbiota predate the initiation of breastfeeding.

Will Breastfeeding After Cesarean Section Delivery Reverse Infant Gut Dysbiosis and Reduce Risk for Overweight?

Cesarean section is associated with changes in gut microbiota beginning soon after birth, as indicated by dramatic reductions in abundance of *Bacteroidetes* at 3 months [73]. The literature is divided, however, on whether child overweight development can be attributed to this surgical intervention [78]. At issue is that both types of cesarean deliveries, elective and emergency, are often combined in published analyses. Interestingly, exclusive breastfeeding 3 months after birth does not contemporaneously alter cesarean-induced microbial changes in the gut but is associated with future resolution of dysbiosis at 1 year of age [73]. This phenomenon is seen primarily in infants delivered by emergency cesarean. On the other hand, mothers giving birth by elective cesarean section possess breast milk microbial profiles which are distinct in composition from those found after emergency cesarean or vaginal birth [79].

Limited evidence suggests that breastfeeding can reverse cesarean-induced changes in the infant gut microbiome, but it is up for debate whether this effect alters risk for overweight.

Do Maternal Probiotics Taken While Breastfeeding Reduce Risk for Overweight?

Depending on the strain and species, *Lactobacillus* has weight-promoting activities; yet this genus has been shown to reduce excessive weight gain in infants when administered to the mother prenatally [24]. Inconsistent weight gain and loss effects have been reported for *Lactobacillus reuteri* across studies [82]. In the randomized controlled trial by Abrahamsson and colleagues [83], unexpected variations in gut microbial composition of breastfed infants were found following maternal treatment with the probiotic, *L. reuteri.* Viewed as evidence for the transmission of the probiotic to breast milk, *L. reuteri* was detected in maternal colostrum; other species of *Lactobacillus* were also elevated in colostrum. Yet, the prevalence of *L. reuteri* declined in breast milk and newborn gut microbiota after the first week of continuous supplementation. Moreover, despite being detected in breast milk, *L. reuteri* levels were lower in the gut microbiota of infants breastfed than those formula-fed. This reduction of *L. reuteri* was interpreted as the outcome of competition from other microbiota and/or immune recognition of *L. reuteri* by immunoglobulin A found in mother's milk.

To conclude, the effectiveness of probiotic treatment in weight control is specific at the species and strain level; maternal probiotic intake while breastfeeding is found to have unpredictable effects on infant gut microbiota.

Conclusions and Future Perspectives

Advances in gene sequencing technologies have yielded considerable evidence for the role of gut microbiota in the control of weight gain. As tempting as it is to proceed to translation into practice, inconsistencies between animal experimentation and human observation must be reconciled. We have also alerted the reader to the fact that gut microbial compositional and metabolite biomarkers for obesity in adulthood are not applicable to infancy, a period of substantial plasticity when gut microbiota are being shaped by early-life exposures. Evidence from studies in adults and children may, in fact, impede understanding of the mediating role of early-life gut microbiota in controlling weight gain. It is imperative that hypotheses that emerge from animal models and human adult studies be verified in human infants. Equally, prospective follow-up studies of birth cohorts are needed to provide unbiased signals of microbiome-health associations for further testing in animals.

Regarding birth cohort studies, the potential for bias remains if analytical strategies do not take into account important confounding factors, such as birth mode, breastfeeding status,

and antibiotic use. Bias arising from study differences in design (prospective vs. nested case-control), selection of subjects (general population vs. high risk for atopy), and variable time points for infant fecal sampling and overweight assessment can also lead to conflicting results. Large, longitudinal cohort studies that employ gene sequencing to profile the whole gut microbial community in fecal samples obtained at age-sensitive time points, and which collect detailed information on early and also later childhood covariates such as diet and level of activity, are required to enhance understanding of how perturbations in infant gut microbiota can lead to overweight.

The effectiveness of breastfeeding, as a dietary intervention discussed in this review, is dependent on the stage of gut microbiota development, complementary diet, and health status of the mother. As we pointed out, women with prepregnancy overweight have altered breast milk composition, and their infants show early, transient, and later changes to gut microbial community structure. Breast milk itself may interact with the host system of the infant to modify the effectiveness of administered probiotics. Timing of the intervention is an important consideration. With the detection of microbes in the placenta and amniotic fluid, and in meconium (infant's first stool) [49], development of gut microbiota has been extended to the time of pregnancy and now subject to maternal influence.

Finally, keystone microbial species or metabolites are potentially too simplistic as biomarkers for overweight and metabolic disorders and require testing and refinement. Microbial SCFAs have been implicated in the development of overweight in humans as well as rodents, though the relative production of acetate and other SCFAs by specific microbes may vary depending on the pH of the large intestine and substrate availability [45]. As new theories emerge on metabolic pathways to overweight, they will guide our search for gut microbial biomarkers. Finally, as suggested by reports of sex differences in gut microbiota and infant risk for overweight [54], new theories may need to consider the influences of infant sex, ethnicity, and geographic location on breastfeeding and pre-/probiotic interventions aimed at preventing childhood obesity.

Editor's Questions

Is it possible that the effects of the microbiome on childhood growth, weight gain, and metabolic function depend upon the complex and changing interactions of many (or all) members of the "microbial community" (including viruses and fungi) rather than on the contributions of single classes of microbes? If so, does this make supplementation of single class or species of microbes less likely to exert dramatic effects on body habitus and metabolic phenotype?

Authors' Responses

Ecosystem interactions among all microorganisms (including viruses and fungi) resident in and transient to the gut are likely more complex than our current knowledge indicates. Microbes constitute the largest metabolic potential within this community and their SCFA metabolites have been implicated in overweight. Many gut microbiota produce the same SCFA (i.e. acetate). While other SCFAs are preferentially produced by specific microbes (e.g., propionate synthesis by members of the *Bacteroidetes* phylum), even these SCFAs can be produced by alternate microbiota depending on the pH of the large intestine and substrate availability (sugars, lactate, proteins, fats). In view of the above, supplementation with a single species of microbes is unlikely to produce anticipated effects.[a]

Reference for Authors' Response Section

(a) Kumari M, Kozyrskyj AL. Gut microbial metabolism defines host metabolism: an emerging perspective in obesity and allergic inflammation. Obes Rev. 2017;18(1):18–31.

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Part III

Adipocyte Development and Function in Obesity and Insulin Resistance

5 White Adipose Tissue Development and Function in Children and Adolescents: Preclinical Models

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Introduction

For decades, adipose tissue was classified into two types, white and brown adipose tissue, harboring either white, unilocular adipocytes or brown, multilocular adipocytes rich in mitochondria [1]. Just recently, a third type of adipocyte has been described. "Beige" or "brite" adipocytes emerge within white adipose tissue depots, are induced by prolonged cold exposure or adrenergic signaling, show a brown adipocyte-like morphology, but have a distinct gene expression pattern compared to classical brown adipocytes [1]. (See also Chap. 7 on "Brown Adipose Tissue and Body Weight Regulation.") This chapter discusses the development and function of white adipose tissue.

Development and Growth of White Adipose Tissue

Almost all studies investigating the early development of human adipose tissue were based on simple morphological methods. In 1965 Wassermann postulated that the "primitive fat organ" develops from the so-called anlagen [2]. In the early weeks of human life, it is not possible to distinguish cells that will give rise to adipocytes from other stromal cell types. Only retrospectively is it possible to identify designated preadipocytes by investigating the first fat deposits, which arise between the 14th and 16th weeks of prenatal life. In 1983, Poissonnet and coworkers showed by light microscopy that there are five morphogenic phases of white adipose tissue (WAT) formation [3]. First, until the 14th week of gestation, future adipose tissue consists of connective tissue and a "ground substance." The second phase is defined by aggregating mesenchymal cells in close connection to evolving capillaries, which are considered the first indications of human adipogenesis. In the third phase, the mesenchymal lobules for the first time form a definitive fat lobule. Fine lipid vacuoles develop within the cytoplasm and expand in number, characterizing the fourth phase of WAT formation. In the fifth and final stage, adipocytes accumulate within a rich capillary network, and the number of fat lobules seems to remain constant after the 23rd week of prenatal life [3].

Interestingly, the first fat lobules in humans are formed in the head and neck region between the 14th and 16th week of gestation and then progressively appear in the trunk and the limbs. By the 28th week, they can be found at all designated subcutaneous and visceral WAT locations [3]. At

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the time of birth, WAT is well developed in both the visceral and subcutaneous depots and accounts for approximately 16% of body weight.

The fastest growth of WAT in the postnatal period occurs between the 4th and 6th months of life [4, 5]. From the 1st to the 18th months of age, the proportion of body fat increases to a peak of 28% of body mass, with no differences in gender [6]. This increase is mainly due to the expansion of subcutaneous WAT. Only a minor portion of adipose tissue is found in the visceral and retroperitoneal regions.

Infants normally have prominent adipose tissue depots in the subcutaneous region throughout the body (panniculus adiposus). At the beginning of the last century, the pediatrician Stratz named this developmental period of adipose tissue growth during the first year of life the "first filling period." It is followed by the "first stretching period," which is usually observed in the second year of life, when the subcutaneous adipose tissue significantly decreases in spite of a decrease in growth velocity [7].

Later in life, this biphasic process is recapitulated. Body fat content and subcutaneous fat depots increase between the 8th and the 10th years of life, the time period just before puberty ("second filling period"). A "second stretching period" follows in boys during the pubertal growth spurt, whereas in girls the second filling period often persists, followed by a further increase in fat mass until young adulthood.

Body composition analysis by dual-energy X-ray absorptiometry (DXA) during child development supports these old descriptions. Relative to whole-body mass, the estimated body fat mass reaches a nadir in the fifth year of life in both genders. Subsequently, body fat percentage in boys increases until around the age of 13 years and then declines, whereas relative body fat mass in girls increases until the age of 18 years [8] (Table 5.1).

Table 5.1 Percentage of body fat (%) (+/− SD) as estimated by DXA

Age	Males	Females
3–6 y	13.7 (12.7–14.8)	17.8 (16.8–18.8)
7–10 y	17.1 (15.6–18.8)	22.6 (20.9–24.6)
11–14 y	18.8 (17.1–20.6)	28.2 (26.1–30.5)
15–18 y	17.2 (15.6–18.9)	31.4 (29.6–33.3)

Data from Taylor RW, Jones IE, Williams SM, and Goulding A. Body fat percentages measured by dual-energy X-ray absorptiometry corresponding to recently recommended body mass index cutoffs for overweight and obesity in children and adolescents aged 3–18 years. Am J Clin Nutr. 12. January 2002; 76(6):1416–21

Origin of the Adipocyte Lineage

In general, adipose tissue is believed to develop from the mesodermal germ layer. The mesoderm represents one of the three primary germ layers in the early embryo and can be found as the middle layer between the endoderm (inner layer) and the ectoderm (outside layer). It gives rise to muscle, connective tissue, blood vessels and blood, and lymph tissue [9]. The bone and cartilage come from the paraxial mesoderm, while parts of the urogenital system are from the intermediate mesoderm, and the peritoneal, pleural, and pericardial cavities are from the lateral mesoderm. In each case the WAT seems to develop from the mesoderm in the respective region [9]. Interestingly, ectodermal neuronal crest cells can be differentiated into adipocytes in vitro, and lineage tracing studies in vivo demonstrated a neuroectodermal origin of adipocytes in the head region [10]; these findings suggest that adipose tissue might arise from multiple germ layers. Moreover, subcutaneous and visceral adipose tissue depots might emerge from different developmental or organogenic progenitors [11].

It is now well accepted that adipose tissue harbors a large number of progenitor (stem) cells. There is no standardized, consistent nomenclature of these adipocyte progenitors, but they are known to reside in the stromal-vascular fraction (SVF). The SVF is a mixture of different cell types. In vitro, these cells are plastic adherent and proliferate and differentiate into mature adipocytes upon stimulation with adipogenic media [11].

Most of our knowledge about adipose stem cells has been gathered in murine model systems, using lineage tracing and fluorescence-activated cell sorting approaches [12]. The latter revealed a Sca1+, CD24+, CD29+,

CD34+, and PDGFRα + population of cells in the SVF capable of differentiating into adipocytes ex vivo and forming an ectopic functional fat pad in mice; these therefore represent adipose stem cells [13, 14].

The developmental origin of these cells has not been fully elucidated. Electron microscopy studies in the 1960s revealed that the progenitors are closely related to capillaries and "peel" away by the beginning of their transition to mature adipocytes [15, 16]. Other studies supported these findings by the observation of vascular structures arising directly before formation of adipocytes, indicating that adipose stem cell recruitment and differentiation are triggered and/or maintained by angiogenesis [17]. The relationship between blood vessels and adipocyte formation seems to be reciprocal, and both processes occur in parallel. Adipocytes and their progenitors secrete a plethora of angiogenic factors [18], and angiogenesis is stimulated by adipose stem cells [19]. Studies in the mouse localize the adipocyte stem cell to the mural cell compartment of the adipose vasculature, awaiting adipogenic signals to undergo a transition to mature adipocytes [14, 20]. Whether or not this is also true in humans remains to be investigated.

Adipogenic Differentiation

Adipogenesis can be separated into two phases: (i) the commitment of pluripotent mesenchymal stromal cells (MSC) to preadipocytes and (ii) their terminal differentiation, whereby preadipocytes develop the appearance and function of mature adipocytes and express adipocyte-specific factors like glucose transporter 4 (GLUT-4), fatty acid-binding protein 4(FABP-4), lipoprotein lipase (LPL), leptin, and adiponectin.

The process of adipogenic commitment is poorly understood. It requires the expression of bone morphogenetic proteins (BMPs) such as BMP2 and BMP4 [21] and other factors including ZFP423, which is a zinc finger protein. It is localized to adipose endothelial and perivascular cells and identifies committed preadipocytes [22].

Terminal adipogenic differentiation requires the serial activation of specific transcription factors (Fig. 5.1) that were initially identified in studies using mouse 3T3-L1 cells. The factors cAMP regulatory element-binding protein (CREB), Kruppel-like factor 4 (KLF4), Krox 20, or signal transducers and activators of transcription (STATs) 3 and 5a are known to directly induce the expres-

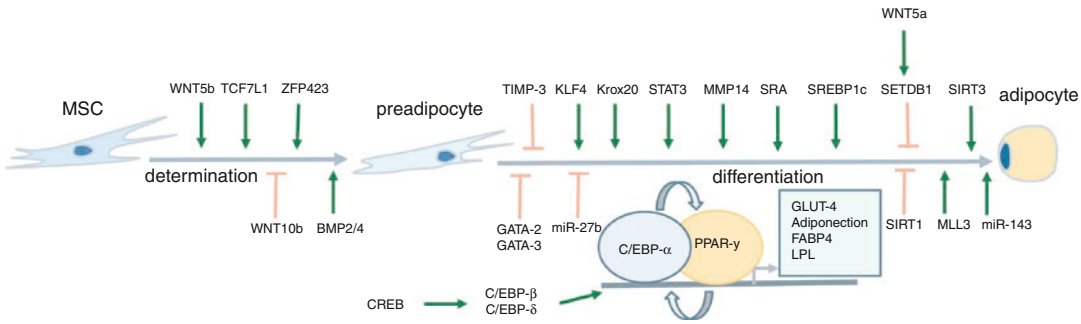

Fig. 5.1 Factors regulating adipogenesis. The adipogenic differentiation is under complex control involving different transcription factors, signaling pathways, histone modification, the ECM, and a lot of other factors. The first step of adipogenic differentiation is the commitment of pluripotent mesenchymal stem (MSC) to preadipocytes. The second step is the terminal differentiation, where the precursor cells gain the signs and function of mature adipocytes and express adipocyte-specific factors like adiponectin, glucose transporter 4 (GLUT-4), FABP-4, and LPL. Abbreviations: bone morphogenetic proteins 2 and 4 (BMP2 and BMP4), CCAAT/enhancer-binding protein beta (C/EBPβ), CCAAT/enhancer-binding protein delta (C/EBPδ), peroxisome proliferator-activated receptor gamma (PPARγ), CCAAT/enhancer-binding protein alpha (C/EBPα), sterol-regulatory-element-binding protein 1c (SREBP1c), GATA-binding 2 (GATA-2) and GATA-binding 3 (GATA-3), SET domain bifurcated 1 (STDB1), Sirtuin 1 (SIRT1), Sirtuin 3 (SIRT 3), matrix metalloproteinase 14 (MMP14), mixed-lineage leukemia protein 3 (MLL3), steroid receptor RNA activator (SRA)

sion of CCAAT/enhancer-binding protein beta (C/EBPβ). C/EBPβ together with CCAAT/enhancer-binding protein delta (C/EBPδ) induce the expression of CCAAT/enhancer-binding protein alpha (C/EBPα) and peroxisome proliferator-activated receptor gamma (PPARγ) by binding to the C/EBP-responsive element in the promoter regions of these genes. C/EBPα and PPARγ are required for terminal differentiation of preadipocytes into lipid-laden adipocytes, as they induce the expression of genes involved in lipid synthesis and insulin sensitivity. Once induced, C/EBPα and PPARγ can upregulate their own expression [23].

PPARγ is the master regulator of adipogenesis; hence overexpression of PPARγ alone can induce adipogenic differentiation in the absence of other adipogenic factors [1]. Adipocyte-specific PPARγ knockout mice are characterized by the absence of adipose tissue, underscoring the central role of PPARγ during adipogenesis [24]. Although many substrates have been proposed as PPARγ ligands, the physiologically relevant PPARγ ligand is still not identified. Possibilities include polyunsaturated fatty acids, eicosanoids, and prostaglandins. Known pharmacological agonists of PPARγ belong to the class of thiazolidinediones; rosiglitazone is a well-known example [25].

Various modifiers of adipogenic differentiation have been identified, most of them affecting the expression of the master regulator PPARγ. For example, the transcription factors GATA-binding 2 (GATA-2) and GATA-binding 3 (GATA-3) are known to suppress adipogenesis by inhibiting PPARγ. Hence, their downregulation is required for the induction of terminal differentiation [26]. Canonical WNT signaling, Hedgehog signaling, and SMAD/TGF-β are additional inhibitors of the adipogenic program [12]. The composition of the extracellular matrix is also an important modifier. For example, fibronectin, via binding to integrin 5a, represses adipogenesis in a Rac-GTP-dependent manner [26].

Functions of White Adipose Tissue

Besides playing an important role in mechanical protection and thermal insulation, adipose tissue is the largest reservoir of energy in the human body. Adipocytes store excess energy as triglycerides, which can be mobilized when needed, e.g., upon fasting. The competing processes of lipogenesis and lipolysis occur simultaneously (Fig. 5.2).

The storage and formation of lipids are mainly regulated by insulin and predominates in times of positive energy balance. Lipids are usually delivered from diet, and fatty acids are taken up into cells by fatty acid transporters such as the fatty acid-binding protein (FABP), the fatty acid translocase FAT/CD36, and the fatty acid transport protein (FATP) family [27, 28]. Free fatty acids taken up by adipocytes are esterified with glycerol to form triglycerides, which are stored in lipid droplets. Adipocytes can also generate lipids from glucose in a process called de novo lipogenesis. Herein, glucose is taken up into the cell by the glucose transporter Glut-4 in an insulin-stimulated manner. Via the glycolytic pathway, glucose is converted to pyruvate and then decarboxylated by the pyruvate dehydrogenase complex, generating acetyl-CoA. Carboxylation by acetyl-CoA carboxylase (ACC) converts acetyl-CoA into malonyl-CoA. Fatty acid synthase (FASN) catalyzes the stepwise elongation of acetyl-CoA with malonyl-CoA, generating fatty acids. The pathway of de novo lipogenesis is negligible in adipose tissue in vivo, where fatty acid uptake is the predominant pathway for the generation of lipids [29].

In a state of negative energy balance, e.g., during fasting or physical activity, the process of lipolysis enables the cell to hydrolyze fatty acids from the lipid droplet and release them into the circulation, where they are transported to peripheral tissues to provide energy. Stimulated by beta-adrenergic agents, triglycerides are hydrolyzed into glycerol and fatty acids involving the stepwise activation of several lipases, i.e., adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoacylglycerol lipase (MAGL) [30]. Insulin is a potent inhibitor of the lipolytic pathway [31].

Starting with the discovery of the adipocyte-derived satiety hormone leptin, adipose tissue is now recognized as an important endocrine organ secreting a plethora of hormones, growth factors, and inflammatory mediators into the circulation [1]. The production and action of these “adipo-

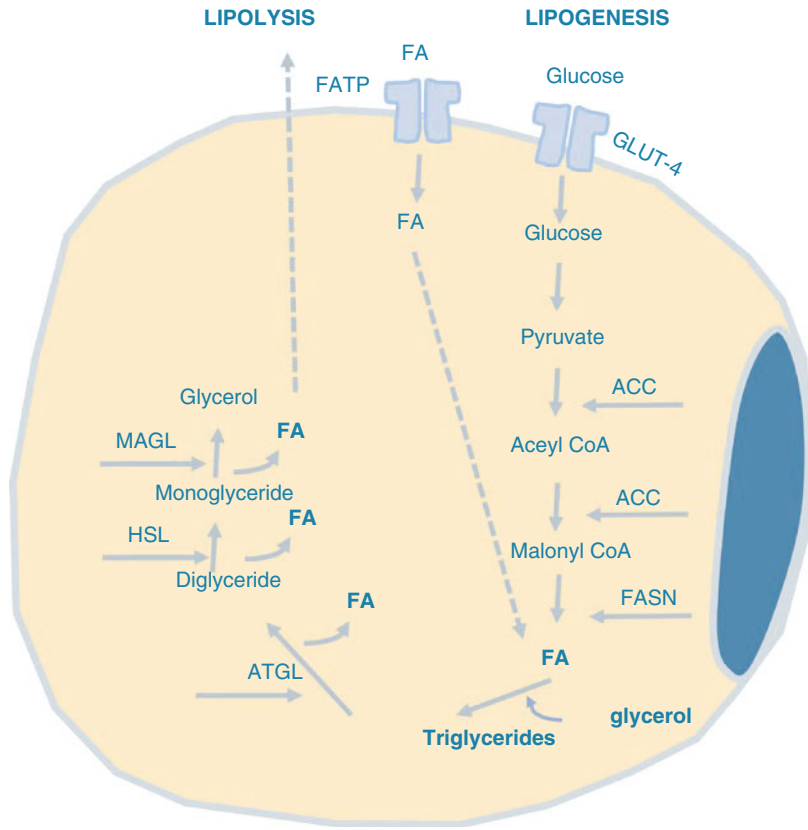

Fig. 5.2 Competing metabolic processes in the adipocyte: lipogenesis and lipolysis. Lipogenesis and lipolysis are counterbalanced depending on whole-body energy balance. Details are given in the main text. *ACC* acetyl-CoA carboxylase, *FASN,* fatty acid synthase, *ATGL* adipose triglyceride lipase, *CD36* cluster of differentiation 36, *FA* fatty acid, *FABP* fatty acid-binding protein, *FATP* fatty acid transport protein, *Glut-4* glucose transporter-4, *HSL* hormone-sensitive lipase, *MAGL* monoacylglycerol lipase, *PDC* pyruvate dehydrogenase complex

kines" are discussed in detail in Chap. 6 by Antje Körner and her colleagues.

Cellular Morphology and Turnover of White Adipose Tissue

Approximately 20–40% of cells within adipose tissue are mature lipid-laden adipocytes. Other cell types, which comprise the stromal-vascular fraction, include progenitor cells at different stages of differentiation, such as mesenchymal stem cells or preadipocytes, as well as fibroblasts, macrophages and other types of immune cells, and neuronal as well as vascular elements [1].

In order to meet the metabolic demand of the organism, WAT has an enormous capacity to either shrink or enlarge. Expansion is mediated primarily by an increase in volume of existing adipocytes, a process called hypertrophy [1]. In addition, new adipocytes can be recruited from the tissue-resident pool of progenitor cells; this process is called hyperplasia [1].

The total number of adipocytes in an individual seems to be set during childhood and early adulthood [32, 33] and remains quite constant in later life in individuals with stable weight. Individuals with early-onset obesity have an increased number of adipocytes as compared to individuals with normal weight in childhood [32, 33]. Only severe weight gain in adulthood may result in a further increase in total fat cell number. In this respect the location of the fat depot was found to be important. In states of overnutrition, hypertrophy could be observed in the adipose tissue located in the upper body and hyperplasia in the depot below the waist [1].

Approximately 10% of the fat cells in the adipose tissue of humans are renewed annually; there is a constant fat cell turnover occurring at all adult ages and at various levels of weight [33]. The renewal process maintains a balance between de novo generation of adipocytes and the elimination of old or dysfunctional cells. New adipocytes are formed from a tissue-resident pool of precursor cells. In vitro, these precursor cells

are able to proliferate in serum-containing media; in vivo, their proliferative capacity can be affected by various parameters including the age of the subject, the anatomical site, and the sympathetic nervous innervation [34]. Interestingly, bone marrow-derived cells were also described as a source of progenitor cells in adipose tissue [35]. This was demonstrated in patients after allogenic transplantation for leukemia. The average percentage of donor-derived cells in white adipose tissue of the recipient was around 5%. Of note, the percentage of donor-derived cells was twice as high in obese subjects, pointing to a role of bone marrow-derived cells as a "reserve pool" for adipogenesis [35].

The elimination of old and dysfunctional adipocytes involves the process of cell death. It is currently unclear if adipocytes die via apoptosis or necrosis. Both types of cell death have been described, but they are hard to distinguish in the tissue context. It might well be that apoptosis occurs during normal tissue homeostasis, while necrosis might be the predominant type of cell death in obesity, but this is currently unresolved. In any case, it appears to be difficult to dispose of adipocytes once they are acquired. Significant weight loss is accompanied primarily by a decrease in adipocyte volume, not by a decrease in adipocyte number [1].

The size or volume of adipocytes represents an important predictor of systemic health. As early as the 1970s, researchers studying the cellularity of white adipose tissue found that an increase in adipocyte size correlates with circulating insulin levels, insulin resistance, and a higher risk of developing type 2 diabetes mellitus [36]. Obese subjects with many small adipocytes show better glucose tolerance and less hyperinsulinemia compared to subjects having the same degree of obesity with fewer, but larger, adipocytes [36]. The metabolic effects of hypertrophy are manifest at the level of the adipocyte, with impaired insulin sensitivity, increased levels of free fatty acids due to increased lipolysis, and a distinct gene expression profile. For example, large adipocytes display enhanced expression of inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) [37, 38]. In line with all these observations, metabolically healthy obese subjects are often characterized by having large numbers of smaller fat cells [38].

The diameter of the adipocytes in an obese individual can exceed 200 μm, which surpasses the maximal diffusion distance of oxygen. Therefore it is not surprising that hypoxic pockets can be found within depots of WAT [39]. Under these conditions, the WAT is infiltrated with immune cells [40] (Fig. 5.3). Macrophages undergo a phenotypic switch from the anti-inflammatory M2-phenotype mainly found in lean, insulin-sensitive adipose tissue toward a pro-inflammatory M1-phenotype, which is associated with insulin resistance [41]. Macrophages form typical crown-like structures, which surround dying adipocytes [42]. Another hallmark of obese adipose tissue is fibrosis, with an increased deposition of fibrous extracellular matrix components [43]. All these alterations contribute to the development of insulin resistance at the level of the adipocyte [1]. The roles of adipose inflammation and fibrosis are described in more detail in Chaps. 6 and 22 by Dr. Körner and colleagues and by Drs. Alwarawrah and MacIver, respectively.

Preclinical Model Systems to Study White Adipose Tissue Function

Preclinical research on white adipose tissue and obesity incorporates the use of mouse models on one hand and cell culture models on the other.

The *ob*/*ob* mouse and the *db*/*db* mouse are probably the most famous mouse models of genetic obesity [44]. They are characterized by mutations in the leptin or the leptin receptor gene, respectively, leading to hyperphagia and massive obesity. Feeding laboratory mice a high-fat diet is the commonly used model for acquired obesity. A comprehensive summary of mouse models for obesity research is given elsewhere [44, 45]. Briefly, these model systems are very useful because they are conducted in living organisms, allowing studies on the interactions between organ systems. Murine obesity mimics

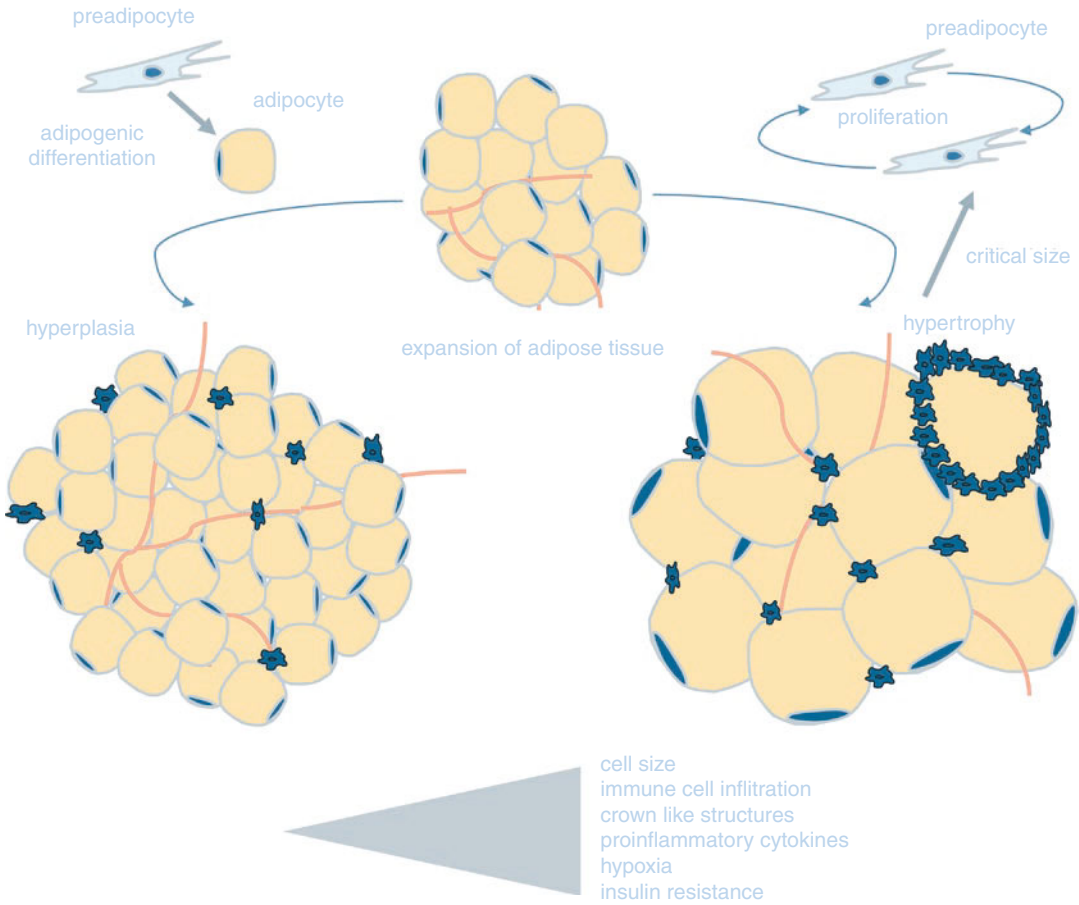

Fig. 5.3 Expansion of adipose tissue by hyperplastic adipocytes and by hypertrophic adipocytes. The expansion of adipose tissue is mainly mediated by an increase of adipocyte volume (hypertrophy). Adipose tissue can expand further by the formation of new adipocytes from progenitor cells (hyperplasia). With increasing size adipocytes show an increased expression of inflammatory genes, a higher release of free fatty acids, and a higher occurrence of apoptotic or necrotic cell death. The recruited immune cells, mainly macrophages, which are required for the clearance of dead adipocytes, form crown-like structures. Further characteristics of hypertrophic adipose tissue include hypoxia and reduced insulin sensitivity

the phenotype of human obesity, with metabolic complications including insulin resistance and hepatic steatosis. Of note, the genetic background of the mouse strain appears to influence the pathogenesis of comorbidities. The most important critique related to the use of mouse models is that there are relevant physiological differences between mice and humans that might limit the direct translation of results to the clinical setting [45].

Our understanding of the molecular regulation of adipogenesis has mostly been gathered in murine 3T3-L1 cells. They were a clonal subpopulation of cells derived from the Swiss 3T3-M line, which originated from 17- to 19-day disaggregated Swiss 3T3 mouse embryos. They are capable of undergoing adipocyte conversion upon appropriate stimulation [46]. 3T3-L1 cells have long been a commonly used cell culture model system to study the biology of adipocytes [47, 48]. In the last couple of years, they have been complemented by human cell systems (summarized in Table 5.2).

Early attempts to culture viable human adipose tissue explants and mature fat cells in vitro

Table 5.2 Human cell culture models

Cell model	Origin	Characteristics	Reference
Primary cells	Stromal-vascular fraction from different fat depots	Limited potential for proliferation and adipogenic differentiation in vitro	[50]
hMADS	1-month- to 7-year-old male and female donors	Differentiate into adipose cells in serum-free, chemically defined medium. Display the key features of human adipocytes	[51, 52]
SGBS cells	Stromal cell fraction of subcutaneous adipose tissue of an infant with Simpson-Golabi-Behmel syndrome	Proliferate for up to 50 generations with retained capacity for adipogenic differentiation. Display the key features of human adipocytes	[53, 54]
iPS cell lines	Human iPS cell lines	Adipogenic potential comparable to embryonic stem cells	[55]

were largely unsuccessful. The identification of fat cell precursors in human adipose tissue, and the demonstration of precursor differentiation into mature adipocytes in vitro, was a major step forward in human adipocyte research [49, 50]. Important progress in the culture of human adipocyte precursor cells was achieved by replacing the former serum-containing media by chemically defined, serum-free media and by better characterization of the hormonal requirements of differentiating human adipocytes [56]. An overview of the hormones and supplements required for human in vitro adipogenesis and their mode of action is provided in Table 5.3.

Human Primary Cells Isolated from White Adipose Tissue

Adipocyte precursor cells can be isolated from the stromal-vascular fraction of human adipose tissue obtained by biopsy or during surgery. A detailed protocol for isolation and cultivation can be found elsewhere [50]. Whereas no distinct cell surface markers are known for human predetermined preadipocytes, the International Society for Cellular Therapy defined minimal criteria for mesenchymal stromal cells, which are often also referred to as mesenchymal stem cells. These criteria include (I) plastic adherence; (II) expression of CD105, CD73, and CD90 and lack of expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19, and HLA-DR surface molecules; and (III) potential for differentiation into osteoblasts, adipocytes, and chondroblasts in vitro. Most of the studies performed in human primary cells after collagenase digestion match these criteria, because cells were selected by plastic adherence and display high rates of adipogenic differentiation. According to the "International Federation for Adipose Therapeutics and Science," this cell type derived from the stromal-vascular fraction of adipose tissue is referred to as "adipose stromal cell" (ASC) [60].

On one hand these freshly isolated ASCs are an excellent model to study adipocyte biology because they reflect the adipose tissue and its microenvironment as closely as possible in vitro. On the other hand, there are technical problems accompanying the use of freshly isolated ASCs. Usually only a small number of cells are available for study, and they have a limited potential to proliferate and differentiate in vitro [60]. There was therefore a need for human cell lines that proliferate and differentiate for prolonged periods in vitro. Here we mention three important cell models, which are currently used by several research groups (Table 5.2).

Human Multipotent Adipose-Derived Stem Cells (hMADS)

In 2004 Rodriguez and coworkers established multipotent adipose-derived stem cell strains isolated from human adipose tissue of six different donors and five anatomical sources (hMADS 1–6) [51]. These cell strains have a normal

Table 5.3 Adipogenic differentiation factors

Factor	Mode of action	Reference
Insulin	The most potent enhancer of adipogenesis → required for induction of AKT/MAPK and CREB in the beginning of adipogenesis	[57]
Cortisol Dexamethasone	Natural or synthetic ligand interacting with the glucocorticoid receptor Required for the induction of C/EBPδ (adipogenic TF) Interacts with the metabolism of arachidonic acid, leading to an increase in the production of prostacyclin able to induce cAMP accumulation	[23, 58, 59]
Triiodothyronine	Potent enhancer of adipogenesis; mode of action so far not known	[56, 58]
Rosiglitazone (thiazolidinediones)	Agonist of PPARγ (adipogenic TF)	[25]
Methylisobutylxantine (IBMX)	Inducer of intracellular cAMP, → activating cAMP regulatory element-binding protein (CREB) during the early adipogenic differentiation	[23]
Transferrin	Required component of the adipogenic inducer cocktail	[53]

karyotype and differentiate into mature adipocytes in serum-free, chemically defined medium [52]. hMADS show a gene expression pattern similar to that described for rodent clonal preadipocytes and human primary preadipocytes. Fully differentiated adipocytes display the key features of human adipocytes, e.g., secretion of adipokines such as leptin or adiponectin, a lipolytic response to agonists of beta-adrenoreceptors, and insulin sensitivity, i.e., insulin-stimulated glucose transport. Therefore, these cells are an excellent tool to study fat tissue development and metabolism. Furthermore, hMADS are able to differentiate in other mesenchymal lineages, such as osteoblasts [51].

Simpson-Golabi-Behmel Syndrome Cells (SGBS Cells)

A very useful and unique tool to study human adipocyte biology is the human Simpson-Golabi-Behmel syndrome (SGBS) preadipocyte cell strain [53]. These cells originated from subcutaneous adipose tissue of a patient suffering from SGBS, a rare congenital overgrowth syndrome. Although these cells are neither transformed nor immortalized, they retain proliferative and adipogenic potential for up to 50 generations [54]. Today, these cells are used by various research labs to study adipocyte differentiation and metabolism. This cell strain has a very high potential to differentiate into adipocytes in the presence of PPAR-γ agonists under serum- and albumin-free conditions. This cell culture model shares all important markers and functions with in vitro differentiated adipocytes from healthy donors [53].

Human iPS Cell Lines

Dani and coworkers showed in 1997 for the first time that embryonic stem cells (ESCs) from the inner cell mass of mouse blastocysts are able to differentiate toward the adipocyte lineage [61]. Considering that working with human ESCs bears ethical and legal concerns, a suitable alternative for pluripotent stem cells was needed. In 2009, Taura and colleagues reported that induced pluripotent stem cells (iPS) derived from human fibroblasts show adipogenic potential comparable to human ESCs. They showed morphological signs of adipogenesis such as lipid accumulation and expressed adipocyte marker genes such as C/EBPα, PPARγ2, leptin, and aP2 [55]. Therefore, they are proposed as a model system to study human adipocyte biology. Adipocytes derived from iPS are particularly suitable for the study of adipocyte function in the context of diseases such as lipodystrophy or progeria.

Summary and Outlook

White adipose tissue is a dynamic endocrine organ. It mirrors the energy homeostasis of the body as well as its endocrine status during growth and development and integrates differences related to gender and changes in hormonal activity. Adipose tissue consists of lipid-laden fat cells and precursor cells at various stages of proliferation and differentiation. New fat cells are formed throughout life. The capacity of white adipose tissue to respond to energetic and metabolic challenges is critical for prevention of metabolic comorbidities related to obesity. With the help of preclinical models (murine and human), our understanding of the molecular mechanisms responsible for adipocyte development and function has increased during the past recent years. This knowledge may help to identify and target molecules for pharmacologic treatment of adipose tissue-related metabolic alterations in obesity and lipodystrophy.

Editor's Comments and Questions

1. You postulate (quite reasonably) that progressive enlargement of adipocytes in overweight people leads to adipose tissue hypoxia, inflammation, cytokine overexpression, free fatty acid excess, and adipocyte and systemic insulin resistance. In theory, an increase in the number of small adipocytes, rather than an increase in the size of pre-existing fat cells, would be less likely to trigger this cascade to metabolic decompensation.

This begs the question: why is obesity in postnatal life associated with hypertrophy of individual adipocytes rather than a massive increase in adipocyte number to accommodate nutrient overload? Do you consider this largely the upshot of normal development, in which proliferative processes predominate in fetal and early postnatal life during critical periods of tissue growth and maturation (e.g., brain, skeletal muscle, beta cells, etc.)?

2. You note that weight loss in adolescents and adults is accompanied by a decrease in adipocyte volume rather than a decrease in adipocyte number. Presumably these cells can be "refilled" with lipid if there is a rebound increase in food intake. Does this contribute to the difficulty in maintaining weight loss in overweight people?

Authors' Responses

1. Our chapter is based on publications describing morphological alterations in different patient cohorts. To our knowledge there is currently no answer to your question why obesity is mainly due to hypertrophy and not hyperplasia.

However, the high intraindividual variations in adipose tissue cellularity lead to the idea of either a genetic predisposition or an acquired susceptibility through fetal or early-childhood programming, which can lead to a certain degree of hyperplasia. It can be also hypothesized that the capacity for increasing the number of adipocytes during periods of positive energy balance determines the metabolic flexibility of the energy stores in adipose tissue.

2. There is no sufficient scientific proof that a refilling of "empty adipocytes" after a period of weight loss in humans contributes to rapid weight gain thereafter. However, this is an old idea, which first emerged in the early 1970s. We would need more sophisticated longitudinal data in obese humans investigating adipose tissue cellularity during and after weight loss in order to strengthen this hypothesis.

A recent review based on data mainly obtained in rat or mouse experiments presents the hypothesis that the cellularity and metabolic characteristics of adipose tissues after energy-restricted weight loss could

explain the persistence of a biological drive to regain weight[a,b].

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White Adipose Tissue Accumulation and Dysfunction in Children with Obesity

6

Antje Körner, Wieland Kiess, and Kathrin Landgraf

Development of Obesity in Early Childhood

Although the consequences of obesity are generally recognized at adult age, obesity and its sequelae develop considerably earlier and often begin in childhood. Clinically and biologically obesity is characterized by an increase in body fat mass and is associated with alterations in adipose tissue that impact the development of obesity-related comorbidities. Given the increasing prevalence and severity of obesity in children and the need for a better understanding of adipose tissue development, it is of interest when obesity develops and whether there are specific critical periods in childhood and adolescence characterized by exaggerated accumulation of fat mass.

Obesity is not defined as an excess of body weight, but rather as an increased adipose tissue mass to an extent that adversely affects health [1]. Even with known limitations, the body mass index (BMI) is an accepted, easily applicable, and standardized proxy for classifying obesity in children. Obesity is commonly referred to as a BMI higher than the 95th (in the US) or the 97th (Europe/Germany) centile for age and sex. However, obesity shows an increasing prevalence with age, even in childhood. It is therefore worthwhile to examine BMI dynamics during childhood.

According to large epidemiological studies, high (and less commonly low) birth weight is among the top risk factors for childhood obesity, closely following parental overweight and low socioeconomic status, and has an even higher odds ratio than physical inactivity [2]. During childhood, BMI reaches a peak in infancy (the first year of life) with subsequent decline when children start to ambulate, before gradually and persistently increasing again from 4 to 7 years of life onwards. This second increment of BMI is referred to as obesity rebound. According to classical auxological doctrines, children find their "individual" centiles for height and weight during the first 2 years of life and then continue to grow along these centiles. Such a "stability" of BMI is more commonly found in children under the 50th centile, whereas higher BMI z-scores tend to increase during childhood [3].

BMI Dynamics over Childhood

Comparison of height and weight data over decades reveals a rise in the upper BMI centiles as opposed to more stable median and lower centiles (Fig. 6.1a), indicating that not only the prevalence but also the severity of obesity has been increasing [4].

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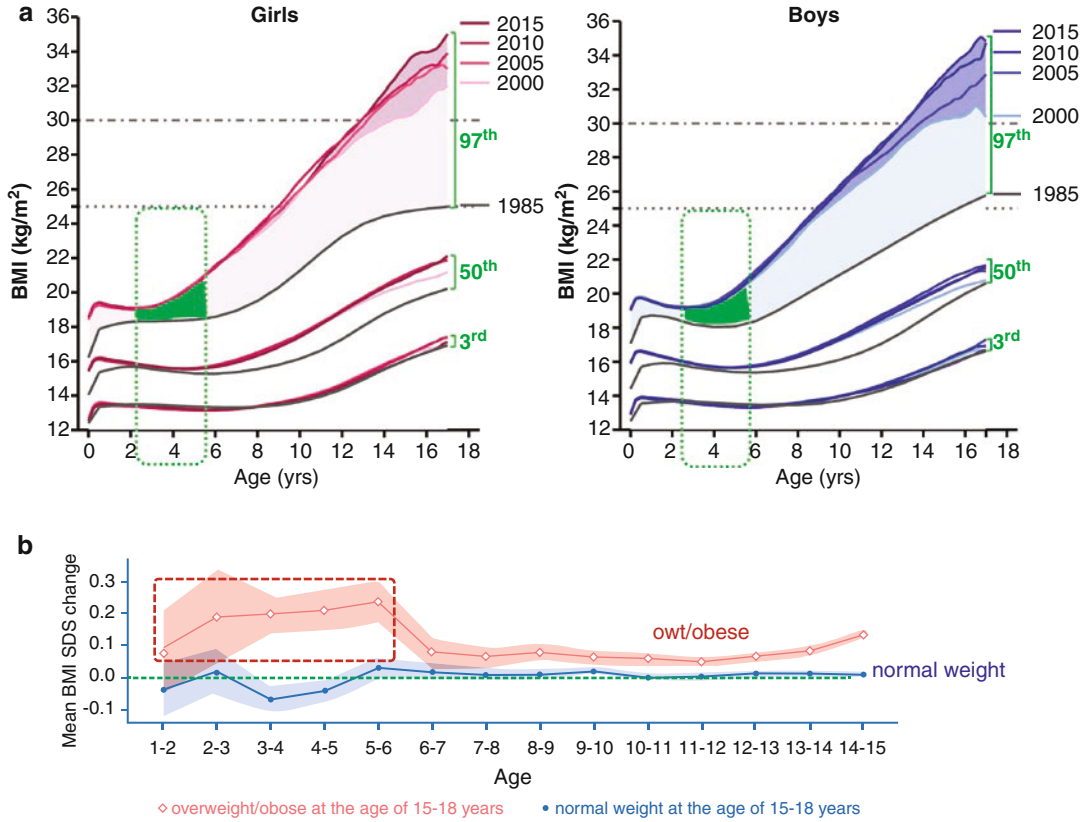


Fig. 6.1 (**a**) Development of BMI centile over the years. Comparison of BMI centile reveals that particularly the 97th centile is increasing, whereas the 50th and the 3rd centiles remain relatively stable over the years (indicated by green bars at the right side). This indicates that not only the prevalence but also the severity of obesity has increased. The rise in the 97th centiles at age 17 years from 1985 to 2000 and 2015 refers to an increased weight for the same height (at 50th centile) of 19–28 kg in girls, respectively. This divergence occurs early in life between 3 and 6 years (indicated in green box and shaded area). Centiles at the year 1985 are derived from data by Hesse et al. and plotted in grey. Centiles from 2000 (n = 66,378), 2005 (n = 158,225), 2010 (n = 156,006), and 2015 (n = 145,830) are derived from the CrescNet® data registry and are plotted in *red* for girls and *blue* for boys (Data courtesy of R. Gausche and Th. Beger; and Data from Körner A, Kratzsch J, Gausche R, Schaab M, Erbs S, Kiess W. New predictors of the metabolic syndrome in children-role of adipocytokines. PediatrRes. 2007;61(6):640–5); (**b**) BMI dynamics during childhood. Tracking intraindividual BMI courses reveals the highest rate of BMI increase in early childhood up to 6 years, followed by persistent positive BMI change in overweight (owt)/obese (*red*) compared to lean (*blue*) children. (Used with permission from Geserick M, Vogel M, Gausche R, Pfäffle R, Kiess W, Körner A. Continuous Tracking of BMI from Infancy to Adolescence Reveals BMI Acceleration During Preschool Age as Critical Risk Factor for Sustained Obesity. Submitted.)

By tracking intraindividual BMIs of children during development from birth to adolescence, 3–6 years appears as the critical age for developing sustained obesity (Fig. 6.1b) [5].

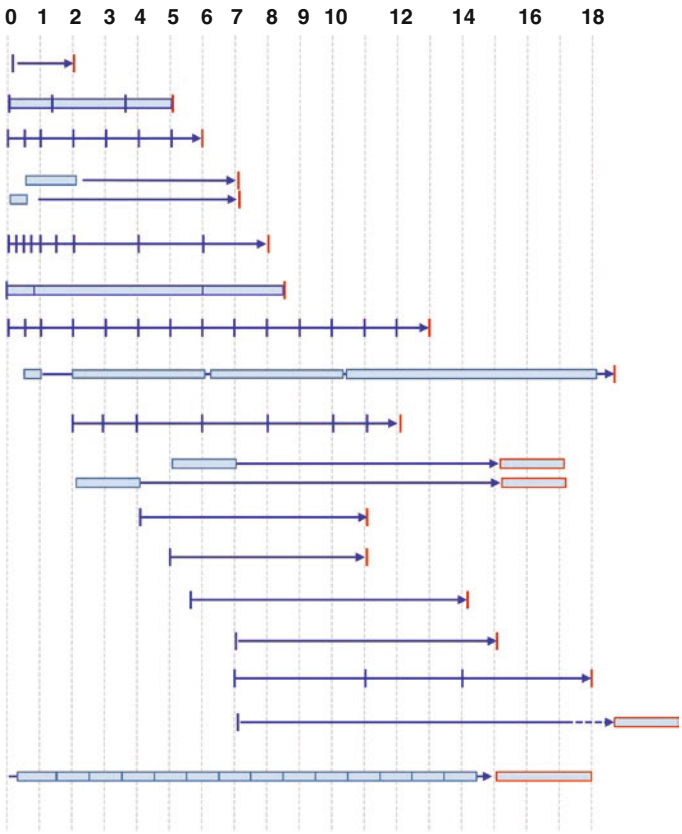
In this early phase, it appears that a later timing and particularly a higher magnitude of the first BMI infant peak is associated with a higher likelihood for obesity [6]. That a high BMI at very early age is not innocent "puppy fat" is further underscored by the finding that babies with a BMI higher than the 97th centile at 2 months of age were obese at 2 years in a large sample of more than 70,000 well-child visits [6]. There are a number of studies of varying sample sizes looking at correlation or prediction of childhood BMI at different ages for persistence of obesity

later in childhood or adolescence [5–21]. There is a considerable correlation between BMI during the years of early childhood and subsequent prevalence of obesity later in life; in general overweight/obesity persists. This concordance is even higher when overweight persists into later childhood (Fig. 6.2). In addition, the type of fat distribution appears to be determined in early childhood, as abdominal obesity persisted from age 7 to 15 years in a study of Polish children [9].

BMI Trajectories

Several studies have aimed to dissect specific BMI trajectories with an emphasis on those individuals who develop obesity. BMI trajectories from childhood to adolescence and onward to adulthood may differentially associate with obesity-related morbidity and mortality risk. As opposed to rather stable BMI trajectories of low or moderate BMI in more than 90% of the children in a Canadian study, a group with "high-rising BMI trajectory" clearly separated from those beginning at approximately 3 years of age [22]. In an Australian study, a rise in BMI to high levels during childhood or a chronically high BMI was associated with higher risk for developing insulin resistance in adolescence [23]. For adult mortality risk, the BMI trajectories appeared to be even more predictive than the static BMI status [24].

The dynamics of those BMI trajectories are not only determined by individual predisposition but may also be influenced by environmental conditions (e.g., living in a rural as opposed to urban area [25]), lifestyle factors (e.g., food intake [26]), and ethnic background [27].



Effect	n	Ref
OR 5.49 for BMI>85th PPV 47% for BMI>85th	73949	(6)
OR 34.3 (3.5 → 5y)	2678	(15)
wt gain 6-12 mo	102	(21)
OR 6.1 ob → ob (♀) OR 6.54 ob → ob (♂)	628	(14)
OR 11.5 ob → 1 BMI-SDS 4y OR 6.0 ob → 1 BMI-SDS 2y	3172	(13)
beta=1.78 for 0-6y	3301	(8)
wt gain 2-3y onward	541	(16)
age 2-6 yr and 10-18y highest predictive value adult owt	762	(11)
OR >5 owt presch → ob 12y	1042	(18)
OR 11.1 ob → ob (PPV 63%) **OR 3 ob → ob (PPV 39.3%)**	532	(12)
OR 13.38 owt → ob	1863	(19)
chance ob → ob 68.1% chance nl → ob 5.7%	12076	(17)
Prob. 47% ob → ob	7738	(10)
OR 5.46 abd ob → abd ob (♂) OR 6.19 abd ob → abd ob (♀)	315 198	(9)
40%/48.6% ob at 7y	4833	(20)
OR 14.02 owt → owt (♂) **OR 12.14 owt → owt (♀)**	72959 25252	(7)
Prob. ob 4y → ob 80 % **2-6y highest increase BMI**	33537	(5)

Fig. 6.2 Compilation of studies on BMI tracking during childhood. Graphical depiction of age range studied (*blue lines* or *boxes*) and obesity outcome ages (*red lines* or *boxes*) and summarized results and sample sizes (color according to samples size: >10,000 *green*, <1000 *red*). Studies with observation period ≥10 years are indicated in bold

Overall, overweight and obesity is determined early in life and once established tends to track into adolescence.

BMI Transition to Adulthood

This positive dynamic of increasing BMI does not end by adolescence but continues into adult age. Nevertheless, obesity rates in adults are considerably higher than those in children. It is therefore not surprising that the predictive accuracy of childhood BMI for adult obesity is only moderate according to a recent Cochrane analysis, underlining that most obese adults had been normal weight children [28]. However, if obesity develops in childhood and continues through adolescence, it tends to persist; most obese adolescents become obese adults [28].

After childhood and adolescence, most women continue to gain some weight; the strongest predictor for weight gain in a Chinese population was the baseline weight [29]. US data also show a continuing annual weight gain of approximately 0.5 kg in adult men and women and upward sloping trajectories in more than 90% of the population, resulting in a higher BMI category at middle age [30]. Consistent with this, BMI centiles spanning the entire age range from infancy to adulthood reveal the continuing upward trend [31].

Relation to Comorbidities

The continuing gain in BMI in most individuals at the transition from adolescence to adulthood is associated with a higher risk for some obesity-related comorbidities such as type 2 diabetes mellitus [32] and predisposes to preclinical cardiovascular complications such as elevated intima media thickness and increased left ventricular myocardial mass [33]. A BMI above the median in adolescence, hence even within currently accepted normal range, has been shown to predict a higher mortality risk from cardiovascular disease in young adulthood and midlife [34]. Though the classical comorbidities of obesity such as diabetes, dyslipidemia, and cardiovascular disease are most often diagnosed at adult age, the early emergence of obesity in childhood, and hence the early exposure to excess and dysfunctional fat, triggers development of preclinical metabolic and cardiovascular changes even in childhood [4, 35, 36].

Hence, early childhood is a critical age for developing sustained obesity. The very early emergence of excess body fat suggests that determinants of obesity have operated very early in life. Clinical-epidemiological studies further show a high persistence of obesity from childhood into adolescence and adulthood, which is further associated with early development of obesity-related comorbidities. The adipose tissue is likely to play a central role in the development of metabolic and cardiovascular sequelae.

Ontogenic Development of White Adipose Tissue

Emergence of White Adipose Tissue During Fetal Development

In humans, the second trimester of pregnancy is the important period for white adipose tissue (WAT) development and hence critical for development of obesity later in life.

Primary fat formation occurs early in the prenatal period around the 14th–16th gestational week, hence at a stage when the human embryo has an approximate weight of 125 g and a crown-to-rump length of 11 cm [37, 38]. Gland-like aggregations of epithelioid precursor cells (lipoblasts, pre-adipocytes) form at six specific locations beginning at the head and neck, followed by adipogenesis in the trunk, and finally at upper and lower limbs (Table 6.1) [37, 38]. By the 23rd week of gestation, they consist of distinct small lobules of adipocytes with predominantly multilocular morphology.

Subsequently, a secondary phase of fat formation takes place after the 23rd week of gestation, which is recognized by further differentiation of precursor cells through accumulation of lipid into

Table 6.1 Chronology of fat appearance in the human fetus (male and female)

Anatomic regions	Total no. of cases (*n*)	Begins at		Completed at	
		CRL (mm)	App. fetal age (weeks)	CRL (mm)	App. fetal age (weeks)
Head (face)					
Buccal pad	333	100	14	153	17
Cheek	330	103	14.5	150	17
Chin	329	103	14.5	150	17
Ocular pad	301	113	15	170	19.5
Neck	216	103	14.5	163	18
Thorax					
Anterior wall	226	135	16	170	19.5
Posterior wall	241	113	15	190	20.5
Mammary	209	106	14.5	156	17.5
Abdomen					
Abdominal wall	226	106	14.5	190	20.5
Perirenal	248	113	15	190	20.5
Upper limb					
Shoulder	220	113	15	216	23.5
Forearm	219	131	16	190	20.5
Arm	226	131	16	190	20.5
Hand	382	131	16	172	19.5
Lower limb					
Gluteal	212	131	16	190	20.5
Thigh	221	141	16.5	212	22.5
Leg	216	131	16	212	22.5
Foot	231	131	16	170	19.5

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large fat droplet laden cells that finally leads to the development of fat depots composed of unilocular white adipocytes [1]. Thereafter, adipocyte volume and number further increase throughout gestation such that the percentage of body fat increases from approximately 5% to around 15% of total body weight at birth (with brown adipose tissue constituting 2–5%) [39].

During the first year of extrauterine life, there is a 0.7–2.8 kg increase in total body fat, which rises from 16% to approximately 28% of total body weight [39]. Hence, the first peak of BMI during infancy is primarily related to accumulation of fat mass.

The volume of fat cells at birth is still small and increases during infancy. Cell proliferation and differentiation are highest during the first year of life, with subsequent deceleration of the rate of cell proliferation during adolescence.

Tissue Development

Embryologically, white adipose tissue (WAT) derives from the mesenchyme. The formation of WAT starts with an accumulation of a dense mass of mesenchymal stem cells at the above-mentioned six principal fat deposit sites. The development of adipose tissue is crucially dependent on angiogenesis, as underscored by the observation that mesenchymal stem cells develop into adipocytes near the networks of capillaries [40]. These early fat cell clusters then further develop into WAT, consisting of densely packed white adipocytes in close proximity to vascular structures [41].

Due to the natural restriction of energy supply and dependent on placental function, the development of WAT is much slower during intrauterine life. A compromised placental nutritional

supply may further restrict the development of fetal adipose tissue, with an accelerated catch-up growth of adipose tissue during the early postnatal period when nutrient supply is restored. This catch-up accumulation of fat appears more pronounced in the visceral depot [1].

Distribution

Naturally, the amount of abdominal omental fat does not differ in normal weight prepubertal girls and boys [42], but prepubertal girls have greater total and abdominal subcutaneous tissue than age-matched boys [43]. With advanced puberty, the sex-specific differences in body fat develop. Total body fat decreases slightly in boys in favor of increasing fat free mass. In girls, total body fat increases [44]. In both genders, body fat shifts from a peripheral to a central distribution. In girls, this centralization appears to plateau in puberty, whereas in boys centralization is ongoing, finally leading to greater central adipose tissue stores in boys and adult men [45].

Adipose Tissue Accumulation during Childhood Development and with Progression of Obesity

As outlined above, physiological and pathological expansion of adipose tissue during normal development and with the progression of obesity begins in early childhood.

Adipose tissue accumulation can be achieved by two mechanisms: *hyperplasia*, which is referred to as an increase in adipocyte number, and/or *hypertrophy*, which is an increase in adipocyte size [46]. One current hypothesis postulates that there is a "critical adipocyte size" which—once achieved—subsequently triggers an increase in adipocyte number. However, it is not clear if the capacity for hyperplastic adipose tissue growth persists over the entire life span since hyperplastic obesity in adults is often linked to early-onset obesity in childhood [47]. In fact, several studies indicate that the extent of adipose accumulation during childhood is closely related to, and potentially determines, adult adipocyte number, suggesting that the final number of adipocytes is set during this period and strictly controlled thereafter. Nevertheless, there is also evidence that adipocyte turnover persistently occurs in subcutaneous adipose tissue of adults. The mean age of an adipocyte has been estimated to approximate 8 years independent of age and obesity state in humans and hence around 10% of adipocytes are replaced each year [48].

Considering the BMI dynamics over childhood outlined above, one wonders if those are reflected by biological alterations in the adipose tissue itself and what the cellular mechanisms are. With the development of techniques for the measurement of adipose tissue cellularity in the late 1960s [49], research groups became interested in the mechanisms of physiological and obesity-related adipose accumulation during childhood and determined alterations in adipocyte number and adipocyte size in subcutaneous adipose tissue samples of lean and obese children in cross-sectional and longitudinal studies.

Early cross-sectional data from infants and children suggested that adipocyte number and adipocyte size both contribute to early adipose tissue development, with adipocyte number being the more prominent factor [50–54]. Both, adipose cell number and adipocyte size steadily increased with age in lean children throughout childhood and adolescence. By 2 years of age, adipocytes of obese subjects were significantly larger compared to nonobese subjects, but did not further increase in size with age of children. Similarly, adipocyte number was already significantly higher in 2-year old obese children compared to normal weight peers and, in contrast to adipocyte size, adipocyte number of obese children further increased with age throughout childhood and adolescence [54]. These data support the hypothesis that there is a maximum adipocyte size that triggers hyperplastic adipose growth.

The results of longitudinal studies contradicted the findings of cross-sectional studies to some extent. One study supported the cross-sectional data, showing that both adipocyte size and number steadily increased with age and were significantly elevated in obese compared to lean

children starting from age 2 onward, with adipocyte number further increasing with age in obese children and adipocyte size remaining constant [54]. In contrast, another study did not observe an increase in adipocyte number in lean children followed over a period of 2 years, whereas obese children showed a slight increase [55]. Moreover, additional longitudinal data found that in the first 2 years of life, adipose tissue depots grow by expansion of adipocyte size alone, which is in contrast to cross-sectional studies [53, 56]. Hence, early studies suggested that both hyperplasia and hypertrophy contribute to healthy and obesity-related adipose tissue accumulation in children, although some discrepancies regarding the relative contribution of these processes are evident. An explanation for this might be a potential bias by the use of different methodologies and rather indirect measurements (based on lipid content per cell) of adipocyte size and number. In fact, this is a general problem with the comparison of adipocyte sizes and numbers between different studies since there is no generally accepted gold standard.

Recently, we have addressed this controversial question by directly measuring adipocyte diameter in lean and obese children (Fig. 6.3a–h). According to our data, both adipocyte size and adipocyte number increased with age from 3 to 5 years onward in healthy weight children and were higher in proportion to the degree of obesity as early as 6 years of age. Interestingly, and in contrast to some of the earlier studies, adipocyte size correlated with age in the obese subgroup. While adipocyte size steadily increased from early childhood to adolescence and adulthood in normal weight children, adipocyte number reached a maximum during early childhood and remained constant thereafter. In contrast to previous analyses, adipocyte number appeared to plateau from 9 to 11 years of age onward, indicating that individual adipocyte number is established by the time the child reaches adolescence [57].

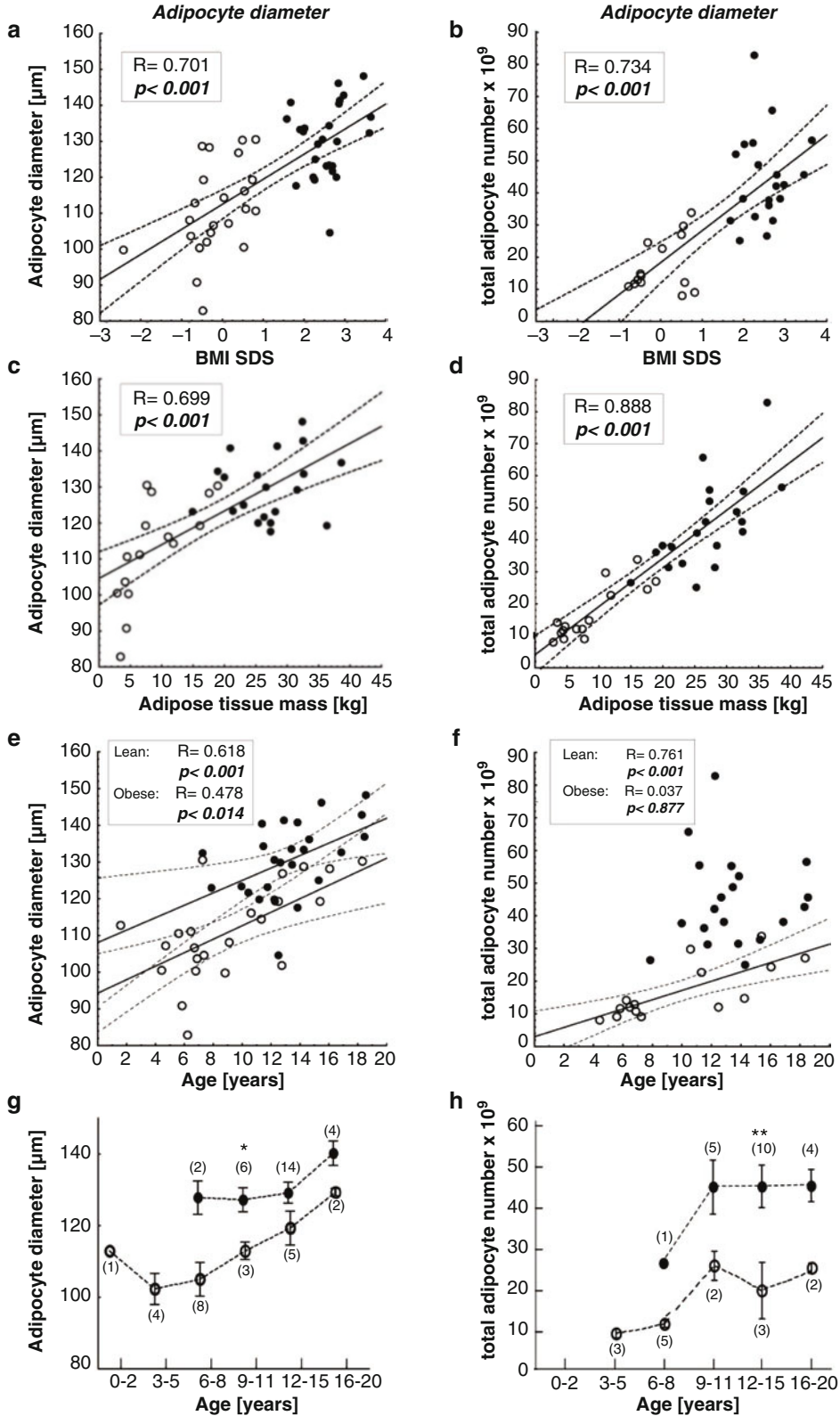
Another dimension that has so far been addressed only rarely is the impact of adipose tissue distribution on hyperplasic and hypertrophic processes in adipose tissue of children. In this regard, a recent study has shown that in obese adolescents a high ratio of visceral to subcutaneous fat is associated with a lower proportion of large adipocytes but a higher peak cell diameter in abdominal subcutaneous adipose tissue [58]. The authors postulate defects in adipose cell differentiation and lipogenesis that limit the ability to store triglyceride in subcutaneous fat.

Taken together, early and recent studies indicate that both hypertrophic and hyperplastic adipose tissue expansion contribute to the development and progression of obesity in children from a very early age onwards. Moreover, most data support the view that the number of adipocytes is determined in childhood and remains relatively constant throughout life, though with constant renewal of the adipocytes from progenitors residing in adipose tissue. Consistent with these childhood studies, investigations in adults proposed that the difference in adipocyte number between lean and obese individuals, which is observed in adulthood, is already set during childhood [48, 52].

Obesity-Related Alterations in White Adipose Tissue Function in Children and Adolescents

Besides the mere accumulation of body fat mass, obesity is often associated with alterations in white adipose tissue biology and function, which are collectively termed white adipose tissue dysfunction. There is no uniform definition of adipose tissue dysfunction, but commonly it encompasses adipocyte hypertrophy, inflammation, and an imbalance in secretory function (adipokines). Studies in rodents and human adults suggest that adipose tissue dysfunction is a major contributor to the development of obesity-related adverse metabolic and cardiovascular consequences, e.g., insulin resistance, cardiovascular disease, dyslipidemia, and fatty liver disease [59].

In particular, the increase in adipocyte size, i.e., adipocyte hypertrophy, has been discussed as a trigger for the initiation of processes leading to white adipose tissue dysfunction [60]. Our own data also supported this relation by showing that adipocyte size was most strongly related to


a
Adipocyte diameter
Adipocyte diameter [µm]
R= 0.701
p< 0.001
BMI SDS
b
Adipocyte diameter
total adipocyte number x 10^9
R= 0.734
p< 0.001
BMI SDS
c
Adipocyte diameter [µm]
R= 0.699
p< 0.001
Adipose tissue mass [kg]
d
total adipocyte number x 10^9
R= 0.888
p< 0.001
Adipose tissue mass [kg]
e
Adipocyte diameter [µm]
Lean: R= 0.618 p< 0.001
Obese: R= 0.478 p< 0.014
Age [years]
f
total adipocyte number x 10^9
Lean: R= 0.761 p< 0.001
Obese: R= 0.037 p< 0.877
Age [years]
g
Adipocyte diameter [µm]
Age [years]
h
total adipocyte number x 10^9
Age [years]

parameters of insulin resistance even after controlling for the degree of obesity or other components of adipose tissue dysfunction such as inflammation [57]. Recent evidence from analyses of white adipose samples of obese human adults indicated the presence of two distinct obesity phenotypes: metabolically healthy obesity and metabolically unhealthy obesity [59, 61, 62]. Compared to the more healthy phenotype, the metabolically unhealthy phenotype is characterized by a deleterious adipose tissue phenotype with increased adipocyte cell size and inflammatory processes in adipose tissue [63].

The obesity-related alterations within adipose tissue itself affect a variety of biological processes including adipocyte cell death, autophagy, hypoxia, lipolytic activity, adipokine secretion, remodeling of the extracellular matrix, and local adipose tissue inflammation [64]. Most of the studies focusing on processes related to adipose tissue dysfunction have been performed in adults. However, since obesity and obesity-related comorbidities develop in childhood, studies of white adipose tissue samples of children might allow better and more unbiased insight into the early events occurring with progression of obesity at the level of adipose tissue. During recent years, several studies have begun to address the early emergence and consequences of adipose tissue dysfunction in obese children and adolescents.

Adipose Tissue Inflammation

Clinically, obesity is often associated with so-called low-grade systemic inflammation, for which elevated high-sensitive C-reactive protein (hsCrP) and proinflammatory cytokines (e.g., TNFa, Il6) serve as proxies. Hence not surprisingly, by now most of the studies addressing the occurrence of processes related to obesity-associated white adipose tissue dysfunction in children and adolescents have focused on adipose tissue inflammation, i.e., infiltration of macrophages and other immune cells as well as the presence of crown-like structures (CLS; macrophages surrounding an adipocyte) within adipose tissue (see also Chap. 22 by Drs. Alwarawrah and Maciver). Such CLS are the preferential site for macrophage activation and proliferation [65]. In adults, adipose tissue inflammation has been identified as an important early event in the pathogenesis of obesity-related comorbidities, in particular insulin resistance [66–70]. Evidence from studies in rodents and adult humans suggested that the main factor driving macrophage infiltration and formation of CLS in white adipose tissue is adipocyte hypertrophy [71]. First evidence for an association between childhood overweight and systemic low-grade inflammation was based on a large cross-sectional analysis (NHANESIII) on the correlation of circulating CRP levels and white blood cell count with centile-adjusted BMI and skinfold measurements [72]. It was shown that both CRP and white blood cell counts were significantly higher in overweight compared to lean children, indicating a state of systemic low-grade inflammation.

The link between immune cell infiltration into white adipose tissue and obesity-state of children and adolescents was first established by Sbarbati and colleagues in 2006 [73], who demonstrated the presence of immune cells, i.e., macrophages

Fig. 6.3 (**a**–**h**) Adipocyte hypertrophy and hyperplasia contribute to adipose accumulation in healthy-weight and obese children. Both adipocyte size and adipocyte number increase with BMI SDS (**a**, **b**) and adipose tissue mass (**c**, **d**) of children. Adipocyte diameter was positively associated with age in lean and obese children (**e**), whereas only lean children showed a positive association between total number of adipocytes and age (**f**). Both adipocyte cell size (**g**) and adipocyte number (**h**) are increased in obese compared to lean children in all age groups from childhood (6–8 years) to early adulthood (16–19 years). Lean children are represented as open, obese as closed circles. (Adapted with permission of The American Diabetes Association from Landgraf K, Rockstroh D, Wagner IV, Weise S, Tauscher R, Schwartze JT, Löffler D, Bühligen U, Wojan M, Till H, et al. Evidence of early alterations in adipose tissue biology and function and its association with obesity-related inflammation and insulin resistance in children. Diabetes. 2015;64(4):1249–61. Copyright 2014 © American Diabetes Association.)

and less frequently also lymphocytes and granulocytes, in subcutaneous adipose tissue obtained from a small group of obese children. These so-called elementary inflammatory lesions were seen especially in perivascular positions. The observation that the inflammatory lesions also involved adipocyte degeneration led to the conclusion that those dying adipocytes trigger the recruitment of macrophages and other leukocytes and that this occurs already in childhood obesity. Similar results were obtained by Kariné Clement and co-workers, who showed that macrophages were present in subcutaneous adipose tissue of even very young children and were slightly higher in overweight compared with healthy weight children [74]. The number of adipose tissue macrophages closely correlated with adipocyte size, but CLS were rarely detectable (1 of 65 adipose tissue samples). In addition, they detected small numbers of T-lymphocytes and mast cells, which were not related to obesity state of children, while neutrophils were completely absent [74].

Those earlier studies evaluated only small numbers of patients and were mainly restricted to overweight and obese children. In our larger cohort of 106 lean and 65 overweight and obese children of different age groups, we detected macrophages in subcutaneous adipose tissue of healthy weight children at all ages analyzed, ranging from 1 month to 18 years; interestingly this also included formation of CLS in 9% of the lean children occurring as early as 6–8 years of age. In contrast to the small percentage of lean children with CLS, almost half of the obese children showed presence of CLS in adipose tissue (Fig. 6.4), which was paralleled by an increase in the number of CD68+ macrophages and expression of CD68 mRNA in the stroma-vascular cell fraction. Again, adipocyte size was the strongest independent predictor of macrophage infiltration and CLS formation in adipose tissue of children, supporting the hypothesis that hypertrophy of adipocytes is an important trigger of inflammatory processes in adipose tissue of children [57].

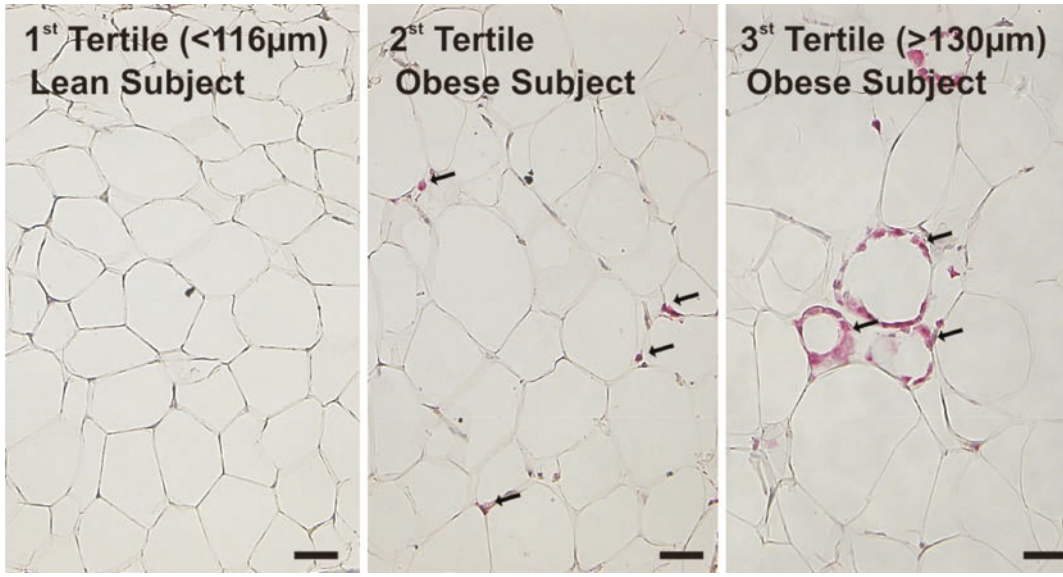


Fig. 6.4 Macrophage infiltration is associated with obesity and adipocyte diameter. The number of adipose tissue macrophages (*black arrows*) and the formation of crown-like structures, which are characterized as macrophages surrounding an adipocyte, increases with size of adipocytes shown here as group stratification into tertiles. (Adapted with permission of The American Diabetes Association from Landgraf K, Rockstroh D, Wagner IV, Weise S, Tauscher R, Schwartze JT, Löffler D, Bühligen U, Wojan M, Till H, et al. Evidence of early alterations in adipose tissue biology and function and its association with obesity-related inflammation and insulin resistance in children. Diabetes. 2015;64(4):1249–61. Copyright 2014 © American Diabetes Association.)

Further studies confirmed the occurrence of enhanced adipose tissue inflammation already during early childhood obesity [57, 75]. However, in contrast to adults, subcutaneous adipose tissue inflammation in children was not clearly associated with inflammatory serum markers, such as IL6, TNF alpha, or hsCRP [57]. Nevertheless, it was demonstrated that macrophage infiltration and CLS formation in subcutaneous adipose tissue correlated with HOMA-IR, a measure of insulin resistance, and with the extent of obesity-related liver fibrosis during childhood [57, 75]. However, whether or not this association is related to adipocyte size remains to be determined.

Studies in animals and adult humans have implicated the NLRP3 inflammasome, which is a multiprotein complex involved in innate immunity in response to non-microbial signals, as a significant contributor to obesity-related metabolic complications [76]. Recent evidence suggested that dysregulation of the NLRP3 inflammasome and its components at the level of the adipose tissue is involved in the development of obesity-associated insulin resistance in adolescents. In particular, obese adolescents with a high ratio of visceral to subcutaneous adipose tissue, i.e., a metabolically unhealthy adipose tissue distribution, showed elevated expression of NLRP3 and components of the NLRP3 inflammasome machinery in abdominal subcutaneous adipose tissue in addition to increased macrophage infiltration and formation of CLS [76].

In conclusion, increased adipose tissue inflammation is a prominent feature of dysfunctional adipose tissue in childhood obesity and, thus, might represent an important link to the formation of obesity-related sequelae in children as well as adults.

Adipose Tissue Fibrosis

Adipose tissue fibrosis has been postulated as another manifestation of adipose dysfunction. White adipose tissue fibrosis is caused by excessive deposition of proteins of the extracellular matrix (ECM) and is a ubiquitous tissue response to chronic inflammation. Studies in mice and obese human adults provided evidence that ECM-related processes are dysregulated in obesity and are associated with impairment of metabolic function and a reduction in the capacity for adipose tissue expansion [77]. ECM remodeling in subcutaneous adipose tissue of obese adults is accompanied by dysregulation of the expression of ECM proteins, such as collagens (COL1a1, COL3a1, COL6a3) and other matrix proteins including SPARC (matricellular secreted protein, acidic and rich in cysteine) [77–80]. The formation of matrix proteins and structures are generally a classical and critical feature in the growing organism and tissue formation. However, there are only limited data on the dysregulation of ECM-related processes in healthy weight and obese children and adolescents.

In 2006, Sbarbati and colleagues demonstrated the presence of microgranulomas as an early sign of adipose tissue fibrosis in children; granuloma formation was considerably increased in extremely obese children [73]. In 2012, Tam and colleagues provided evidence that collagen was present in lobular areas of subcutaneous adipose tissue of children, with collagen bundles traversing the adipose tissue and its abundance decreasing with age. The presence of collagen was considered an indicator of ECM remodeling. While the amount of total collagen in subcutaneous fat was diminished in overweight compared to lean children, it was independent of adipocyte size. Based on this finding it was hypothesized that factors other than adipocyte size may be associated with the regulation of ECM processes in children and adolescents [74].

In contrast to adult studies, bundles of collagen in adipose tissue of children did not stain positive for COL6, the collagen subtype which is most abundantly expressed in adipose tissue of obese adults and which has been linked to inflammation and obesity-associated metabolic impairment [78]. In line with this, there were no obesity-related alterations in adipose tissue expression levels of ECM marker genes in children. The results obtained in this study point to unique features of developing adipose tissue in children that are distinct from those obtained from analyses of adipose tissue from adults [74].

Noteworthy, up to now the study performed by Tam and colleagues is the only one with a detailed characterization of processes related to ECM remodeling and fibrosis in children, and the described differences between children and adults remain to be confirmed by future studies.

More recently, results from Walker and coworkers indicated a relationship between the presence of fibrosis in samples of subcutaneous adipose tissue and risk for type 2 diabetes [75]. They quantified the total amount of collagen in subcutaneous white adipose tissue and detected an inverse and BMI-independent relationship with the insulinogenic index and the disposition index, which are measures of insulin secretion and sensitivity. These findings suggest that adipose tissue fibrosis could play a role in the pathogenesis of insulin resistance and type 2 diabetes risk in childhood obesity [75].

Taken together, the phenomenon of adipose tissue fibrosis, which is a feature of white adipose dysfunction in human adults, is already detectable in subcutaneous adipose tissue of obese children. However, further studies in larger cohorts are necessary to determine its regulation and its contribution to the early development of obesity-associated diseases during childhood.

Metabolic Activity of Adipocytes

White adipose tissue functions as a critical regulator of energy homeostasis and metabolism by the storage of energy in the form of lipids and by supplying nutrients to other tissues through lipolysis upon demand. Storage and mobilization of fat are mainly coordinated by the action of two enzymes, lipoprotein lipase (LPL) and hormone-sensitive lipase (HSL), which drive the key steps of lipogenic and lipolytic processes in response to insulin and catecholamines.

Obesity-associated alterations in metabolism, in particular lipolysis, are characteristic of white adipose tissue dysfunction in adults and may contribute to enhanced adipose tissue accumulation during the development of childhood obesity [81, 82]. Such alterations in lipid metabolism may underlie the observed hypertrophy in adipose tissue of obese children. In this context, Kursawe and coworkers showed that in obese adolescents a high ratio of visceral to subcutaneous fat is associated with a higher peak cell diameter in abdominal subcutaneous adipose tissue [58]. Indeed, these changes in tissue cellularity were accompanied by a decreased expression of adipogenic (PPARG2, LPIN1, ADIPOQ) and lipogenic marker genes (SREBF1, FASN, ACACA) and a reduced de novo lipogenesis in vitro. Such alterations in cellularity and the inhibition of adipogenic and lipogenic genes may limit the expandability of subcutaneous adipose tissue, favoring ectopic fat deposition in visceral adipose tissue and liver and subsequently leading to insulin resistance [58]. In line with this model, reduced expression of PPARG2 and ADIPOQ in subcutaneous adipose tissue has been shown to be associated, independent of BMI, with higher liver fat content and insulin resistance in obese adolescents [83]. Moreover, analyses of equally obese adolescents across the spectrum of glucose tolerance, i.e., prediabetic, insulin resistant, and diabetic, revealed that reduced subcutaneous adipose expression of ChREBP, which is a major regulator of de novo lipogenesis, is associated with insulin resistance and glucose intolerance [84].

The opposing component to anabolic lipogenesis is catabolic lipolysis. We observed a significant decrease in basal lipolytic activity of adipocytes in obese compared to lean children and in relation to the degree of obesity, while there was no difference in the response of lipolytic activity to beta-adrenergic stimulation. This decreased basal lipolytic activity was independently related to adipocyte size [57]. These findings are somewhat in contrast to adult studies that showed enhanced basal lipolytic activity and a decreased effect of catecholamines in adult obesity [85–89], but are in line with previous clinical studies on lipid mobilization in obese children in vivo indicating lower lipolytic activity in adipose tissue [81]. Hence, lower lipolytic activity of adipocytes may well contribute to adipocyte hypertrophy in obesity.

Proliferation and Differentiation Capacity of Adipose Progenitor Cells

White adipocyte hyperplasia is another phenomenon commonly seen in adipose tissue of obese patients. The increase in adipocyte number observed during development of childhood obesity may result from two distinct mechanisms. One is enhanced proliferation of adipose progenitor cells residing within the stroma-vascular fraction and their subsequent differentiation into mature adipocytes. The second is enhanced differentiation of available adipose progenitor cells. According to a current hypothesis, proliferation of adipose progenitor cells is increased when a critical adipocyte size is reached, allowing further expansion of adipose tissue [47]. In line with this hypothesis, analyses of subcutaneous adipose progenitor cells derived from adipose tissue of lean and obese adult humans showed that proliferative capacity of adipose progenitor cells positively correlates with BMI [90].

In 2005, Grohmann and coworkers established a protocol allowing the in vitro analyses of subcutaneous and visceral adipose progenitor cells from very small biopsies of adipose tissue samples obtained from lean and obese prepubertal children and demonstrated a clear but distinct proliferative activity in vitro. Cells of subcutaneous origin proliferated more efficiently compared to visceral cells. In contrast, efficiency of in vitro differentiation from precursor to mature adipocyte did not differ between subcutaneous and visceral precursor cells despite differences in lipid size and number [91].

A first comparison between lean and obese children pointed to a similar abundance of adipose progenitor cells (CD34−/CD31+) in the stroma-vascular fraction of children with a low BMI compared to children with a high BMI [92]. Also, the expression of genes related to adipose tissue development (see Chap. 5 by Martin Wabitsch and his colleagues), including the adipogenic transcription factors PPARG and SREBP-1c, was not altered in white adipose tissue of obese children. In contrast, Haro-Mora and coworkers observed an inverse correlation of adipose progenitor cell number with adipocyte size. However, presumably due to limitations in the amount of adipose tissue obtained during elective surgery, they did not provide data on proliferation or differentiation capacity of adipose progenitor cells in different weight groups [92].

In a recent study, we have analyzed the proliferation and differentiation potential of stroma-vascular cells isolated from subcutaneous adipose tissue samples of normal-weight and obese children and adolescents in vitro. Similar to Haro-Mora and coworkers, we found that the number of stroma-vascular cells in adipose tissue was comparable between lean and obese children, as was the percentage of plastic-adherent stroma-vascular cells, which serves as a proxy for the number of adipose progenitor cells [57, 92]. However, the in vitro doubling time of stroma-vascular cells was accelerated in obese compared to lean children, indicating enhanced proliferative capacity. Interestingly, cell-doubling time of stroma-vascular cells was not associated with adipocyte size, suggesting that it is regulated by stimuli which act independently of adipocyte hypertrophy. Moreover, the in vitro differentiation potential of isolated stroma-vascular cells did not differ between lean and obese children and was not associated with adipocyte size [57]. Similar results have been obtained in several studies in adults showing that the capacity of adipose progenitor cells to differentiate into mature adipocytes is not associated with the degree of obesity [93, 94].

Hence, the proliferation potential of adipose progenitor cells seems to be related to adipose tissue accumulation in childhood obesity, providing a potential mechanistic link between adipose progenitor cell function and hyperplasia in adipose tissue of obese children.

Adipokine Secretion

During recent years adipose tissue has emerged as an important endocrine organ releasing various bioactive substances, so-called adipocytokines or adipokines, which are involved in the regulation of metabolic, endocrine, and immunological

processes in adipose tissue itself or in other target organs, such as hypothalamus, liver, muscle, vascular system, etc. [95]. Circulating levels of most of these adipokines increase with increasing body fat mass; in contrast, adiponectin is decreased in obese adults [96]. When assessing the situation in children, the specific physiological and developmental aspects of the pediatric population must be considered. Many adipokines, including leptin (and its soluble receptor) [97, 98] and adiponectin [99], have a clear dynamic regulation with physical development in normal healthy children from infancy through puberty to adulthood, and this must be considered when comparing their levels to obese children. The close relation to body fat content does not necessarily imply a relation to adipocyte differentiation, which does exist for some adipokines (such as adiponectin, RBP4 [100, 101]), but not for all secretory factors. Indeed, the adipose tissue is not the exclusive (and may in some cases be only a minor) source of circulating adipokines. Independent of their associations with BMI, systemic levels of some adipokines are associated with obesity-related comorbidities, such as cardiovascular alterations or metabolic dysfunction. Important examples in addition to leptin, adiponectin, and RBP4 include plasminogen activator inhibitor-1, tumor necrosis factor alpha, visfatin, monocyte chemoattractant protein 1, and chemerin [95], which is a chemoattractant protein potentially linking obesity-related adipose tissue accumulation and early vascular inflammation in children [102].

Adipose tissue dysfunction and especially adipocyte hypertrophy and low-grade inflammation in obesity have indeed been linked to dysregulation in adipokine expression and secretion [103, 104], which is proposed to contribute to the development of obesity-related metabolic and cardiovascular diseases [105]. The best studied are leptin and adiponectin. Leptin is a hormone involved in the central regulation of food intake and energy balance. Circulating leptin levels correlate positively with adult BMI and are linked to the amount of body fat mass and adipocyte size. The obesity-related increase in leptin contributes to low-grade systemic inflammation by stimulating the secretion of pro-inflammatory cytokines, e.g., interleukin 6 and tumor necrosis factor alpha [106]. In contrast, adiponectin is an anti-inflammatory hormone with insulin-sensitizing, antiatherogenic, and antidiabetic properties [107]. Adiponectin expression and synthesis is inhibited under conditions of hypoxia, oxidative stress, and inflammation and is negatively correlated with BMI and adipocyte size in adult humans [108, 109].

Similar to what has been found in adult studies, recent data in children provided evidence that adiponectin expression and synthesis in subcutaneous and omental adipocytes are related inversely to the degree of obesity [110]. As in adults adiponectin mRNA levels are significantly higher in subcutaneous compared to omental adipose tissue in overweight children and are closely related to *PPARG* expression in both depots [83, 111].

We evaluated the links between serum levels of adiponectin and leptin and obesity-related alterations in adipose tissue biology in subcutaneous samples of children and adolescents. As expected, we confirmed changes in serum leptin and adiponectin during development of obesity in children. Both leptin (positively) and adiponectin (inversely) correlated with BMI z-score and age of children and with the presence of adipose tissue inflammation, i.e., number of adipose tissue macrophages and CLS, and inflammatory serum parameters. Interestingly, leptin levels but not adiponectin levels were closely correlated with adipocyte size, suggesting that elevated leptin may reflect early adipocyte hypertrophy [57]. Hence, dysregulation of the secretory function of adipocytes as a sign of adipose tissue dysfunction during early childhood obesity might underlie the

development of obesity-related metabolic and cardiovascular alterations.

Evidence for White Adipose Tissue Dysfunction in Visceral Adipose Tissue of Obese Children

Adipose tissue distribution and especially the amount of visceral adiposity have been linked to metabolic and cardiovascular impairment. It is hence of great interest to understand processes related to white adipose tissue dysfunction occurring with progression of obesity in visceral adipose tissue of children. However, due to the accessibility of adipose tissue samples during elective surgery, most studies on white adipose tissue dysfunction with childhood obesity have focused on subcutaneous adipose samples. Only recently, analyses of genome wide expression profiles have begun to shed light on obesity-related-processes of AT dysfunction in visceral adipose of children [112–115]. In these, visceral adipose tissue was characterized by an overrepresentation of genes related to immune and inflammatory responses, including MHC class I and II genes; Fas; interleukins 2, 7, and 18; CD4 and TNF superligand family-member 14; and chemokines like macrophage migration inhibitory factor, CCL5, CXCL6, and CXCR4. In contrast, subcutaneous adipose tissue showed an overrepresentation of genes related to adipocyte growth and development, including fibroblast growth factors 1–2, transforming growth factor and beta receptor III. Based on these results, it was proposed that the inflammatory gene expression pattern in visceral adipose tissue combined with chronic obesity may contribute to increased risk for obesity-associated metabolic and cardiovascular complications [115].

Evidence for the early presence of obesity-related visceral adipose tissue dysfunction in children was further provided by recent data from Aguilera and coworkers, who analyzed genome-wide expression profiles from lean and overweight prepubertal children. According to their results, genes related to lipid and amino acid metabolism, oxidative stress and extracellular matrix regulation, adipogenesis, and inflammation are upregulated in visceral adipose tissue of overweight compared to lean children [112]. Many of these genes have been previously proposed to be involved in the pathogenesis of adult obesity, suggesting that dysfunction of visceral adipose tissue is already evident in early childhood obesity [113, 114].

In summary, genome-wide expression profiles provided first hints for the presence of adipose tissue dysfunction in children, but more detailed experimental analyses are needed to confirm these results.

Summary

Early childhood is a critical age for developing sustained obesity. Adipose tissue accumulation during development and progression of early obesity in children occurs by both hypertrophy and hyperplasia of adipocytes. According to current hypothesis, the number of adipocytes is determined in childhood and remains relatively constant throughout life, though some adipocyte turnover takes place by adipose progenitor cell proliferation and differentiation. Early childhood obesity is already accompanied by the presence of white adipose tissue dysfunction, in particular adipocyte hypertrophy, adipose tissue inflammation, remodeling of the extracellular matrix and fibrosis, enhanced proliferation of adipose progenitor cells, and adipokine imbalance (Fig. 6.5). These alterations in adipose tissue biology and function are likely to be causative factors for the development of obesity-related comorbidities, such as diabetes and cardiovascular diseases, later in life.

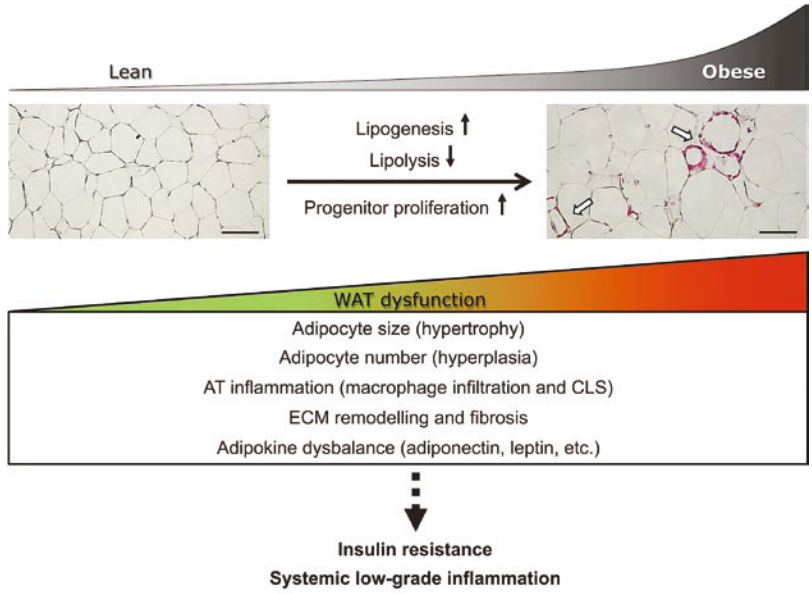


Fig. 6.5 White adipose tissue (WAT) dysfunction in obese children. Early childhood obesity is characterized by an increase in adipocyte size (hypertrophy) and number (hyperplasia), which might be attributable to diminished basal lipolytic activity of adipocytes and an enhancement of stromal vascular cell proliferation. Adipocyte hypertrophy and hyperplasia in adipose tissue of obese children is associated with parameters of adipose tissue dysfunction including increased inflammation through macrophage infiltration and formation of CLS (*white arrows*), ECM remodeling and fibrosis, and adipokine imbalance. These obesity-associated alterations in adipose tissue biology are already linked to insulin resistance and systemic low-grade inflammation in children

Editor's Comment and Questions

You note that hypertrophy of adipocytes is an important trigger of inflammatory processes in adipose tissue of children. Can you speculate why this might be? Could this represent an adaptive mechanism by which adipocyte hypertrophy promotes adipocyte apoptosis and/or necrosis in order to limit further fat deposition?

Authors' Responses

Hypertrophy of adipocytes results in alterations in the secretion of certain cytokines and chemoattractant proteins which might be triggered by local hypoxia occurring during adipose tissue expansion. These alterations in adipocyte secretory function lead to processes, collectively termed adipose tissue remodeling, including the initiation of macrophage infiltration into adipose tissue. Hence, the adipose tissue microenvironment is switched from an anti-inflammatory to a pro-inflammatory state which might finally result in adipocyte apoptosis in order to limit fat deposition by hypertrophy and to allow for hyperplastic adipose tissue expansion. Another conceivable and interesting possibility is that adipocyte hypertrophy itself leads to necrotic adipocyte cell death, which might be caused by local adipose tissue hypoxia, and in turn leads to macrophage infiltration and crown-like structure formation in order to remove remnants of dead adipocytes, such as lipids.

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Brown Adipose Tissue and Body Weight Regulation

7

Michael Freemark and Sheila Collins

Introduction

Adipose tissue assumes three histologic signatures in humans and other mammals (Fig. 7.1). *White adipose tissue* (WAT) is comprised of adipocytes containing large, unilocular lipid droplets and relatively few mitochondria; it serves as a reservoir of energy and regulates whole-body metabolism, immune function, and tissue growth and function through triglyceride storage and mobilization and the production of adipocytokines and growth factors. In contrast, *brown adipose tissue* (BAT) generally consists of uniform smaller cells with multilocular lipid droplets and numerous mitochondria; the brown adipocytes are enmeshed in dense array of blood vessels and nerves. Detected in abundance in newborn human infants (Fig. 7.2), BAT dissipates energy and generates heat (nonshivering and diet-induced thermogenesis) by uncoupling mitochondrial substrate oxidation from ATP production. This effect, catalyzed by a 32 kDa transmembrane protein called uncoupling protein 1 (UCP1), provides thermoprotection that is critical for newborn survival.

The major depot (interscapular) of classic BAT regresses after birth, and it had been thought that residual stores of BAT are too limited to exert a significant impact on postnatal energy balance. However, investigations conducted during the past 9 years demonstrate the presence of functional brown adipocytes, often in small islands (Fig. 7.1), in the supraclavicular, mediastinal, and perirenal fat pads of children, adolescents, and adult women and men (Fig. 7.3) [1–6]. The "brown-like" cells stain strongly positive for UCP-1 under stimulated conditions. An adipose deposit containing a mixture of these brown and white adipocytes is termed *beige (or brite) adipose tissue*.

The apparent mass and "activity" of brown/beige adipose in children and adults have been assessed by analysis of positron emission tomography (PET)/computed tomography (CT) scans following the administration of ^{18}F-fluorodeoxyglucose (^{18}F-FDG), which is taken up by metabolically active BAT. The "activity" of brown/beige adipose in adults, determined by ^{18}F-FDG uptake, appears to correlate inversely with ambient temperature, light exposure, BMI, and visceral fat mass [1–7]; thus BAT activity is low or absent in obese adults under basal conditions (Fig. 7.3).

Ablation of BAT [8] or a genetic knockout of Ucp1 [9] causes obesity, insulin resistance, and

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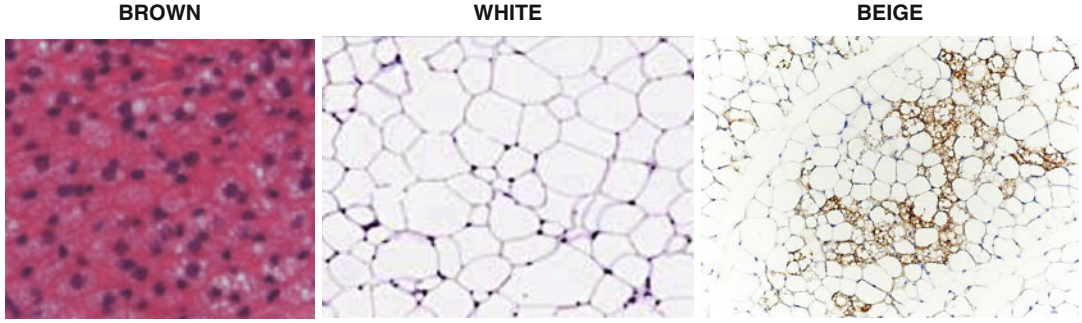

Fig. 7.1 Typical appearance of BAT in the late fetal and neonatal periods and white and beige adipose (*right*) in postnatal life (*Right* image courtesy of Dr. Patrick Seale, University of Pennsylvania School of Medicine, Institute for Diabetes, Obesity and Metabolism.)

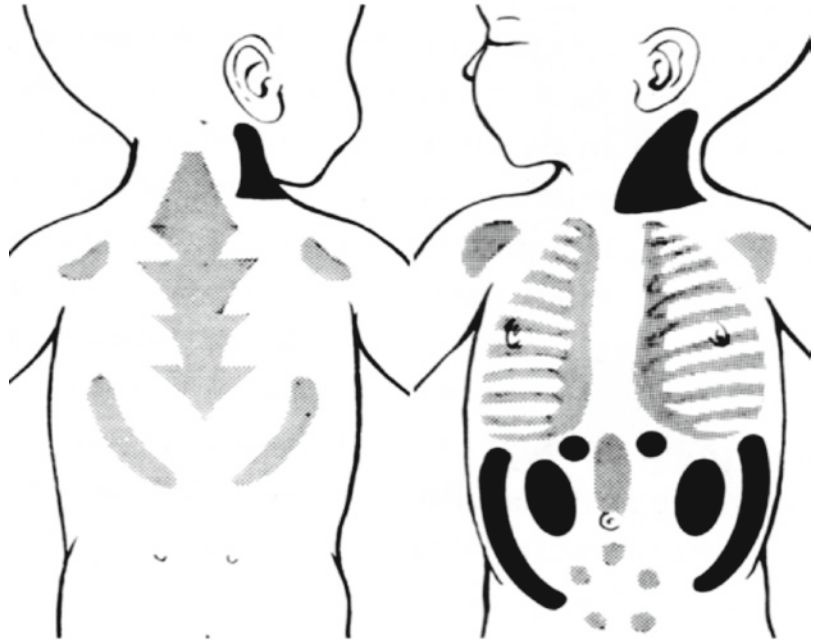

Fig. 7.2 Distribution of brown adipose tissue in the newborn human infant (From van Marken Lichtenbelt W. Human brown fat and obesity: methodological aspects. Front Endocrinol (Lausanne). 2011 Oct 17;2:52; Inspired by Merklin RJ. Growth and distribution of human fetal brown fat. Anat. Rec 1974;178: 637–645.)

glucose intolerance in mice housed under thermoneutral conditions. In addition, a selective defect in beige adipocyte function [10] in mice is reported to promote subcutaneous fat deposition and hepatic steatosis. Conversely, Fox C2 transgenic mice with enhanced BAT mass and function are protected against diet-induced obesity and its comorbidities [11]. While these findings implicate roles for brown and beige adipose tissue in the defense against obesity and metabolic dysfunction, their relevance to human brown fat development and function remains unclear.

Origin and Lineage of Brown and Beige Adipocytes

From a cell lineage perspective, "classic" brown adipocytes (i.e., interscapular brown adipocytes) have been considered to arise from Pax7+, Myf5+ progenitor cells in the dermatomyotome [12–14]. Bone morphogenic protein 7 (BMP7) and the transcriptional co-regulators PRDM16 and PGC1α act in concert to promote differentiation of these progenitors to brown adipocytes rather than myocytes.

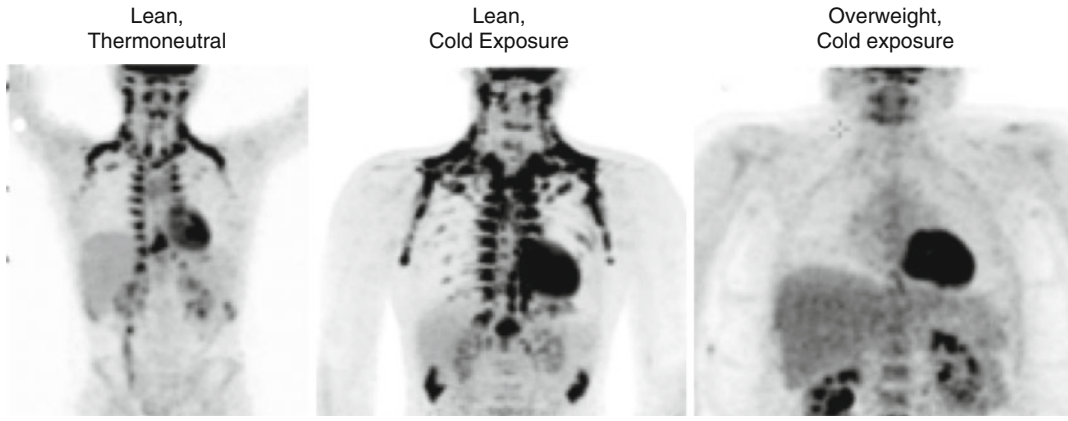

Fig. 7.3 Cold induction of brown adipose tissue FDG uptake (*Left*: Used with permission of Springer Science from Hong T.S, Shammas A, Charron M, Zukotynski KA, Drubach LA, Lim R. Brown adipose tissue ^{18}F-FDG uptake in pediatric PET/CT imaging. Pediatr. Radiol 2011;41: 759–768; Middle: Used with permission of NEJM from van Marken Lichtenbelt W D, Vanhommerig JW, Smulders NM, Drossaerts MAFL, Kemerink GJ, Bouvy ND, Schrauwen P, Teule GJJ. Cold-activated brown adipose tissue in healthy adult men. N. Engl. J. Med. 2009;360: 1500–1508; Right: From Vijgen GHEJ, Bouvy ND, Teule GJJ, Brans B, Schrauwen P, van Marken Lichtenbelt WD. Brown adipose tissue in morbidly obese subjects. PLoS ONE 2011;6, e17247.)

The developmental origin of beige adipocytes remains unsettled. A subset of beige adipocytes may derive from vascular smooth muscle precursor cells [12]. Alternatively, "beiging" may occur through stimulus-dependent (see below) transdifferentiation of white adipocytes. The absence of changes in adipocyte DNA or number during the "beiging" process suggests (to some) that beige adipocytes largely originate from nondividing, mature adipocytes [13, 14]. It is possible that the origin and/or development of beige adipocytes might vary by location of the fat depot, the nature of the browning stimulus, and genetic background, considering evidence from inbred strains of mice that show quite a range in ability to elaborate brown/beige adipocytes within their white fat depots [15, 16].

Ontogenesis of Classical BAT

Studies of mutant mice [8, 9] suggest that normal development of BAT and expression of Ucp1 during the formative stages are essential for postnatal energy homeostasis. Thus, studies of BAT development in humans and experimental animals may have important implications for the pathogenesis of human obesity.

The ontogenesis of BAT has been studied most extensively in the fetal sheep [17]. The nascent perirenal fat pad, which contains precursors for both white and brown adipocytes, undergoes a proliferative stage at mid-gestation in association with high-level expression of PRDM16, BMP7, and several HOX genes (A1, C9). Classic gene markers of BAT thermogenesis [PGC1α, beta 3 adrenergic receptor (Adrb3), CIDEA, type 2 deiodinase, Ucp1] are not expressed until late in fetal development. Ucp1 expression peaks on the day of birth and declines soon thereafter, as brown adipocytes are replaced by large, unilocular white adipocytes that express adiponectin and leptin.

In the mouse, the interscapular depot of BAT is first detected on embryonic day 16.5 (e16.5), in association with high-level expression of PRDM16. BAT mass increases progressively toward term, with striking upregulation of Ucp1 and the type 2 deiodinase (Dio2) and downregulation of PRDM16 [18]. The histologic appearance of the BAT depot changes soon after delivery, with the accumulation of large, unilocular white adipocytes [19] (Fig. 7.4).

In humans, brown adipocytes are detected in the area of the axial skeleton and perirenal fat pad by mid-gestation [20–22]. The mass of BAT rises

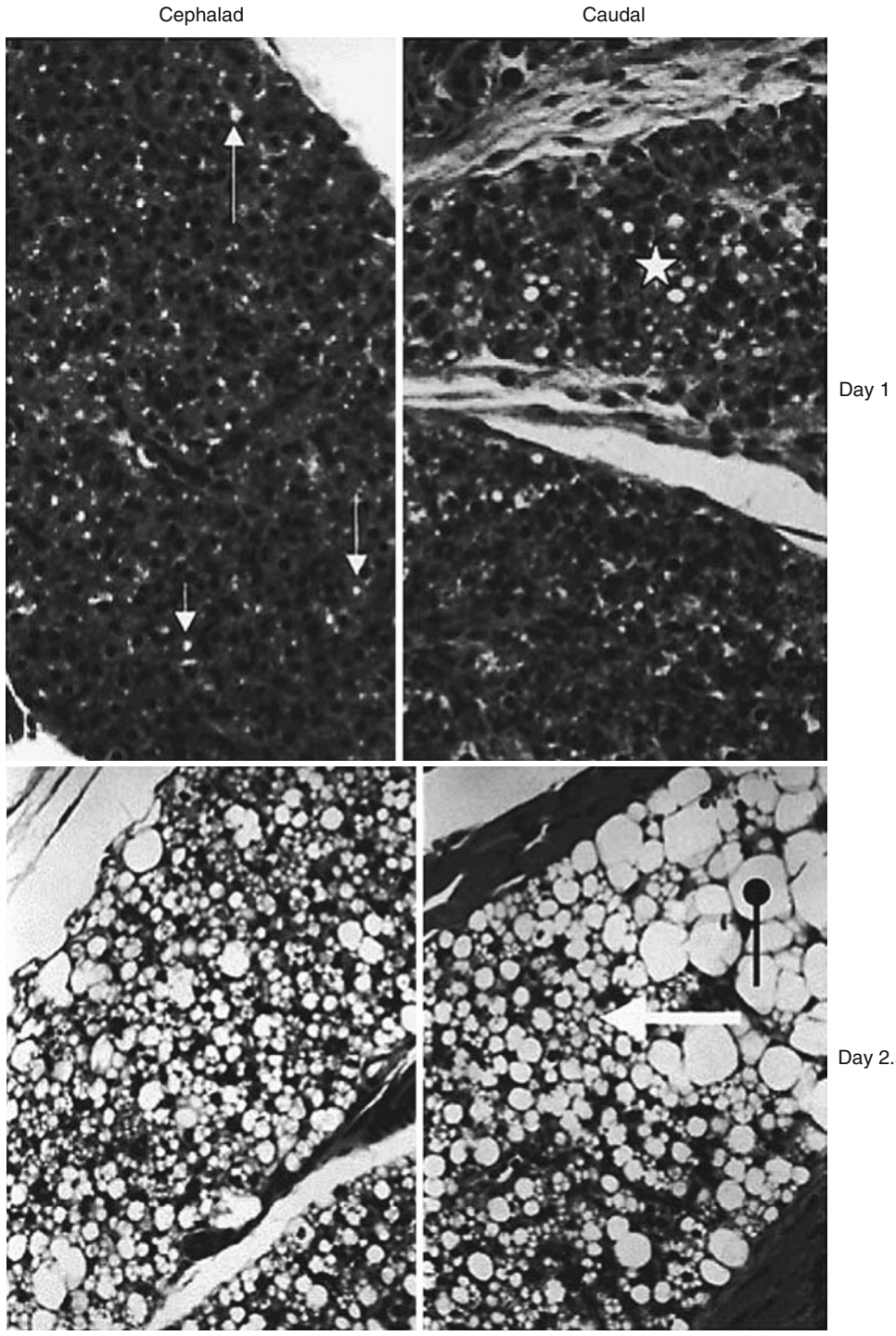

Fig. 7.4 Changes in BAT morphology in the newborn mouse. On day 1, the *white arrows* point to lipid droplets in brown adipocytes; the star shows a group of small unilocular adipocytes in the caudal portion of the interscapular BAT depot. On day 2.5 the *white arrow* points to multilocular brown adipocytes; the black drumstick points to a large unilocular white adipocyte (Used with permission of Karger from Oden J, Fleenor D, Driscoll P, Freemark M. Leptin in the newborn mouse. Plasma concentrations, characterization of the circulating hormone, and tissue source. Biol Neonate. 2002 Aug;82(2): 109–16.)

to a peak at the time of birth (*at term*); major deposits in newborn children are found in the interscapular, supraclavicular, pericardial, and perirenal fat pads (Fig. 7.2). Limited data demonstrate a sharp rise in human fetal BAT Ucp1 content and deiodinase activity after 30 weeks of gestation [23]. The late maturation of BAT function explains in part the susceptibility of preterm infants to neonatal hypothermia. As in the sheep, there is gradual replacement of brown by white-appearing adipocytes in the neonatal period. Nevertheless, "browning" of the interscapular, supraclavicular, perirenal, and visceral fat can be induced in postnatal life by a variety of physiologic and pharmacologic stimuli in children as well as adults (Fig. 7.3 and below).

The mass and "activity" of BAT vary widely among children but appear to increase significantly during pubertal development [24, 25]. While BAT activity measured by fluorodeoxyglucose uptake appears to be higher in adult women than adult men, there are no clear differences in BAT activity between boys and girls [25] studied under basal conditions (fasted 4 h, ambient temperature 21°C).

Hormonal Control of Brown Adipose (BAT) Development During the Late Fetal and Perinatal Periods

Insulin/IGF Signaling

Both insulin and the insulin-like growth factors (IGFs) promote adipogenesis in primary brown preadipocytes and preadipocyte cell lines [26, 27], and a knockout of the IGF-1 receptor in the mouse reduces by 25% the mass of brown adipose tissue at 3 months of age, but not during the neonatal or early postnatal periods [28]. A targeted deletion of the mouse insulin receptor has no effect on BAT mass at 2.5 weeks of age and *increases* BAT mass dramatically at 8–12 weeks. Paradoxically, this is associated with striking reductions in the expression of genes critical for thermogenesis including Ucp1, Cidea, Adrb3, Dio2, and Tfam and increased sensitivity to cold. Interestingly the combined deletion of both insulin and IGF-1 receptors [28] reduces markedly (−80%) the mass of BAT by the time of weaning and dramatically impairs thermogenic gene expression and the response to hypothermia. In sum, the findings suggest that insulin and IGF-1 signaling may act in concert during the late fetal or neonatal periods to promote BAT development and function (Fig. 7.5).

Thyroid Hormone Signaling

A critical role for thyroid hormone in the control of *BAT development* is suggested by the hypothermia of human infants with severe congenital hypothyroidism [29] and the reduction in UCP content and thermogenic activity in BAT of newborn lambs thyroidectomized in utero [30]. In the human fetus, the plasma concentrations of free thyroxine (FT4) increase progressively between 18 and 36 weeks of pregnancy. Levels of T3, on the other hand, are exceedingly low until 30 weeks of gestation and increase thereafter toward term. Circulating and tissue levels of T3 are modulated by deiodinases that induce (Types 1 and 2) or disrupt (Type 3) peripheral conversion of T4 to T3. The expression of type 2 deiodinase (Dio2) in human fetal BAT increases sharply after 30 weeks of pregnancy [23]. In BAT of mice, high levels of type 3 deiodinase (Dio3) predominate during early development (e16.5), preventing intracellular generation of active T3 and thereby limiting thyroid hormone receptor signaling. During BAT maturation (e16.5–e18.5), there is a progressive increase in the expression of Dio2 and a corresponding decrease in Dio3 [30]. This stimulates an increase in intracellular T3, which forms a complex with the nuclear thyroid hormone receptor and regulates transcription of T3-responsive genes. The induction of Dio2 is essential for BAT *maturation*, as Dio2 knockout mice have striking reductions in fetal BAT expression of key thermogenic genes including PGC1α and Ucp1 [18]. Thyroid hormone signaling, however, does not appear to regulate BAT *growth*, as Dio2 knockout mice have normal BAT mass [18].

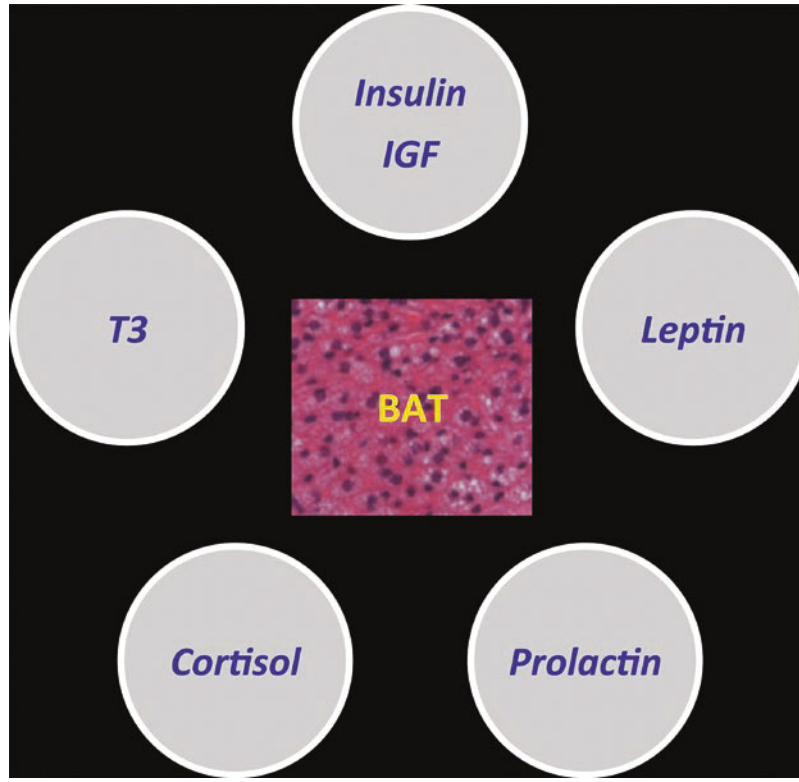

Fig. 7.5 Hormonal control of BAT development during the late fetal and perinatal periods

Cortisol

There is a surge of cortisol in the human fetus during the last 5 weeks of gestation. Studies in the sheep suggest that cortisol may modulate fetal BAT development through effects on T3. Fetal adrenalectomy in late gestation decreases type 1 deiodinase activity in perirenal adipose and reduces fetal plasma T3 levels and adipose Ucp1 content; T3 levels and UCP1 are restored by fetal cortisol infusion [31, 32]. In some ways this seems surprising, because glucocorticoids reduce T3 levels in children and adults and inhibit BAT thermogenic activity in postnatal rats and mice [33]. It is possible that the effects of cortisol in the ovine fetus are mediated in part by a rise in adipose leptin expression [31] or induction of beta adrenergic receptors (see below). Cortisol upregulates beta 2 adrenergic receptors (but downregulates beta 1 and 3 receptors) in human and mouse preadipocytes [34, 35]. Nevertheless, the role of cortisol in human BAT development and function remains unclear.

Leptin

Leptin levels in the human fetus rise during the last 5 weeks of gestation. In the newborn infant, the ratio of leptin to soluble leptin receptor is high, suggesting the availability of free/bioactive hormone [19, 36]. Several lines of evidence suggest a role for leptin in BAT development and function. For example, continuous administration of leptin to fetal sheep for 4 days in late gestation increased the proportion of multilocular adipocytes in perirenal adipose tissue and marginally increased tissue expression of Ucp1 [37]. Moreover, leptin increases oxygen consumption in weanling and adult mice; this effect appears to be mediated by sympathetic outflow to BAT [38]. On the other hand, leptin had no effect on oxygen consumption in perinatal (<10 days) wildtype or *ob/ob* mice, which have a nonsense mutation in the leptin gene [39]. We do not yet know if leptin promotes BAT growth and/or function in the human fetus or infant.

Prolactin and Growth Hormone

The roles of prolactin and growth hormone in fetal BAT development are also poorly understood. Human fetal prolactin levels rise markedly during the final 10 weeks of gestation, and prolactin receptors in brown adipose are induced in the fetal rat and sheep near term [40, 41]. In contrast, plasma growth hormone levels in the human fetus decline between mid-gestation and term; GH receptor expression in BAT has not yet been examined. One study found that BAT mass and expression of Ucp1, PGC1α, and the beta 3 adrenergic receptor (Adrb3) were reduced in newborn mice with a global knockout of the prolactin receptor [42]. Interestingly, browning of perirenal and subcutaneous white adipose tissue and increases in energy expenditure were noted in adult PRLR knockout mice fed a high-fat diet [43]. Adult growth hormone receptor knockout mice have increased interscapular BAT mass and UCP1 activity [44], but the effects of growth hormone on BAT thermogenesis in the perinatal period have not yet been studied.

Induction of BAT Thermogenesis in the Neonatal Period

In response to the stress of delivery and the rapid fall in ambient temperature, there is a surge in *plasma catecholamines and T3* and an increase in *sympathetic outflow* from the dorsomedial hypothalamus [45]. Norepinephrine promotes brown adipocyte thermogenesis through a cascade of actions that include fatty acid and glucose uptake, de novo lipogenesis, and activation of adipose triglyceride lipase and hormone-sensitive lipase [46, 47]. The consequent breakdown of triglyceride (lipolysis) provides essential fatty acids for mitochondrial oxidation; direct activation of UCP1 by fatty acids uncouples mitochondrial respiration from ATP production and generates heat. In this way, the induction of BAT thermogenesis in the newborn infant maintains body temperature and thereby serves a critical survival function (Fig. 7.6).

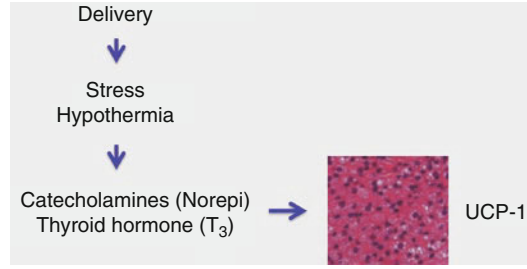

Fig. 7.6 Induction of BAT thermogenesis in the neonatal period

The thermogenic effects of norepinephrine are attenuated or abolished in the absence of thyroid hormone [48]. Thyroid hormone modulates BAT development and thermogenesis through a number of mechanisms. Binding of T3 to thyroid hormone receptor α increases brown adipocyte sensitivity to beta-adrenergic stimulation but does not appear to regulate Ucp1 transcription [49]; in contrast, binding to thyroid hormone receptor β acts in synergy with norepinephrine to induce transcription of the Ucp1 gene [50]. This effect is mediated by the recruitment of PGC1α, PRDM16, and T3-bound thyroid hormone receptor β to an enhancer element located 2.5 kb upstream of the UCP1 transcription start site [51, 52]. Thyroid hormone induction of Ucp1 gene expression can be demonstrated in fetal brown adipocytes in vitro [53, 54], suggesting a direct hormonal effect at the tissue level.

Thyroid hormone also has an indirect role in BAT thermogenesis by promoting sympathetic outflow from the ventromedial hypothalamus [55–57]. Norepinephrine released from sympathetic nerve endings binds to beta-adrenergic receptors and increases the expression of type 2 deiodinase. This increases brown adipocyte concentrations of T3, which potentiates the thermogenic effects of the catecholamines. Thus, the catecholamines and thyroid hormone appear to act in concert to promote BAT thermogenesis in the newborn infant.

Control of Browning and Beige Adipose Development and Function in Postnatal Life

The ability to generate and/or expand the mass of brown adipocytes within white adipose depots determines in part the ability of a rodent to resist obesity and maintain glucose tolerance [10, 11]. Whether or not this is true in humans is currently unclear; however, the inverse relationship between BMI and BAT activity in children and adults (Fig. 7.3 and below) implicates a role for "beiging" in human metabolic homeostasis (Fig. 7.7).

"Beiging" is defined as the presence of UCP1-staining adipocytes in white adipose tissue biopsies or depots. In children, islands of beige adipocytes have been demonstrated in the perirenal, visceral, and subcutaneous fat deposits [58]. As noted previously, the presence and "activity" of brown or beige adipose in children or adults can be assessed by the uptake of ^{18}F-FDG on PET/CT [59, 60]. Under resting, thermoneutral conditions, the uptake of FDG in obese adults is generally very low; uptake is higher in younger, leaner subjects (Fig. 7.3).

The major physiological stimuli for induction of BAT "activity" (i.e., increases in FDG uptake) are cooling and exercise. Mediators of the effects of cold, exercise and other "beiging" agents are shown in Fig. 7.7

Cooling

The effect of cold is mediated through increases in sympathetic nervous system outflow and can be mimicked by chronic treatment with beta3 adrenergic agonists [61]. As shown in Fig. 7.3, cold-induced ^{18}F-FDG uptake is symmetrical and

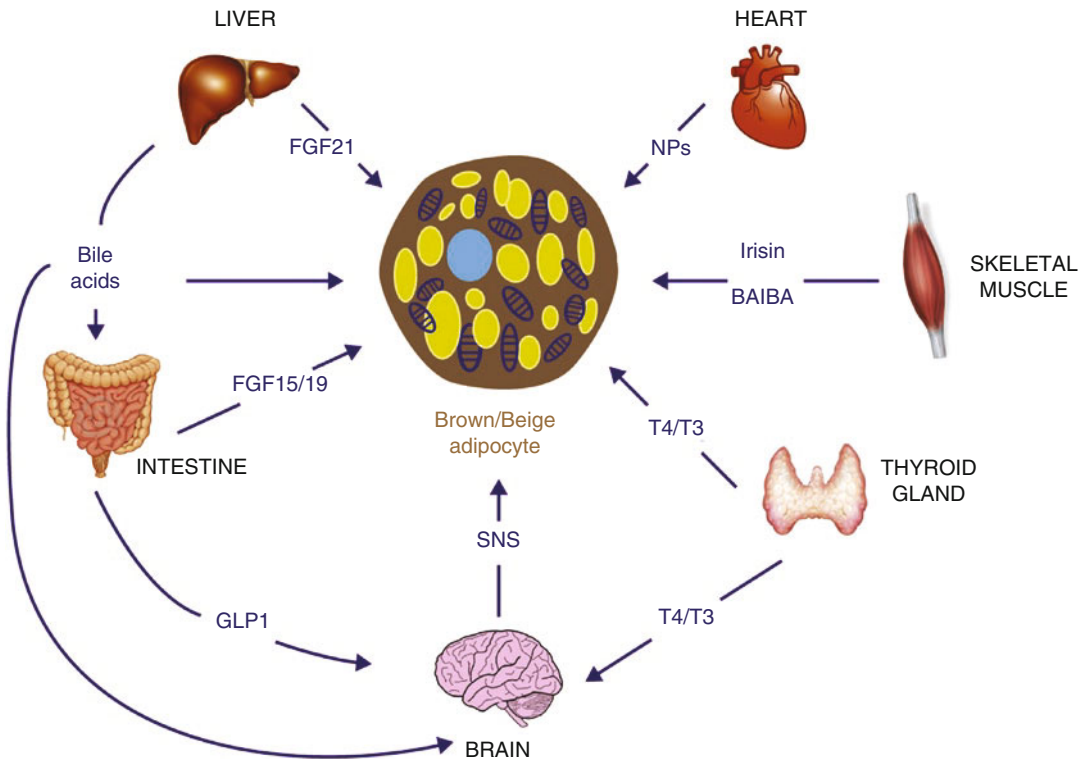

Fig. 7.7 Control of beige adipocyte development and function in postnatal life (Used with permission of Elsevier from Giralt M, Cairó M, Villarroya F. Hormonal and nutritional signaling in the control of brown and beige adipose tissue activation and recruitment. Best Pract Res Clin Endocrinol Metab. 2016;30(4):515–525.)

localized primarily in the cervical and supraclavicular regions.

Cooling is associated with a rise in plasma levels of fibroblast growth factor 21 (*FGF21*) [62, 63], which increases expression of PGC1α and Ucp1 in primary rodent white adipose tissue and human beige adipocytes [63–65]. The principal source of circulating FGF21 appears to be the liver. Nevertheless, induction of FGF21 mRNA levels in BAT and increases in BAT release of FGF21 [66] may facilitate the "browning" process in WAT.

Exercise

Acute exercise in humans and rodents stimulates a rise in plasma *norepinephrine and epinephrine* and promotes sympathetic nervous system activity, which in theory could enhance lipolysis and promote brown adipogenesis, PGC1α expression, and mitochondrial biogenesis. The effects of exercise are likely potentiated by increases in circulating levels of cardiac natriuretic peptides, an increase in plasma interleukin 6 (IL6), and, possibly, a rise in the levels of a muscle-derived protein termed "irisin."

Natriuretic peptides are released in response to stretching of atrial cardiomyocytes and rise in humans during a bout of exercise [67]. Cooling can also stimulate a rise in circulating natriuretic peptides, at least in rats [68]. The natriuretic peptides are potent lipolytic hormones that act in concert with norepinephrine to induce PGC1α, mitochondrial biogenesis, Ucp1 expression, and uncoupled respiration in human white adipocytes [69, 70] (Fig. 7.8). Plasma levels of atrial natriuretic peptide (ANP) are reduced in obese adults [71], and the lipolytic response to ANP is impaired in subcutaneous white adipocytes of obese women and men; this appears to reflect a reduction in the natriuretic receptor that mediates signal transduction (NPR-A) and an increase in the receptor that clears the peptides (NPR-C) [72–74].

The inflammatory cytokine *IL6* rises acutely in response to exercise in rodents [75] and when overexpressed can induce Ucp1 and BAT thermogenesis [76]. Interestingly IL6 levels are elevated in obese adolescents and children and decline following bariatric surgery, in association with an increase in insulin sensitivity [77, 78].

A circulating peptide named *irisin* was described as a cleavage product of skeletal muscle fibronectin type III domain containing 5 (FNDC5); this gene is expressed at far higher levels in mouse heart than skeletal muscle (http://biogps.org/#goto=genereport&id=384061). In some but not all studies, the blood levels of irisin rose modestly following acute (but not chronic) exercise [79]. FNDC5 or *irisin* were reported to act in concert with FGF21 to induce lipolysis and PGC1α expression in human neck adipocytes and promote their transformation to beige-like cells. These effects were reported to be potentiated by norepinephrine [80].

Preliminary studies have reported that plasma irisin, like IL6, is markedly elevated in obese children [81], suggesting that levels might rise as an adaptation to weight gain. It should be noted, however, that measurements of irisin in human serum and plasma have yielded widely disparate results, and the existence of irisin as a human myokine has been questioned, in part, because the specificity of irisin antibodies has not been fully validated [82, 83].

Other Signaling Pathways

Various other signaling pathways modulate the browning of WAT; the effects of bile acids, short-chain fatty acids, and the sex steroids are of particular interest.

Bile Acids, GI Hormones, and Short-Chain Fatty Acids

The gastrointestinal tract appears to play an important role in the browning process. *Bile acids* released following a meal activate intestinal farnesoid X receptors (FXR), which are enriched in the ileum. This stimulates a rise in circulating levels of FGF15 (the human homolog is FGF19), which promotes thermogenesis and the expression of type 2 deiodinase, PGC1α, and Ucp1 in BAT and the "browning" of WAT, with

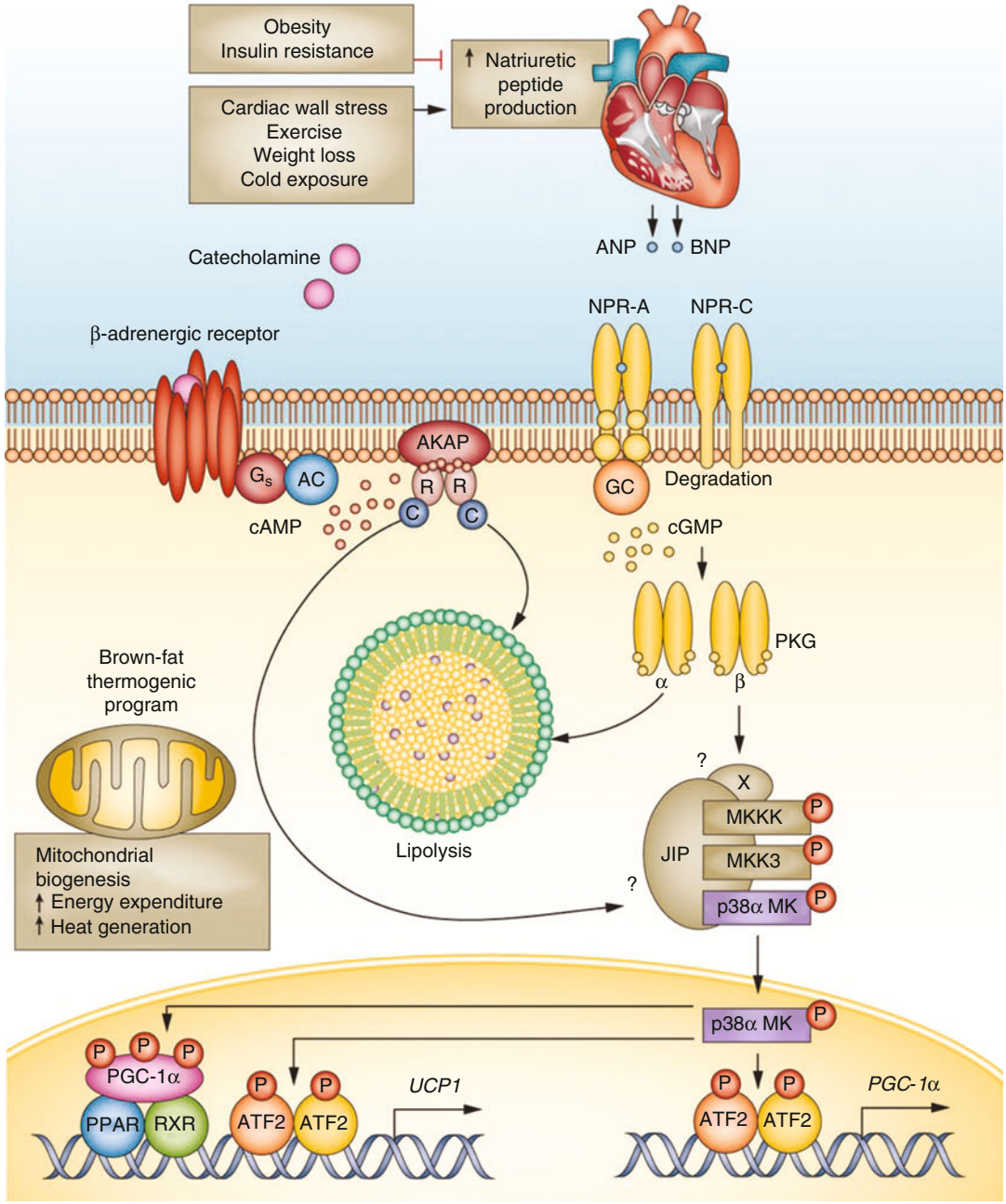

Fig. 7.8 Cardiac natriuretic peptide signaling in adipocytes. The natriuretic peptides ANP and BNP are produced by the heart and regulate adipocyte lipolysis by binding to two homodimeric receptors, NPR-A and NPR-C. Binding of natriuretic peptides to NPR-A activates guanylyl cyclase, producing cGMP, which activates cGMP-dependent protein kinase (PKG). In turn, PKG-mediated phosphorylation triggers a signaling cascade that results in enhanced lipolysis and activation of p38 mitogen-activated protein kinase, as well as inducing the brown fat thermogenesis pathway. In parallel with this mechanism, β-adrenergic signaling activates adenylate cyclase, producing cAMP. Binding of cAMP to the regulatory subunits of cAMP-dependent protein kinase releases its catalytic subunits, initiating a signaling cascade that also independently stimulates these two pathways. The so-called clearance receptor, NPR-C, binds and internalizes natriuretic peptides, which targets them to be degraded. The ratio of NPR-A to NPR-C is, therefore, an important determinant of the strength of NPR-A–PKG signaling (Used with permission of Nature Publishing Group from Collins S. A heart-adipose tissue connection in the regulation of energy metabolism. Nat Rev. Endocrinol. 2014;10(3):157–63.)

upregulation of beta 3 adrenergic receptors and hormone-sensitive lipase. Body temperature, locomotor activity, and energy expenditure are increased [84–86]; see also Chap. 3 on Gastrointestinal Hormones and the Control of Food Intake and Energy Metabolism.

The browning effect of bile acids may be potentiated by their binding to the G-protein coupled receptor TGR5, which increases ileal production of *glucagon-like peptide 1* (*GLP-1*) [87]. GLP-1 acts centrally at the ventromedial hypothalamus to increase sympathetic outflow and induce Ucp1 expression in interscapular BAT and inguinal WAT [88].

Acetate and other short-chain fatty acids, which are generated by microbial fermentation of colonic carbohydrates, can act directly on brown adipocytes to increase PGC1α, mitochondrial biogenesis, and Ucp1 [89].

Sex Steroids

Sex steroids may modulate the browning process, as adult women have higher fluorodeoxyglucose-PET uptake than adult men. Estrogen receptors α and β are expressed in human BAT as well as WAT**,** and estrogen treatment induces brown adipocyte lipolysis and thermogenesis in association with increases in adrenergic receptors and mitochondrial biogenesis [90, 91]. At the same time, a thermogenic effect of estrogen may be mediated indirectly through increases in sympathetic outflow from SF-1 neurons in the ventromedial hypothalamus. Deletion of estrogen receptors in both SF1 and POMC neurons caused hypometabolism, hyperphagia, and obesity [91]. Interestingly, the thermogenic response to estrogen is blunted in pregnancy [92].

In contrast to estrogen, testosterone treatment of mice induces, and a deletion of androgen receptors reduces, PGC1α and mitochondrial biogenesis in skeletal muscle but not in BAT [93].

Relationship Between BAT Activity and BMI in Children

Many, but not all, studies in adults find that basal- and cold-stimulated BAT activity is higher in lean than obese subjects. An inverse relationship between BMI and BAT mass or activity has also been reported in children by some investigators but not others [24, 25, 94]; one investigative group finds that the volume of BAT, as determined by MRI, correlates positively with muscle mass but is not related to body fat mass [24]. A study [93] of healthy 9–15-year-old children using diffusion-weighted MRI found that supraclavicular adipose tissue of obese subjects has higher fat content and lower mitochondrial content; this finding suggests reduced thermogenic activity. Whether this is a cause or consequence of pediatric obesity is currently unclear.

Diet-Induced Thermogenesis and the Response of BAT to Bariatric Surgery

Following consumption of food, there is a transient increase in energy expenditure that reflects the energy costs of nutrient digestion, absorption, and storage and the induction of thermogenesis in skeletal muscle and, to a lesser extent, BAT [95, 96]. This "diet-induced thermogenesis (DIT)" can be quantified in absolute terms (kcal or kjoules per hour) or as a percent of the energy content of the food ingested.

Meta-analyses of a relatively limited set of studies in adults conclude that (a) absolute energy expenditure related to DIT after a single meal (breakfast) is relatively low, approximating 46–72 kj (11–17 kcal) per hour; (b) energy expenditure from DIT is generally proportional to caloric intake (~ 1.1% of energy intake); (c) DIT is higher after protein- and carbohydrate-enriched meals than after meals enriched in saturated fat; and (d) the thermogenic response to a high-fat meal is variably and inconsistently attenuated in obese adults [97–99]. A single small study showed a blunted thermic response to a liquid mixed meal in obese prepubertal children [100]. An additional investigation [101] found no significant differences in DIT or total daily energy expenditure among adults ingesting 50% excess energy as fructose, sucrose, or glucose over a 4-day period. It is unclear if variations in DIT contribute to the development or maintenance of adult or childhood obesity.

Certain food extracts appear to stimulate BAT fluorodeoxyglucose uptake and whole-body

energy expenditure in rodents and humans; examples include capsaicin-like compounds (capsinoids) found in sweet red peppers [102]; rutin found in capers, black olives, buckwheat, asparagus, berries, and green tea [103]; and an African ginger-like species called grains of paradise [104]. Whether or not these or other nutrients could reduce body weight by increasing energy expenditure is currently unclear.

Limited evidence in human subjects demonstrates that weight loss following bariatric surgery is associated with increases in conjugated bile acids [105] and B-type natriuretic peptides [106]. Bypass surgery in mice increases expression of the natriuretic (NPR-A) and beta-adrenergic receptors and Ucp1 in gonadal white adipose tissue [107]. These findings suggest that surgical weight loss might be facilitated or enhanced by browning of white fat.

Critical Gaps in Knowledge and Future Outlook

Although destruction or incomplete development of BAT or a knockout of Ucp1 in mice can cause obesity, insulin resistance, and glucose intolerance, the roles of BAT in childhood growth and metabolism and the pathogenesis of childhood obesity remain poorly understood. The factors controlling development of BAT in the fetal and postnatal periods and puberty have not been clearly elucidated, and the relative contribution of BAT thermogenesis to whole-body energy expenditure in infants and children is unknown [108]. It is unclear if changes in BAT development and function cause, or reflect, changes in fat mass or lean body mass. It is also unclear if activation of BAT thermogenesis can be employed therapeutically to prevent or treat childhood (or adult) obesity or its comorbidities. Nevertheless, proteins secreted by BAT such as FGF21 and neuregulin 4 [109–111] can increase insulin sensitivity and defend against hepatic steatosis, while BAT activity increases in response to exercise and weight loss. Thus, changes in BAT metabolism and function may generate a virtuous cycle that might promote long-term metabolic health.

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Part IV

The Genetics of Childhood Obesity

Monogenic Obesity

8

Marie Pigeyre and David Meyre

Introduction

Childhood obesity is characterized by excessive accumulation of adipose tissue and is defined by specific age and sex-matched body mass index (BMI) cutoffs (e.g., BMI Z-score ≥ 95th percentile) to account for growth [1]. Globally, 42 million children under the age of 5 years, and 224 million children between the ages of 5 and 17 years, were overweight or obese in 2013 [1, 2]. Although originally considered a problem unique to high-income countries, obesity cases are now rising in developing countries at rates more than 30% higher than those of developed countries [1, 2]. The major environmental contributors of childhood obesity include diet (excessive food intake and/or the consumption of energy-dense food, snacks, and sweetened beverages), lack of exercise, sedentary behaviors, low family socioeconomic status, and poor sleeping patterns [3]. However, not all individuals with an obesogenic lifestyle develop obesity. This discrepancy can be explained by various biological factors that also influence the onset of obesity, including age, gender, ethnicity, family history, and, in particular, genetic predisposition. Family history of obesity is a well-established risk factor for childhood obesity, and parental BMI or overweight/obesity status is associated with BMI or the risk of overweight/obesity in children [4]. Twin studies have shown that genetic inheritance contributes toward 40–75% of the obesity cases [5].

Genetic obesity results from structural deletions, variations, or mutations affecting genes that encode proteins involved in appetite regulation and metabolism and is transmitted under Mendelian autosomal or X-linked patterns [6]. It can be characterized as syndromic obesity, which is commonly associated with mental retardation, dysmorphic features, and organ-specific abnormalities (see Chap. 9 by Drs. Irizarry and Haqq), and monogenic non-syndromic obesity, caused by a single-gene mutation that leads to intense hyperphagia, early-onset obesity, and in some cases endocrine abnormalities. Studying cases of extreme obesity caused by single-gene mutations has provided valuable information on the role of leptin-melanocortin pathway in energy balance (Fig. 8.1). Congenital leptin deficiency was discovered to be the first of the group of monogenic disorders [7]. The identification of mutations in

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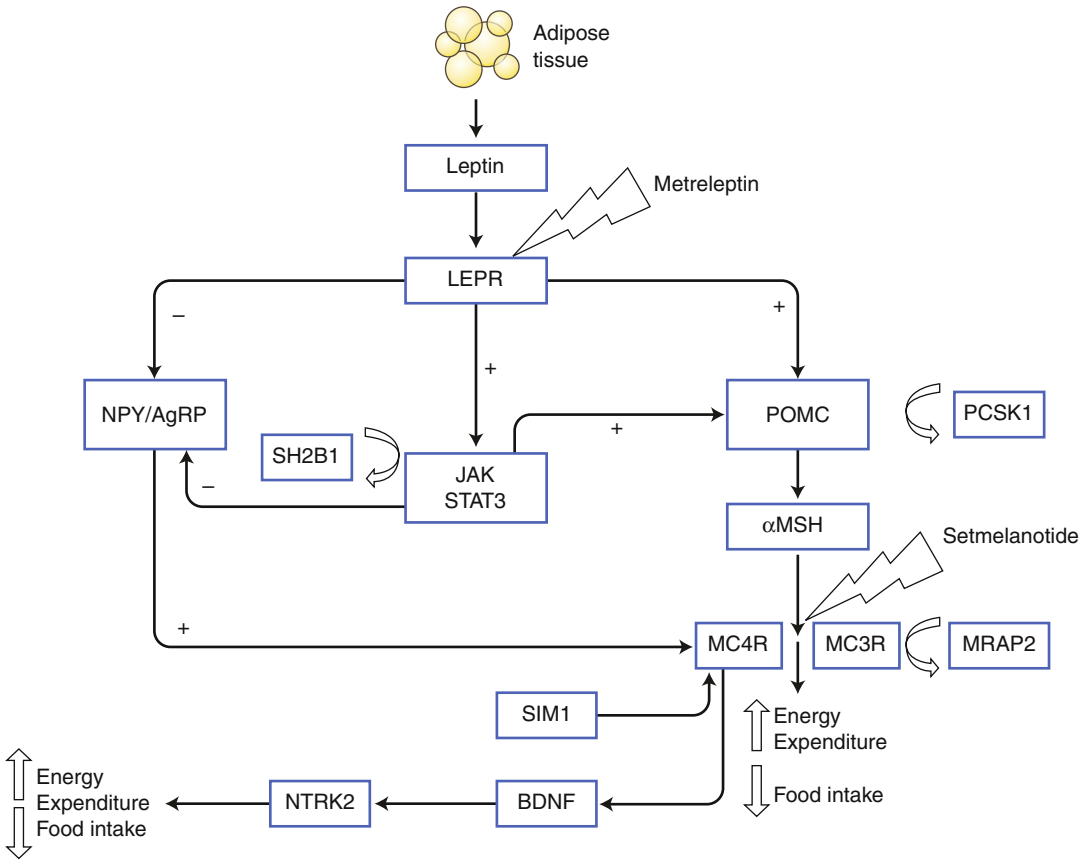

Fig. 8.1 Genes involved in the leptin-melanocortin pathway that have been associated with monogenic obesity through their influence on food intake and energy expenditure. Leptin secreted from adipose tissue binds to the leptin receptor in the hypothalamus. Leptin binding inhibits the neuropeptide Y/agouti-related protein (NPY/AgRP) production and stimulates proopiomelanocortin (POMC) production, which undergoes posttranslational modifications to produce peptides such alpha- and beta-melanocyte-stimulating hormone (α- and β-MSH) via the processing of prohormone convertase 1(PC1/PC3). Alpha- and β-MSH bind to melanocortin-3 and melanocortin-4 receptors (MC3R and MC4R) and induce their activity. Melanocortin-2 receptor accessory protein 2 (MRAP2) can reduce the responsiveness of both MC3R and MC4R to α- and β-MSH and result in obesity. On the other hand, single-minded homolog 1 (SIM1) acts as a facilitator of MC4R activity. Increase in the MC3R and MC4R activities results in a decrease in food intake and increase in energy expenditure. MC4R activity also stimulates release of brain-derived neurotrophic factor (BDNF), which will bind to the neurotrophin receptor (TrkB) and influence food intake and energy expenditure. Aside from activation of the POMC, leptin binding to its receptor also activates the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling. This pathway, through the help of Src homology 2 B adapter protein 1 (SH2B1), results in activation of signal transducer and activator of transcription 3 (STAT3). STAT3 will then migrate to the nucleus and activate its target genes related to energy homeostasis and mediate in the anorexigenic effects of leptin. As current therapy, leptin therapy (metreleptin) is highly effective in case of *LEP* deficiency. The emerging α-MSH analog therapy (setmelanotide) can bypass normal leptin delivery pathway to stimulate MC4R

this pathway has been enhanced by research in animal models, which showed phenotypic parallels between patients with inactivating mutations in specific genes and mice with targeted knockout of the same genes [8].

Monogenic obesity disorders are a heterogeneous group of conditions that affect whole-body energy homeostasis by increasing food intake and reducing energy expenditure (Table 8.1). In all recognized disorders, the effects on food

Table 8.1 Clinical and biochemical presentation of monogenic forms of obesity

Gene	Mutation	Prevalence	Physical presentation	Biochemical presentation
LEP	Homozygous mutation	27 patients reported worldwide, more than half in Pakistan	Severe hyperphagia Incapacity of feeling satiety Early-onset obesity within the first year of life Rapid weight gain during childhood and adolescence Hypogonadotropic hypogonadism Hypothalamic hypothyroidism, with puberty delay Reduced adult height Increased risk of infections Decreased risk of hypertension despite severe obesity	Indetectable leptin or decreased (bioinactive) leptin Fasting hyperinsulinemia Decreased/normal FSH, LH Decreased TRH, increased (bioinactive) TSH, decreased T4 Decreased or normal GH Decreased CD4 cells and T-cell responsiveness
LEPR	Homozygous mutation or heterozygous compound mutation	3% within severely obese children from cohort enriched in consanguineous families	Severe hyperphagia Incapacity of feeling satiety Early-onset obesity within the first year of life Rapid weight gain during childhood and adolescence Hypogonadotropic hypogonadism Hypothalamic hypothyroidism, with puberty delay Reduced adult height Increased risk of infections Decreased risk of hypertension despite severe obesity Increased bone mineral density	Increased or normal leptin Fasting hyperinsulinemia Decreased or normal FSH, LH, estradiol, testosterone Decreased TRH, increased (bioinactive) TSH, decreased T4 Decreased or normal GH Decreased CD4 cells and T-cell responsiveness
POMC	Homozygous or compound heterozygous mutation	11 patients reported	Neonatal adrenal insufficiency (causing hypoglycemia, liver failure, seizures) Early-onset obesity Hyperphagia Red hair and skin hypopigmentation only among Caucasians Central hypothyroidism (TSH) GH deficiency Hypogonadotropic hypogonadism (FSH and LH)	Absent ACTH, absent cortisol Hyponatremia Hyperkalemia Hypoglycemia Decreased TSH Decreased or normal GH Decreased FSH, LH
PCSK1	Homozygous or compound heterozygous mutation	19 patients reported	Hyperphagia Obesity (or normal range BMI when intestinal phenotype is predominant on appetite phenotype) Intestinal dysfunction Malabsorptive diarrhea Postprandial hypoglycemia Central hypothyroidism Hypogonadotropic hypogonadism Diabetes insipidus	Increased POMC/low or normal ACTH (basal and stimulated)/decreased or normal cortisol (basal and stimulated) Increased proglucagon/normal GLP-1 and GLP-2 Increased postprandial proinsulin/decreased postprandial insulin Hypoglycemia (oral glucose tolerance test) Low-normal TSH Decreased or normal T4 Decreased LH, FSH, estradiol, testosterone Decreased vasopressin, dilute urine (< 300 mOsm/kg, during water deprivation test)

(continued)

Table 8.1 (continued)

Gene	Mutation	Prevalence	Physical presentation	Biochemical presentation
MC4R	Homozygous or compound heterozygous or heterozygous mutation	3–5% within children with early-onset severe obesity	Hyperphagia Early-onset obesity Rapid weight gain during childhood and adolescence Increased linear growth and height Increased bone mass Increased fat and lean mass Lower risk of hypertension despite the obesity Subclinical hypothyroidism	Hyperinsulinemia High-normal TSH, low-normal T4
MC3R	Heterozygous mutation	22 patients reported	Obesity Pathogenic role of *MC3R* requires further investigations	No specific biochemical phenotype reported
MRAP2	Heterozygous mutation	4 patients reported	Hyperphagia Early-onset severe obesity Acanthosis nigricans Advanced bone age with increased growth in childhood and increased final height in adulthood Subclinical hypothyroidism	Hyperinsulinemia High-normal TSH, low-normal T4
SIM1	Translocation between chr 1p22.1 and 6q16.2 or 6q16.1-q21 deletion or heterozygous mutation	*Translocation*: one case report *Deletion*: 45 patients reported *Mutation*: 21 patients reported	*Translocation*: Increased birth weight Increased linear growth with advanced bone age Normal development No facial dysmorphisms Childhood-onset hyperphagia *Deletion*: Intrauterine growth retardation Neonatal hypotonia Feeding difficulties Failure to thrive Short stature with delayed bone age Severely delayed development Mild facial dysmorphisms Childhood-onset hyperphagia Hypogonadism *Mutation*: Normal birth weight Cognitive deficits with behavioral abnormalities +/− Prader-Willi-like syndrome features	Fasting hyperinsulinemia, mild decrease of cortisol consistent with the obesity
BDNF	Heterozygous 11p13–11p15 deletion or inversion	5 patients reported worldwide	Hyperphagia Severe obesity Cognitive impairment Behavioral abnormalities Hyperactivity	Decreased BDNF Fasting hyperinsulinemia
NTRK2	Heterozygous mutation	Only one reported case, associated with severe obesity	Hyperphagia Early-onset obesity Developmental delay Impairment in short-term memory Impaired nociception	Fasting hyperinsulinemia

Table 8.1 (continued)

Gene	Mutation	Prevalence	Physical presentation	Biochemical presentation
SH2B1	Heterozygous mutation or 16p11.2 deletion	*Mutation*: 0.8% within severe early-onset obese individuals *Deletion*: 0.7% within morbidly obese individuals	*Mutation*: Hyperphagia Severe early-onset obesity Insulin resistance (acanthosis nigricans) Type 2 diabetes in adolescence Reduced adult height Behavioral abnormalities: speech and language delay, aggression, and social isolation *Deletion*: Obesity Insulin resistance Behavioral disorders Autism and schizophrenia	Fasting hyperinsulinemia Fasting hyperinsulinemia
KSR2	Heterozygous mutation (one case carrying compound heterozygous mutation)	2% of the cases within unrelated severely obese individuals	Hyperphagia Early-onset obesity Severe insulin resistance Low heart rate Reduced basal metabolic rate	Increased fasting insulin Increased C-peptide

intake are most dramatic and clinically apparent, leading to hyperphagia. Pathogenic mutations in many of these genes have effects on energy expenditure as well. Homozygous/compound heterozygous loss-of-function mutations in monogenic obesity genes are exceptionally rare in humans. A substantially higher proportion of affected children carry heterozygous deleterious coding mutations in these genes, resulting in non-fully penetrant/oligogenic obesity [6].

Here, we review the main advances in the elucidation of monogenic forms of childhood obesity. We provide a strategy for routine clinical genetic testing and detail the current options and future directions for clinical management and treatment of monogenic obese children.

Genotype-Phenotype Presentation

Leptin Deficiency

Congenital leptin deficiency is a rare autosomal recessive disorder described in subjects from inbred marriages. A frameshift homozygous mutation (c.398delG) in the leptin (*LEP*) gene was first discovered in two severely obese cousins within a highly consanguineous family of Pakistani origin [7]. Eight other pathogenic mutations were subsequently reported in probands from consanguineous families in Pakistan [9–12], India [13], Turkey [14], and Egypt [15] and from a non-consanguineous family in Austria [16]. These subjects presented with no detectable leptin in the circulation, due to truncated transcription of leptin. However, detectable circulating leptin levels have been recently reported in four patients of German, Pakistani, and Turkish ancestry with severe early-onset obesity carrying two different homozygous *LEP* mutations (D100Y and N103 K), indicating that the mutation can affect protein function rather than expression [17–19].

Leptin-deficient children manifest severe, early-onset obesity within the first year of life, accompanied by insatiable hyperphagia and intolerant behavior when food is restricted [7]. Onset of puberty is often delayed due to centrally mediated suppression of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) causing hypogonadotropic hypogonadism as well as mild hypothalamic hypothyroidism [20]. Affected subjects may also exhibit low blood pressure despite severe obesity [21] and defective T-cell-mediated immunity, explaining their high rates of infection [20]. Though described as an autosomal

recessive disorder, there is a subtle increase in adiposity (percentage body fat) among heterozygous carriers of *LEP* mutations [22].

Leptin Receptor Deficiency

Leptin receptor deficiency is another autosomal recessive disorder, caused by mutations that inactivate the leptin receptor (*LEPR*). Congenital *LEPR* deficiencies were first identified in 1998 in three severely obese siblings of Kabilian origin [23] who exhibited highly elevated serum levels of leptin, reflecting the loss of sensitivity of the receptor [24]. Homozygous/compound heterozygous pathogenic mutations in *LEPR* have since been described in 24 children from European [25–28], Egyptian [29], Pakistan [11, 12], and Turkmenian ancestries [30]. They constitute the second most common defect of the leptin-melanocortin pathway after melanocortin-4 receptor (*MC4R*) deficiency, with a prevalence estimated at 3% of the severely obese children from a cohort enriched in consanguineous families [24] and up to 10% of the severely obese children from Pakistani consanguineous families [12]. The identification of novel homozygous mutations in *LEPR* in a consanguineous Pakistani population [11], as well as a novel frameshift mutation in a French population from Reunion Island [26], suggests a founder effect in genetically isolated populations.

Clinical manifestations of children with homozygous/compound heterozygous *LEPR* mutations are similar to those with homozygous *LEP* mutations. Children present with severe hyperphagic obesity and additional clinical features including altered immune function/T-cell numbers [11, 24, 27, 29], hypogonadotropic hypogonadism [25, 26, 29], reduced growth hormone (GH) secretion [23, 26], hypothalamic hypothyroidism [23, 26], increased bone mineral density [28], and low blood pressure [21]. Linear growth in childhood is normal, but adult height may be reduced because of a lack of a pubertal growth spurt [24]. Leptin levels in homozygous patients are very high but may overlap with levels in other subjects with extreme obesity: in a cohort of adults and children with complete loss-of-function *LEPR* mutations [24], mean plasma leptin approximated 200 ng/ml, and nearly all levels exceeded 50 ng/ml. Subjects with extreme exogenous obesity had mean leptin levels approximating 90 ng/ml.

Subjects with heterozygous mutations of the *LEPR* have normal or slightly increased BMI but have higher percentage of body fat mass than lean subjects [24].

Proopiomelanocortin Deficiency

The first cases of obesity due to proopiomelanocortin (*POMC*) deficiency were discovered in 1998 in two probands from distinct German non-consanguineous families; the first proband carried compound heterozygote mutations that interfere with appropriate synthesis of adrenocorticotropin hormone (ACTH) and alpha-melanocyte-stimulating hormone (α-MSH), and the second proband was homozygous for a mutation that abolishes *POMC* translation [31]. *POMC* deficiency is a rare autosomal recessive disorder reported in probands from consanguineous Caucasian [32] and North-African [33] families and non-consanguineous Caucasian [34], Egyptian [35], Indian [36], and Turkish [37] families. Altogether, approximately 50 subjects have been identified to date in large-scale screening studies.

Sequential cleavage of the precursor POMC generates the melanocortin peptides adrenocorticotropin hormone (ACTH) and alpha-melanocyte-stimulating hormone (α-MSH), in addition to others such as β-endorphin. Obesity is thought to be due to deficiency of α-MSH signaling at the melanocortin-4 receptor, resulting in a failure to suppress appetite. The deficient production of ACTH ligand for the melanocortin-2 receptor results in adrenal insufficiency, which can cause severe hypoglycemia and liver failure [31–36].

POMC-deficient newborns typically present in the neonatal period with adrenal crisis, hypoglycemia, cholestasis, and hepatic failure [31, 33, 34, 36]. Obesity then develops in infancy secondary

to hyperphagia. Red hair is thought to be present only among Caucasian individuals with light skin and not in non-Caucasian ethnic groups [33, 35]. It has been attributed to reduced signaling of α-MSH at the melanocortin-1 receptor in the skin. Later in childhood or adolescence, central hypothyroidism (TSH), growth hormone (GH) deficiency, and hypogonadotrophic hypogonadism (FSH and LH) may develop [33]. Other clinical features such as severe motor mental retardation were reported in a female with a homozygous *POMC* loss-of-function mutation [37].

As observed in *LEP* and *LEPR* deficiencies, *POMC* deficiency can be considered codominant because null alleles have measurable effects on body weight in the heterozygous state. Heterozygous loss-of-function mutations in *POMC* result in a non-fully penetrant/oligogenic form of obesity [38–42]. A heterozygous mutation in the *α-MSH* region of the *POMC* gene was found in a 12-year-old girl with early-onset obesity, due to a dramatic impairment of α-MSH binding to MC4R [40]. A heterozygous loss-of-function missense mutation in β-MSH has also been associated with childhood obesity. The lack of function of β-MSH reduces the amount of MSH peptide in the POMC/MC4R pathway, resulting in hyperphagia and obesity [38].

Proprotein Convertase 1 Deficiency

The first recessive monogenic form of obesity to be reported (1995) was due to a deficiency in the proprotein convertase subtilisin/kexin type 1 (*PCSK1*) gene [43]. Three obese carriers of *PCSK1* compound heterozygous mutations were identified in distinct Caucasian non-consanguineous families [43–46] along with obese carriers of *PCSK1* homozygous mutations in a North-African consanguineous family [47] and in a Turkish family with possible consanguinity [48]. Thirteen carriers of *PCSK1* homozygous mutations were also reported in children exhibiting chronic diarrhea from a cohort enriched in consanguineous families of multiethnic origins; the probands represented 6.7% of this particular childhood population [49, 50].

Null mutations causing complete congenital deficiency in prohormone convertase 1 (PC1/PC3) result in hyperphagia, postprandial hypoglycemia, central hypothyroidism, diabetes insipidus, intestinal dysfunction, and hypogonadotropic hypogonadism. These are thought to reflect deficient cleavage of POMC-, proinsulin-, prothyrotropin-, provasopressin-, proglucagon-, and progonadotropin-releasing hormone (proGnRH) [43–46, 50]. The severity of the condition is highly variable and may depend on the functional consequences of the specific mutations; hyperphagia may be counterbalanced by severe malabsorptive diarrhea, resulting in a normal range BMI in some instances [50].

The diagnosis is suspected on clinical features; levels of many precursor proteins (such as proinsulin and proglucagon) are elevated, whereas levels of key hormones (such as insulin, GLP-1, GLP-2) are decreased.

A rare nonsense null mutation of *PCSK1* in the heterozygous state causes a dominant form of Mendelian familial obesity associated with glucose intolerance/diabetes [51]. Therefore, mutations in *PCSK1* may be associated with a dominant or recessive form of monogenic obesity, depending on whether the mutation causes partial or total loss of function [51]. This is further supported by the existence of PC1/PC3 mutations with dominant negative effects that alter the expression of the wild-type protein and reduce PC1/PC3 availability [52]. Partial loss-of-function heterozygous mutations in *PCSK1* present a non-fully penetrant form of Mendelian obesity, with a prevalence estimated at 0.83% of the extreme obesity in European children and adults [53].

Melanocortin-4 Receptor Deficiency

Deficient activity of the melanocortin-4 receptor (*MC4R*) is the most common monogenic cause of severe early-onset obesity [54]. The first heterozygous mutations in *MC4R* were discovered in 1998 in a French cohort of morbidly obese adults and a British cohort of severely obese children [55, 56]. *MC4R* mutations were once considered

an autosomal dominant form of obesity, but not all heterozygous carriers of *MC4R* become obese. In contrast, homozygous mutants display fully penetrant early-onset obesity [57, 58].

α-MSH and AgRP antagonize each other by competing for binding to the MC4R, making the MC4R a key receptor for the regulation of appetite. Mutations of *MC4R* impair the ability of second-order neurons in the paraventricular nucleus to respond correctly to the appetite-suppressing signal sent by POMC neurons via α-MSH [55, 56].

A prevalence of 0.5–5.8% of the *MC4R* heterozygous, heterozygous compound, and homozygous loss-of-function mutation carriers has been reported in severely obese children and adults from different ethnic backgrounds [57, 58], with the highest prevalence being reported in cohorts enriched in consanguineous families [12, 54]. Homozygous/heterozygous compound carriers of this mutation are hyperphagic and show rapid weight gain and excessive fat deposition beginning in the first few months of life [57]. Insulin levels are high, and there are increases in linear growth, bone mass [59–61], and lean body (as well as fat) mass, findings not typically observed in other forms of monogenic obesity [54]. Patients appear to have a lower prevalence of hypertension than would be expected on the basis of BMI, because leptin signaling through the MC4R is a major mechanism that connects obesity with hypertension [21]. TSH may be slightly elevated, while free T4 levels are in the low-normal range [54]. Carriers of *MC4R* heterozygous loss-of-function mutations have milder forms of obesity and exhibit an interaction with the "obesogenic" environment [62, 63].

Melanocortin-3 Receptor Deficiency

Twenty-two heterozygous mutations in melanocortin-3 receptor (*MC3R*) have been identified to date: in two obese patients in Singapore [64], in subjects among a North American cohort [65], in Italian and French subjects [66], and in children and adolescents from Belgium [67].

Loss-of-function *MC3R* mutations were associated with obesity in subjects of Italian, French, and Belgium origin [66, 67] but not in North Americans [65]. No other specific phenotype is reported. Detailed functional analyses of *MC3R* mutations suggest that MC3R functions differently from MC4R, playing a nonredundant role in regulating energy homeostasis through mitogen-activated protein kinases (MAPKs), especially extracellular signal-regulated kinases 1 and 2 (ERK1/ERK2), which are known to alter gene expression [68]. However, the pathogenic role of *MC3R* in the development of obesity awaits further investigation.

Melanocortin-2 Receptor Accessory Protein 2 Deficiency

Four rare heterozygous mutations of melanocortin-2 receptor accessory protein 2 (*MRAP2*) have been found to be associated with early-onset severe obesity in humans [69]. No syndromic features or specific endocrine abnormalities were reported in these individuals. MRAP2 is expressed in the brain and adrenal gland [70]. The MRAP2 protein couples to MC4R and is thought to enhance MC4R signaling and expression of single-minded homolog 1 (SIM1) in the paraventricular nucleus [71]. Targeted homozygous knockout of the *Mrap2* ortholog causes obesity in mice. Thus, reduced MC4R signaling provides a plausible mechanism, whereby *MRAP2* mutations might interfere with body weight regulation [70]. Indeed, a rare variant in *MRAP2* has been recently associated with reduced MC4R signaling and obesity [72]. Features reminiscent of Prader-Willi syndrome may result from effects of the *MRAP2* mutation on *SIM1* [73].

Single-Minded Homolog 1 Transcription Factor Deficiency

Single-minded homolog 1 (*SIM1*) is considered a highly relevant candidate obesity gene among the 12 genes present in the 6q16 region [74–78]. Sim1 is expressed in the CNS and plays an essential role in formation of the paraventricular nucleus (PVN) of the hypothalamus [79, 80].

Whereas complete *SIM1* deficiency is lethal in mice, *SIM1* haploinsufficiency leads to hyperphagia, obesity, and reduction in size of the PVN [81]. *SIM1* haploinsufficiency has been shown to inhibit signaling through the leptin-melanocortin-oxytocin pathways [82, 83].

Excessive growth and severe early-onset obesity were observed in a girl with a balanced translocation leading to *SIM1* haploinsufficiency [84]. In contrast, children with deletions encompassing *SIM1* have a Prader-Willi-like phenotype including intrauterine growth retardation, neonatal hypotonia, feeding difficulties, failure to thrive, reduced linear growth with delayed bone age and short extremities, and mild facial dysmorphism [85]. Severe developmental delays as well as hyperactivity affect motor and cognitive spheres, including language [85]. Hypogonadism is frequent, and structural malformations of the heart and central nervous system may be seen [85]. Although childhood-onset hyperphagic obesity was initially considered characteristic, the largest series reported to date showed that only 8 of 13 patients with *SIM1* deletion exhibited obesity, suggesting an incomplete penetrance of *SIM1* haploinsufficiency [78].

Patients who are heterozygous for mutations that impair Sim1 activity manifest normal height and early-onset hyperphagic obesity, with or without features simulating Prader-Willi syndrome [73]. Hyperinsulinemia is consistent with the degree of obesity. There is some impairment of sympathetic tone in *SIM1* mutation carriers. Cognitive deficits and neurobehavioral abnormalities are common, including poor concentration, poor memory, emotional lability, and autistic spectrum disorders. Respiratory quotient is increased, though basal metabolic rate is normal [86–88].

Brain-Derived Neurotrophic Factor Deficiency

One case of severe obesity was reported in a girl with loss of one functional copy of the gene encoding Brain-Derived Neurotrophic Factor (*BDNF);* she presented with hyperphagia, cognitive impairment and hyperactivity [89]. Circulating levels of BDNF protein were approximately 50% of normal [89]. Hyperphagia and obesity in a subgroup of patients with WAGR syndrome have been attributed to deletions on chromosome 11p14 that induce haploinsufficiency of *BDNF* [90]. Variable degrees of developmental delay, behavioral problems, and obesity have been reported among four patients with overlapping interstitial deletions on 11p14.1 encompassing *BDNF* [91]. BDNF appears to be an important downstream target of MC4R-mediated signaling that participates in the regulation of energy balance and feeding behavior [92].

Neurotrophic Tyrosine Kinase Receptor Type 2 Deficiency

A missense heterozygous mutation in the neurotrophic tyrosine kinase receptor type 2 (*NTRK2*) gene was identified in a boy with early-onset obesity, hyperphagia, developmental delay, impairment in short-term memory and impaired nociception [93]. Impaired hypothalamic neurogenesis may explain the hyperphagia and obesity [94]. However, further analysis showed an alteration of BDNF-stimulated protein kinase phosphorylation [93]. The developmental and neurological impairments in this case are consistent with the wide distribution of Tyrosine receptor kinase B (TrkB - encoded via *NTRK2*) throughout the central nervous system (CNS), where it is responsible for neuronal survival and differentiation and regulation of synaptic function [95].

SH2B Adaptor Protein 1 Deficiency

SH2B adaptor protein 1 (*SH2B1*) deficiency is a rare autosomal dominant disorder [96]. *SH2B1* is a key regulator of leptin action, as it enhances leptin signaling by both stimulating Janus Kinase 2 (JAK2) activity and assembling a JAK2/IRS1/2 signaling complex [97–99].

Nine loss-of-function mutations in *SH2B1* have been associated with severe early-onset

obesity, with a prevalence estimated at 0.8% in severely obese European children [96, 100]. Clinical features include hyperphagia, childhood-onset obesity, insulin resistance, reduced height, and behavioral abnormalities such as speech and language delay, aggression, and social isolation [96]. Acanthosis nigricans and type 2 diabetes develop in adolescence. Possibly, as a result of impaired growth hormone signaling, the final adult height is reduced. Genomic imbalances and recurrent deletions of the *SH2B1*- containing region on the short arm of chromosome 16 have been associated with behavioral disorders such as autism and schizophrenia as well as insulin resistance and obesity [101, 102].

Kinase Suppressor of Ras 2 Deficiency

Kinase suppressor of Ras 2 (KSR2) is a scaffolding protein involved in multiple signaling pathways through kinase cascades [103] that are linked to regulation of food intake, body fat content, and glucose homeostasis [104]. By using a whole-exome sequencing strategy, *KSR2* loss-of-function mutations were identified in 2% of the unrelated Europeans with early-onset severe obesity; accompanying features included hyperphagia, low heart rate, reduced basal metabolic rate, severe insulin resistance, and impaired oxidation of both glucose and fatty acids [103]. The disorder appears to be a fully penetrant monogenic form of dominant obesity, though one severely obese compound heterozygote has been described [103].

Strategy for Diagnosis

Deep Phenotyping

Diagnosing monogenic forms of obesity is important because specific management, provided by specialized and multidisciplinary teams, is ideally needed as early as possible [105].

Deep phenotyping is essential in patients presenting with early- or rapid-onset severe obesity and hyperphagia (see Table 8.1 for detailed clinical and biochemical phenotypes). Particular note should be made of cognitive difficulties, endocrine anomalies (especially growth trajectory and basal and dynamic testing of hypothalamic and pituitary hormones), and clinical features including hypopigmentation of the hair and skin, intestinal dysfunction, and coexistence of normal-weight and obese siblings in the family consistent with a Mendelian pattern of inheritance [106]. Additional measurement of circulating hormones may be useful: insulin and proinsulin levels if *PCSK1* deficiency is suspected, cortisol and ACTH if *POMC* deficiency is considered, and leptin if *LEP* or *LEPR* deficiency is suspected. It should be noted that some patients with functional defects in leptin may have a bioinactive form of the protein that is detected at "normal" levels in commercial leptin assays [17–19]. In the future, custom panels that quantify various hormones, neuromediators, and metabolic/inflammatory/immune markers should be available for specialty care [107]. The lower cost of biomarker panels compared to multiple individual biochemical tests ($40–100 per person to up to 100 biomarkers) and the minimal blood volumes required for analysis represent promising advantages in children that may enhance phenotyping and thereby improve screening for monogenic forms of obesity.

Clinical Assessment and Approach to Genetic Testing

There are as yet no clinical practice guidelines to guide the physician for the genetic testing of severe early-onset obesity. We propose here a strategy based on clinical manifestations in children having a history of early-onset obesity.

The first step is a careful assessment of clinical features and cognitive function. Most forms of "syndromic" obesity (see Chap. 9 by Drs. Irizarry and Haqq) are accompanied by cognitive impairment and dysmorphic features and may be associated with retinal and/or renal anomalies and hearing loss. Some forms of monogenic obesity (*SIM1*, *BDNF*, *SH2B1*) may also be associated with cognitive dysfunction and retinal

degeneration, but the more common varieties (*MC4R*, *LEPR*, *LEP*, *POMC*, *PCSK1*) have normal psychomotor development (Fig. 8.2).

Consultation with a clinical geneticist is useful for initial assessment of a child with *early-onset obesity and intellectual/behavioral disability.* Once the Prader-Willi syndrome, Bardet-Biedl syndrome, and Alstrom and WAGR (and other) syndromes are excluded, a cytogenetic microarray, with comparative genomic hybridization (CGH), is a reasonable first approach to detect structural abnormalities (insertions, deletions, translocations), in chromosomal regions containing the genes for *SIM1*, *BDNF*, and *SH2B1* [108, 109].

In the *absence of intellectual disabilities*, it is useful to measure the levels of leptin, ACTH, and cortisol in early-morning samples. Leptin levels are absent or barely detectable in patients with leptin deficiency and are usually (but not always) markedly elevated in patients with mutations in the leptin receptor. ACTH deficiency may be detected in children and adolescents with *POMC* and *PCSK1* mutations; there may be a history of adrenal insufficiency and/or hypoglycemia in infancy. If a specific monogenic form of obesity is suspected after clinical investigations, direct sequencing of the candidate genes can be performed to confirm the diagnosis [109]. Targeted sequencing of *LEP*, *LEPR*, *POMC*, *PCSK1*, and *MC4R* is available in several certified laboratories (see www.genetests.org for an up-to-date listing of genetic tests and centers worldwide).

Next-generation sequencing (NGS) panels are increasingly replacing individual gene testing. These panels allow sequencing and analysis of duplications/deletions in multiple genes, including *LEP*, *LEPR*, *POMC*, *PCSK1*, *MC4R*, *MC3R*, *NTRK2*, and *SIM1*; they can be performed in several certified laboratories in Europe, the USA, and Canada (see www.genetests.org).

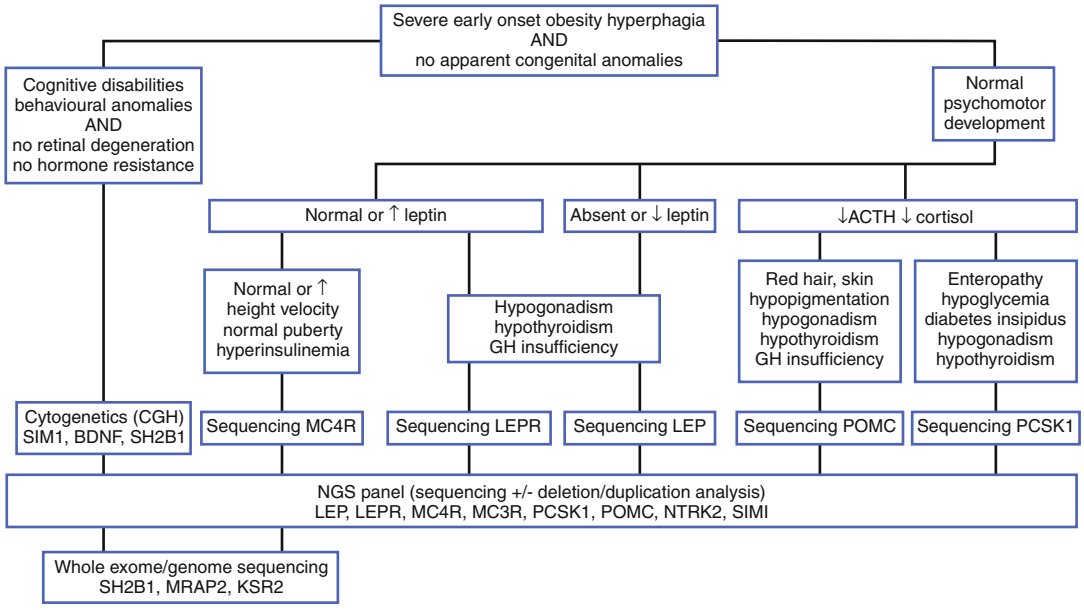

Fig. 8.2 Diagnostic strategy for monogenic obesity. The strategy is based on clinical manifestations in children having a severe early-onset obesity accompanied with hyperphagia, when a "syndromic" form of obesity is ruled out (such as ciliopathy, Prader-Willi syndrome, pseudohypoparathyroidism; see Chap. 9), and therefore a "monogenic" form of obesity is suspected. We propose a first line of genetic testing, consisting of CGH array if cognitive and behavioral abnormalities are present, else a targeted sequencing candidate gene (individually especially if the diagnostic is evident or within available NGS panels). In case of non-evident clinical diagnosis, whole-exome/whole-genome sequencing can be useful to elucidate the molecular diagnosis and has the potential to discover new molecular anomalies

In some cases no specific diagnosis is evident after medical history, family history, physical exam, hormonal testing, and initial genetic testing; in such cases, whole-exome/whole-genome sequencing may be considered as it may detect pathogenic mutations in the *KSR2*, *MRAP2*, and *SH2B1* genes and might identify new rare variants [109]. However, the consequences of variants in coding and splice regions must be interpreted using algorithms provided by the American College of Medical Genetics and Genomics (ACMG) [110]. Variant pathogenicity is estimated by using referent databases (such as Exome Aggregation Consortium (ExAC), ClinVar) that aggregate information on all known variants; in silico variant prediction tools (such as PolyPhen-2) may also be useful. A variant of uncertain or benign significance does not inform clinical decision-making [110].

Importantly, testing of other family members to establish co-segregation is recommended for suspected recessive cases or when a new pathogenic variant is discovered.

Current and Emerging Treatments

Congenital *LEP* deficiency is one of the few genetic forms of obesity for which a specific treatment is available and highly effective. Twelve months of leptin therapy (metreleptin) in a 9-year-old girl with *LEP* deficiency reduced food intake and body fat, restored gonadal function and pubertal development, and corrected immune deficiency [20, 111]. In another study, *LEP*-deficient patients in a fed state gave higher ratings to food images, but these ratings were reduced after leptin treatment [112]. Studies using magnetic resonance imaging techniques confirmed alteration in functional cortical activity to food cues in key feeding and reward-related areas, suggesting the role of leptin in both homeostatic and hedonic regulation of appetite [113]. The effect of leptin therapy on heterozygous carriers of *LEP* mutations remains to be tested but is likely to produce beneficial effects.

Because of a nonfunctional receptor, leptin treatment is useless in homozygous *LEPR*-deficient children. It is possible that such patients might respond to activation of melanocortin signaling downstream of the leptin receptor (see below). Supportive behavioral and educational (when developmental delay) interventions may also be of some benefit. Emphasizing the importance of permanent lifestyle modifications at a young age is essential in monogenic obesity mutation carriers, as children with *MC4R* functional mutations are able to lose weight with lifestyle intervention but have greater difficulties maintaining this weight loss [114]. A similar observation was reported in children carrying a rare mutation in *POMC* [115].

Hormone replacement (in deficient patients) and treatment of metabolic complications (insulin resistance, type 2 diabetes) follow standard protocols. Metformin has been suggested as a rational therapy for patients with *KSR2* mutations due to metformin's role in 5′ adenosine monophosphate-activated protein kinase (AMPK) activation, which might bypass the metabolic block created by inactivating mutations of the KSR2 protein. Anecdotal reports suggest that patients carrying *KSR2* mutations have lost weight on metformin treatment, though controlled trials have not yet been done [103].

Specific emerging drugs that could safely bypass the leptin signal are being developed (Fig. 8.1). Recently, Kuhnen and colleagues reported dramatic weight loss in two patients with complete *POMC* deficiency treated with an α-MSH analog (setmelanotide) [116]. This α-MSH-based therapy may pave the way for the treatment of monogenic forms of obesity. Homozygous carriers of mutations in the *LEPR*, *PCSK1*, and *MC4R* genes may derive similar benefits. Heterozygous carriers of mutations in the aforementioned genes and other genes from the leptin-melanocortin pathway (*MC3R*, *MRAP2*), who display less penetrant forms of obesity but represent up to 10% of the cases, may considerably expand the therapeutic spectrum of this ultra-orphan drug. Obese patients carrying mutations/deletions at *NTRK2*, *SIM1*, and *SH2B1* loci might also benefit from the therapy, owing to their molecular cross talk with the leptin-melanocortin pathway. However, *BDNF* deletions and mutations

may lie downstream of MC4R signaling and might therefore prove resistant to α-MSH analog therapy.

The role of bariatric surgery in the management of monogenic obesity remains highly controversial. Case reports found that bariatric surgery was poorly efficient on weight loss in subjects with homozygous *LEPR* and compound heterozygous *MC4R* mutations [25, 26, 117]. A more complex relationship has been reported for surgical treatment of heterozygous loss-of-function *MC4R* mutations. The magnitude of weight loss in carriers of functional *MC4R* mutations or *MC4R* variants was comparable to that in two randomly paired controls without mutation [118]; however, functional characterization of the mutations and variants was questionable [119]. Carriers of rare variants of *MC4R* matched with their *MC4R* reference allele carriers also demonstrated comparable weight loss after bariatric surgery [120]. However, in the largest series, heterozygous *MC4R* mutation carriers exhibited less postoperative weight loss and more frequent complications and reoperations after gastric banding than after gastric bypass [121]. Thus, the long-term efficacy and safety of bariatric surgery in genetic forms of obesity need further evaluation. Moreover, severe eating disorders in patients with monogenic obesity may in some cases mitigate against bariatric surgery [105].

Another promising surgical approach for treatment-refractory obesity seems to consist of deep brain stimulation (DBS) targeting the hypothalamus and the nucleus accumbens, two regions that mediate responses to food stimuli. Clinical trials will have to evaluate the efficacy of DBS for monogenic forms of obesity [122].

Conclusions

Candidate gene approaches based on information from obesity mouse models have shown that defects in 12 genes involved in the leptin-melanocortin pathway and its modulation lead to monogenic forms of early-onset severe obesity with hyperphagia as a key feature [8]. Elucidation of these gene defects delineates obesity as an inherited disorder of central regulation of food intake and energy expenditure. As leptin therapy and new emerging treatments are effective in some monogenic cases, it is important to establish a diagnosis at an early age. Clinical features provide a guide to diagnosis that can be confirmed by cytogenetic analysis or targeted or next-generation gene sequencing. Applying whole-exome/whole-genome sequencing can also help physicians to elucidate non-evident clinical cases and has the potential to discover new molecular anomalies. These will enhance our understanding of the pathophysiology of monogenic obesity and improve its management.

Editor's Comments

1. In the modern era, the primary care provider is increasingly confronted with children who have gained excessive weight during infancy and early childhood. The clinical strategy outlined in this chapter provides valuable guidance regarding the identification of a genetic obesity disorder and the approach to establishing a genetic diagnosis.
2. Establishment of a genetic diagnosis in early childhood now carries clinical import, as pharmacologic agents (recombinant leptin, setmelanotide) targeting the leptin and melanocortin signaling pathways have proved remarkably effective in small cohorts of patients with homozygous leptin deficiency and *POMC* mutations and may be useful in other subjects with molecular defects proximal to the melanocortin-4 receptor. It is currently unclear if these agents can attenuate weight gain in patients with hypothalamic damage, as often occurs following surgical treatment of craniopharyngioma. This question is addressed in more detail in Chap. 2, "Central Control of Energy Metabolism and Hypothalamic Obesity."

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Syndromic Obesity

9

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Overview

It is well established that genetic mutations and chromosomal abnormalities can cause excess weight gain and white adipose storage in children and adults. The term "syndromic obesity" is used to describe obese patients with cognitive delay, dysmorphic features, organ-specific abnormalities, hyperphagia, and/or other signs of hypothalamic dysfunction [1, 2]. Obesity syndromes are often distinguished by specific phenotypes and may be inherited in either an autosomal or an X-linked pattern.

This chapter focuses on two of the most common obesity syndromes, Prader–Willi syndrome and Albright's hereditary osteodystrophy and highlights other unique disorders including Bardet–Biedl syndrome (BBS), Alstrom syndrome, Rapid-onset Obesity with Hypothalamic dysregulation, Hypoventilation, and Autonomic Dysregulation syndrome (ROHHAD), and recently characterized overgrowth syndromes. We also review mutations and chromosomal deletions associated with three genes – *SIM1*, *BDNF*, and *TRKB* – that are implicated in the development and plasticity of hypothalamic neurons (Table 9.1).

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Prader–Willi Syndrome (PWS)

Overview: Prader–Willi syndrome (PWS) was originally described by Andrea Prader, Alexis Labhart, and Heinrich Willi in 1956 [3]. It is the most common syndromic cause of childhood and adult obesity [4, 5].

Incidence: PWS occurs in both sexes and all races with a frequency of approximately 1 in 10,000 to 1 in 15,000 live births and affects an estimated 350,000–400,000 people worldwide [4, 6].

Clinical Features: A characteristic facial appearance is noted in PWS: features include narrow bifrontal diameter, almond-shaped palpebral fissures, and down-turned mouth with a thin upper lip. Small, narrow hands with a straight ulnar border and tapering fingers and short, broad feet are typical in Caucasians with the disorder [4]. These features are summarized in Fig. 9.1 [7]. One-third of patients with PWS are also fairer (lighter skin, hair, and eye color) than other members of their families. Additional common features include strabismus, scoliosis, and/or kyphosis.

PWS is distinguishable from other obesity syndromes by its distinct developmental phenotype.

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Table 9.1 Overview of causes of syndromic obesity

Syndrome	Overview	Incidence	Clinical features	Etiology	Diagnostic considerations	Treatment and future research
Prader–Willi syndrome (PWS)	Originally described in 1956 Common genetic obesity syndrome	1:10,000–1:15,000 live births	• Characteristic facies, small hands and feet, hypopigmentation • Hypotonia and FTT in newborn • Short stature, hyperphagia, obesity, hypogonadism, delayed motor/cognitive development, sleep disturbances, and behavior abnormalities in childhood	Lack of expression of paternally derived genes on chromosome 15q11-q13 due to: • Deletion (~70%) • Uniparental disomy (~20–30%) • Imprinting center defect (~5%)	Consider in infant with hypotonia and FTT or obese child with short stature and hypogonadism All forms of PWS are detected by methylation analysis	Appropriate use and dosage of rhGH therapy Possible central adrenal insufficiency Regulation of ghrelin and design of specific ghrelin antagonists Understanding abnormalities leading to the abnormal partitioning of body fat in PWS Understanding autonomic nervous system function in PWS Understanding branched chain amino acid and fatty acid metabolic changes in PWS
Albright's hereditary osteodystrophy (AHO)	Originally described in 1942	1:20,000 (estimated)	• Short stature, round face, obesity, brachydactyly, subcutaneous calcification, dental and sensorineural abnormalities • Generalized hormonal resistance to PTH, TSH, GHRH, and gonadotropins • Biochemical functional hypoparathyroidism (low Ca, high phosphate but with increased PTH levels) • Pseudo-pseudohypoparathyroidism is AHO phenotype with normocalcemia and no hormonal resistance	Heterozygous inactivating mutations in the *GNAS*1 gene on chromosome 20q13.3 Mutations can result in impaired expression of $G_s\alpha$ mRNA or dysfunctional $G_s\alpha$ proteins Genomic imprinting of *GNAS*1 explains variable phenotypes	Consider in cases of functional hypoparathyroidism (low Ca, high phosphate, with increased PTH levels), obesity, round face, brachydactyly, and mental retardation Hypomagnesemia and vitamin D deficiency should be ruled out	Treat with oral calcium supplements and 1,25-dihydroxyvitamin D Monitor blood chemistries and urine calcium excretion to avoid hypercalciuria

Bardet–Biedl syndrome (BBS)	Originally described in 1866	1:13,500–1:125,000 Depends on geographic region	• Progressive rod–cone dystrophy • Obesity in first year of life postaxial polydactyly • Primary hypogonadism • GU and renal abnormalities	Rare recessive, genetically heterogeneous condition 12 genes (BBS1–12) implicated Defect in primary cilia and intraflagellar transport	Diagnosis often delayed until vision deteriorates Major cause of mortality is renal disease Association with renal cell carcinoma may warrant monitoring	Treatment of renal disease includes dialysis or transplantation Further studies are needed to understand and identify key defective pathways
Alstrom syndrome (ALMS)	Rare multi-organ disorder first described in 1959	<1:100,000 ~450 cases described	• Progressive rod–cone dystrophy leading to juvenile blindness • Sensorineural hearing loss • Early-onset childhood obesity • Diabetes, adult short stature • Mortality due to cardiac failure secondary to dilated cardiomyopathy or renal failure	ALMS1 gene on chromosome 2p13 80 different ALMS1 mutations reported Defect in centrosomes or basal bodies of cilia	Clinical features manifest during teen years Often confused with other diagnoses Presence of dilated cardiomyopathy and early hearing loss and absence of digit abnormalities distinguish from BBS	No treatment that will cure ALMS or delay disease progression Management of photophobia Close cardiac monitoring May require insulin and/or metformin
ROHHAD	Complex multisystem disorder with hypothalamic dysregulation, hypoventilation, and autonomic dysregulation	Exceedingly rare, less than 100 reported cases	• Early-onset, rapid, extreme obesity between ages 2 and 7 years • Previously healthy and normal weight child • Hypothalamic dysfunction • Alveolar hypoventilation with high risk of cardiopulmonary arrest if not identified • Autonomic dysregulation (temperature instability, GI dysmotility, ophthalmologic abnormalities)	• As yet of yet, unknown • Spontaneously occurring • No familial inheritance pattern	• Consider in children with constellation of syndromic findings • Onset of clinical features is variable, with exception of the rapid weight gain between 2 and 7 years in a previously healthy, normal weight child	• No specific treatment • Strict diet and exercise to help BMI • Sleep study to diagnose and initiating treatment for alveolar hypoventilation is essential • Screening and monitoring for hypothalamic dysfunction, neurocognitive dysfunction, seizures, and ganglioneuromas

(continued)

Table 9.1 (continued)

Syndrome	Overview	Incidence	Clinical features	Etiology	Diagnostic considerations	Treatment and future research
SIM1 deletion syndrome	Originally described in 2000	Five individuals reported in the literature	• Similar phenotype to PWS – hypotonia, obesity, hyperphagia, developmental delay, almond-shaped eyes, strabismus, thin upper lip, hypogonadism, short extremities • Cardiac and neurological abnormalities distinguish SIM1 from PWS	SIM1 is a member of the basic helix–loop–helix period aryl hydrocarbon receptor family Expressed in the supraoptic and paraventricular nuclei of the hypothalamus SIM1 gene may function downstream of the MC4R to control energy balance	Consider SIM1 deletion syndrome in patients with PWS-like features but a normal PWS testing Most patients with SIM1 deletion have a 6q16.2 deletion	Further studies are needed to examine the relationship between common variants of SIM1 and body weight gain
BDNF and tropomyosin-related kinase B (TrkB)	First described in 2006	Rare, case reports	• Hyperphagia, morbid obesity • Complex neurobehavioral phenotype including impaired cognition, memory, and nociception	BDNF acting through TrkB receptor regulates the development, differentiation, and survival of neurons BDNF haploinsufficiency in mice or humans leads to morbid obesity and hyperphagia	Consider BDNF or TrkB deficiency in patients with morbid obesity and hyperphagia	Further research is needed to understand the role of BDNF, and its receptor, TrkB, in the regulation of energy balance in humans

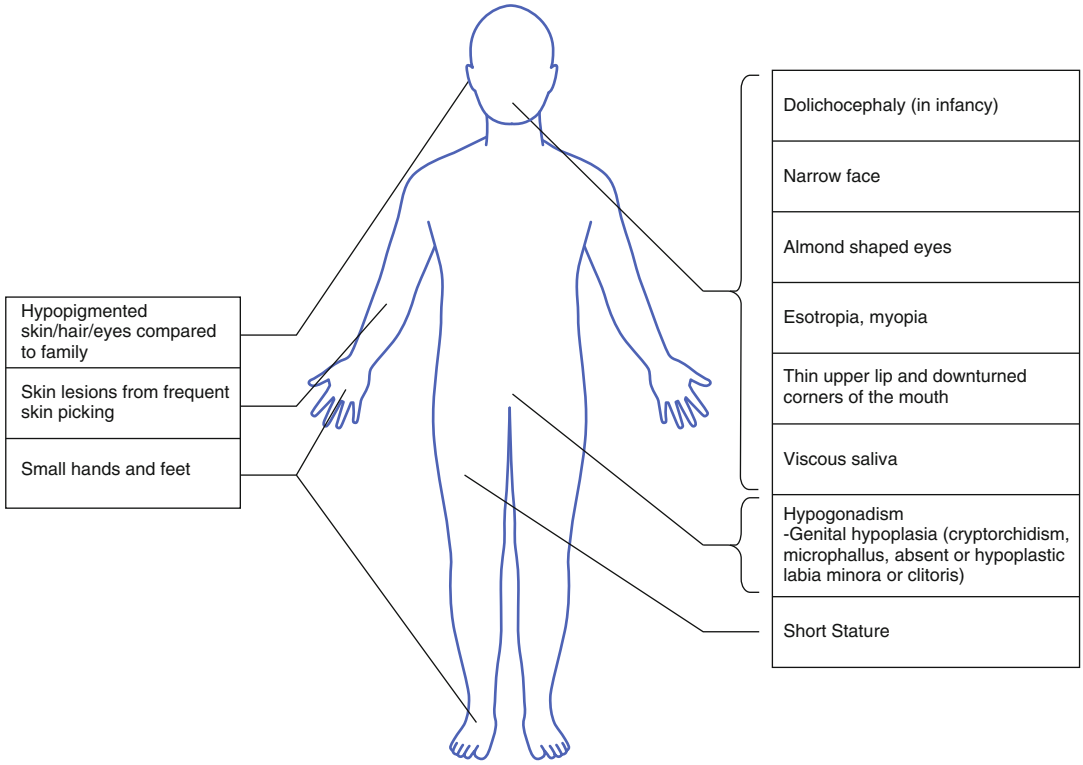

Fig. 9.1 Physical findings in Prader–Willi syndrome (Used with permission of Elsevier from Irizarry KA, Miller M, Freemark M, Haqq AM. Prader Willi Syndrome: Genetics, Metabolomics, Hormonal Function, and New Approaches to Therapy. Adv Pediatr. 2016;63(1):47–77)

Newborns with PWS have hypotonia, poor suck, decreased arousal, and failure to thrive and often require tube feedings for several weeks to months. This period is followed by progressive obesity by 1–6 years of age with insatiable appetite, short stature, delayed motor and cognitive development, behavioral difficulties, and sleep disturbances. Stages in the progression from failure to thrive to hyperphagia and obesity are shown in Fig. 9.2 [8].

The hypothalamic dysregulation of PWS can be associated with pituitary hormone deficiencies. A recent report showed that as many as 60% of PWS patients have an insufficient ACTH response to metyrapone, consistent with central adrenal insufficiency [9]. PWS patients can also develop central hypothyroidism, which should be periodically assessed. Short stature is a common characteristic, due in part to deficient or insufficient growth hormone secretion. PWS patients may also have hypogonadotropic hypogonadism or arrested pubertal development. Establishing care with a pediatric endocrinologist is essential for long-term management.

Autonomic nervous system dysfunction is thought to be responsible for viscous saliva, high pain threshold, skin picking, and high threshold for vomiting [10]. Importantly, individuals with PWS commonly have a high prevalence of central and obstructive sleep apnea; sleep dynamics must be assessed prior to initiating growth hormone treatment [11].

Lastly, individuals with PWS are likely to have mental health, behavioral, and cognitive disorders. It is important to counsel families as these behavioral disorders may include obsessive compulsive disorder, impaired language development, anxiety, temper tantrums, skin picking, stealing food, and, in more extreme cases, psychosis [4, 12]. Some studies suggest that

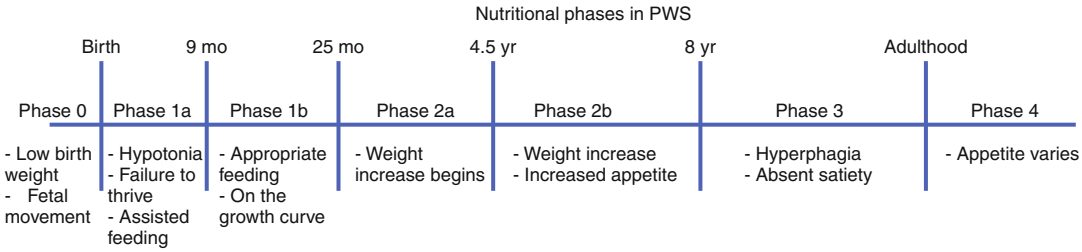

Fig. 9.2 Timeline of nutritional phases in Prader–Willi syndrome (Used with permission of Elsevier from Irizarry KA, Miller M, Freemark M, Haqq AM. Prader Willi Syndrome: Genetics, Metabolomics, Hormonal Function, and New Approaches to Therapy. Adv Pediatr. 2016;63(1):47–77. Data from Miller JL, Lynn CH, Driscoll DC, Goldstone AP, Gold JA, Kimonis V, et al. Nutritional phases in Prader-Willi syndrome. Am J Med Genet A. 2011;155a(5):1040–9)

neurobehavioral outcomes in PWS may be linked to either maternal uniparental disomy or paternal deletion of 15q11-q13, though additional investigations are required [12]. While these patients have multiple comorbidities, it is the complications of obesity that are the main contributors to the morbidity and mortality in PWS.

Etiology: PWS is caused by lack of expression of paternally derived genes on chromosome 15q11-q13 [13]. The genes in this region of the chromosome are imprinted: imprinted genes are modified by methylation or histone acetylation in different ways depending on the gender of the parent from whom they were inherited. The majority of PWS cases (~70%) are due to deletions spanning 4–4.5 Mb of the paternal 15q11-q13. The next most common cause of PWS is maternal uniparental disomy (UPD) (20–30%), which is due to maternal meiotic nondisjunction followed by mitotic loss of a single paternal chromosome 15. PWS caused by deletions or UPD does not recur in siblings. Additionally, two types of imprinting defects occur in ~5% of cases. In one case there is a submicroscopic deletion of a genetic element called the imprinting center (IC); in the other case, there is an abnormal imprint but no detectable mutation [14, 15]. There is as much as a 50% risk of recurrence in a sibling in these latter cases; prenatal diagnosis may be possible.

The exact gene(s) responsible for PWS is not known, though several candidate genes have been identified. Analysis of targeted knockouts in mice has provided important insights into the roles that candidate genes may contribute to the clinical and biochemical features of PWS; however, no single gene has been determined to be causative. It is likely that more than one gene may be required to cause the complete complex clinical picture of PWS.

The SNURF-SNRPN gene is a major candidate. Its gene locus is very complex, spanning ~465 kb and consisting of >148 exons, which can undergo alternative splicing [16]. *SNRPN* (small nuclear ribonucleoprotein polypeptide N) is an imprinted and paternally expressed gene located on chromosome 15q11.2 within the PWS locus. SNRPN mRNA is expressed throughout the brain and codes for SNURF (SNRPN upstream reading frame), a small nuclear ribonucleoprotein complex, whose exact function remains unknown. SNRPN knockout mice have hypotonia and impaired feeding, which are also seen in infants with PWS [17].

Several additional paternally expressed imprinted genes have been identified in 15q11-q13 including *NDN* (encoding NECDIN protein) and *MAGEL2* [18–20]. NECDIN protein is expressed within the hypothalamus, and the NECDIN knockout mice exhibit respiratory defects, including abnormal central respiratory drive, a decrease in GnRH neurons, skin scraping behaviors (similar to skin picking seen in PWS patients), and increased pain tolerance [17, 21].

MAGEL2 is highly expressed in the hypothalamus. Mice lacking *MAGEL2* have increased body weight with excess adiposity [22]. Mercer and colleagues recently showed that *Magel2*-null mice do not display anorexia following

peripheral administration of leptin [23], suggesting a state of leptin resistance. Indeed, arcuate nucleus pro-opiomelanocortin (POMC) neurons did not depolarize in response to leptin in *Magel2*-null mice; there was a progressive loss of leptin sensitivity beginning at 4 weeks of age. However, *Magel 2*-null mice retained an anorectic response to the melanocortin receptor agonist, MT-II. Therefore, the loss of *MAGEL2* in PWS may explain the blunted or absent POMC hypothalamic response to leptin, resulting in hyperphagia and obesity [23]. A progressive loss of leptin sensitivity provides a potential explanation for the later-onset hyperphagia developing in PWS children in early childhood [24].

Gene expression studies have also generated interest in a novel translocation t(4;15)(q27;q11.2) that implicates the snoRNA, PWCR1/HBII-85, as the cause of PWS in at least one individual [25]. The function of known snoRNAs is to guide 2′-*O*-ribose methylation of mainly ribosomal RNAs; however, this novel imprinted snoRNA has no known target. It is postulated that snoRNAs might be involved in the posttranscriptional regulation of a gene responsible for PWS.

SNORD116 is one snoRNA that is expressed within the appetite-controlling center of the hypothalamus. SNORD116 deletions in mouse models result in growth retardation [17] in association with hyperghrelinemia and hyperphagia, similar to the biochemical and clinical picture of PWS; however, unlike PWS patients, these mice do not become obese [26].

A recent innovative study has highlighted the role of prohormone bioactivity in the pathogenesis of PWS. Burnett and colleagues determined that SNORD116-null mice had functional defects in the processing of proinsulin, pro-GH-releasing hormone, and proghrelin and hypothesized that this was due to a deficiency of proconvertase enzyme 1 (PC1) activity [27]. They measured the prohormone levels in SNORD116-null mice and wild-type mice, as well as PWS patients and controls. Their results showed a functional defect in PC1, with higher prohormone compared to hormone levels. This may explain several features of the PWS phenotype including hyperghrelinemia [7], as a result of defective proghrelin processing, and relative hypoinsulinemia due to impaired proinsulin. Additionally, hypothalamic dysfunction may explain the multiple neuroendocrine findings, including adrenal insufficiency due to impaired processing of corticotropin-releasing hormone, low growth hormone due to impaired processing of growth hormone-releasing hormone, hypothyroidism due to impaired thyrotropin-releasing hormone, and hypogonadotropic hypogonadism due to impaired pro-GnRH processing [27]. Still, there is not a clear explanation for cardinal hyperphagic obesity. Theories include impaired pro-opiomelanocortin (POMC) processing to α-MSH and impaired processing of prohormone precursors of appetite-regulating hormones such as neuropeptide Y, Agouti-related peptide (AgRP), oxytocin, and brain-derived neurotrophic factor. As pro-AgRP is antagonistic toward α-MSH, the increased levels of pro-AgRP may contribute to the characteristic hyperphagia [27].

Diagnostic Considerations: An expert consensus committee published clinical diagnostic criteria for PWS and created a scoring system of major and minor criteria for infants aged 0–36 months and children aged 3 years to adult [28]. These criteria are summarized in Table 9.2. A recent study found global developmental delay and neonatal hypotonia in over 97% of patients; feeding difficulty in infancy, followed by exaggerated weight gain after 1 year of age, hyperphagia, and hypogonadism were noted in 93% of patients [29]. Thus, a diagnosis of PWS should be considered in infants with hypotonia and failure to thrive at birth and in those with developmental delays, early childhood-onset obesity, hypogonadism with genital hypoplasia, short stature, and behavior disorders in early childhood.

Since clinical criteria were initially defined, molecular genetic testing has now been refined. DNA methylation analysis will detect three forms of PWS and is therefore the most efficient test available [30]. If the methylation pattern is abnormal (signifying one parent of origin), then fluorescence in situ hybridization (FISH) can be used to confirm a chromosomal deletion, and microsatellite probes may be used to verify

Table 9.2 Clinical manifestations at various ages suggestive of Prader–Willi syndrome

Age	Decreased fetal movement	Failure to thrive	Hypotonia	Developmental delays/cognitive impairments	Hyperphagia	Short stature (disproportional small hands/feet)	Hypogonadism and pubertal delay	Behavioral disorder[a]
Infancy	x	X	X	X				
Toddlers to early childhood			X	X	X			
Early childhood to adolescence			X	X	X	X	X	
Adolescence to adulthood			X	X	X	X	X	X

Additional Supportive Findings
Characteristic physical exam features: narrow bifrontal diameter, almond-shaped eyes, palpebral fissures, down-turned mouth, thin upper lip, narrow hands with straight ulnar borders, thick viscous saliva, sleep disturbance/sleep apnea
[a]Behavioral disorders: temper tantrums, obsessive compulsive behaviors, skin picking, sneaking food

maternal UPD. Note that high-resolution chromosome analysis alone is insufficient because false positives and false negatives have occurred with this method without FISH. An abnormal methylation pattern in the presence of normal FISH and uniparental disomy studies suggests an imprinting center mutation. Analysis for mutations in the imprinting center is now available for clinical diagnosis in selected laboratories.

Pathogenesis of Weight Gain and Treatment of Obesity in PWS

Dysregulation of Appetite-Controlling Hormones: The specific cause of hyperphagia in PWS remains elusive. Several recent clinical studies have characterized the secretion of appetite-regulating hormones (ghrelin, PYY, leptin) and found unique patterns in PWS compared to controls with generalized exogenous obesity. Ghrelin, an orexigenic hormone produced by the oxyntic cells of the stomach, normally rises prior to meals and falls in response to nutrient ingestion (particularly carbohydrate and protein; see also Chap. 3 on GI Hormones and the Control of Food Intake and Energy Metabolism). Ghrelin levels are lower in obese subjects than in lean individuals but are consistently higher in PWS children and adults than in BMI-matched obese controls [7, 31, 32] and may in some cases exceed levels seen in age- and gender-matched lean subjects.

A critical question concerns the ontogenesis of hyperghrelinemia in PWS and its relationship to feeding and weight gain. Circulating ghrelin concentrations are normally high in infancy and decline progressively during the course of childhood development. In a cross-sectional study of 33 infants and young children with PWS and 28 healthy controls, Haqq and colleagues [33] found that one-third of the PWS subjects had ghrelin levels greater than the upper range of normal controls. Interestingly, the hyperghrelinemia in PWS infants was noted prior to the onset of hyperphagia and adiposity; indeed highest levels were observed in PWS infants with lowest weight for age z-scores. It has been proposed that the relative hyperghrelinemia of PWS in early childhood might be a biologic response to neonatal failure to thrive. This, however, does not readily explain the persistent hyperghrelinemia of PWS adolescents and adults.

As expected with excess fat deposition, leptin levels are high in obese children with PWS. Yet even prior to onset of obesity in young children, the anorexigenic hormone peptide YY (PYY) is lower in PWS compared to obese controls [34]; the response to a high-fat meal was blunted in a study of PWS adolescents and children [35]. This yielded an increase in the ratio of ghrelin to PYY, which might serve as a marker of orexigenic drive in PWS [35]. Nevertheless, no clear relationships have yet been identified between PWS eating patterns and the levels of appetite-regulating hormones in the circulation.

Treatment of Obesity in PWS: Until our understanding of appetite allows for more targeted treatment, nutritional management and prevention of the complications of morbid obesity are the mainstay of treatment in PWS. Prior data from preschool and school-aged children have shown that a calorie-restricted diet of 7 kcal/cm/day (600–800 kcal/day) can result in weight loss; a diet of 8–11 kcal/cm/day (800–1300 kcal/day) allows for weight maintenance [7, 36]. However, the optimal macronutrient content of diet has yet to be determined. It is recommended that nutritional management begin early in toddlerhood to best prevent obesity and related comorbidities, including type 2 diabetes and hyperlipidemia. A regular feeding schedule, monitoring of caloric intake and weight, and behavior modifications that may include restricting access to food supply are important [7].

More recently, bariatric surgery has been considered for treatment of morbid obesity in PWS. This was first studied in *MAGEL2* knockout (KO) mice that had been fed a high-fat diet for 10 weeks. When KO mice underwent sleeve gastrectomy, they had loss of body fat, lower fasting glucose levels, and reduced dietary fat intake [37]. In a recent clinical study, 24 PWS patients between 5 and 18 years with morbid obesity underwent sleeve gastrectomy and had annual follow-up for 5 years [38]. Prior to surgery these

patients had several obesity comorbidities, including obstructive sleep apnea, dyslipidemia, hypertension, and type 2 diabetes. After surgery, patients had marked reductions in BMI and remission of approximately 80% of comorbidities. Sleeve gastrectomy is thought to alter appetite and satiety and induce weight loss by changing the metabolic and neuroendocrine milieu of the gut, with increased postprandial concentrations of the anorexigenic hormones GLP1 and PYY and decreases in the levels of the orexigenic hormone ghrelin [39, 40]. Certainly questions of the long-term sustainability of bariatric surgery in PWS have been raised, and follow-up studies are needed to determine long-term efficacy as well as safety, including effects on skeletal growth and bone mineralization.

Neuroendocrine Dysfunction: Individuals with PWS may have hypothalamic dysfunction beginning early in utero with continuation in infancy and childhood. Therefore, close monitoring of neuroendocrine function is warranted. In particular, identifying and treating *central adrenal insufficiency* is critical; it is suspected to be a cause of death in some patients. While some of these had been treated with growth hormone, the effects of growth hormone therapy on adrenal function remain unknown [41]. Metyrapone testing has estimated that central adrenal insufficiency may occur in up to 60% of PWS cases, though more recent low-dose ACTH stimulation tests estimated prevalence to be as low as 14% [42].

Central hypothyroidism occurs in as many as 20–30% of PWS patients [11]. It is recommended that children be screened for thyroid dysfunction at diagnosis and yearly thereafter. In infants, screening should be conducted within the first 3 months of life as thyroid hormone plays a central role in neurodevelopment. Thyroid function tests should also be monitored after beginning growth hormone treatment, as growth hormone can increase peripheral conversion of free T4 to triiodothyronine [11]. Treatment with levothyroxine should be initiated if hypothyroidism is identified.

Adolescents with PWS may have delayed or arrested *pubertal development*. Treatment with estrogen or testosterone should be initiated and monitored by experienced centers. Sex steroid replacement can have many benefits including improved bone mineralization and bone mass accrual, increased muscle mass, and heightened well-being with achievement of secondary sex characteristics. Pubertal induction with sex steroids is timed to best track along a normal pubertal time course. Less commonly, PWS children can develop precocious puberty; however, treatment with gonadotropin-releasing hormone analogs is usually withheld as pubertal advancement is self-limited [43]. While no cases of paternity have been found with PWS, there are case reports of pregnancies in PWS females. These pregnancies have resulted in two children without genetic mutation and two children with Angelman syndrome [44, 45].

Growth Hormone Treatment: The use of growth hormone (GH) is now FDA approved for treatment of short stature in PWS. GH treatment of PWS infants and children has been shown in randomized trials to exert favorable effects on growth, body mass index, body composition, and motor and cognitive development [46–48]. Growth velocity is increased in childhood and final height is augmented [49]. GH reduces fat mass, increases lean body mass and bone mineral density, and increases resting energy expenditure (REE), with improved fatty acid oxidation [49–54]. Improvements in physical strength, respiratory muscle tone, and peripheral chemoreceptor sensitivity to carbon dioxide have also been reported [49, 50, 54]. One study has also reported a trend toward improvement in overall sleep quality, including reduction in the number of hypopnea and apnea events with administration of GH [54]. Further studies investigating the optimal timing of initiation, dosage, and duration of growth hormone treatment in children and adults with PWS are needed.

Controversy persists about whether growth hormone treatment causes an excess of mortality

beyond that expected from PWS alone. There have been approximately 28 cases of sudden death in PWS children undergoing treatment with GH [55, 56]. These have been concentrated in young children with a history of respiratory obstruction/infection or severe obesity [57–59] and have occurred early in the course of GH therapy. The exact cause of the sudden deaths has not been determined. Possibilities include impaired ventilatory responsiveness to hypercapnia and hypoxia, increased lymphoid tissue or tonsillar hyperplasia, and adrenal insufficiency. Alternatively, there may in fact be no true increased mortality above that expected from the PWS diagnosis alone. Indeed, other studies suggest that GH increases ventilator responsiveness to carbon dioxide and improves sleep quality in children with PWS [54]. Until studies definitively address these issues, we recommend that a pretreatment airway and sleep evaluation be performed prior to GH therapy, with close monitoring of sleep quality (Fig. 9.3) [7].

As with sex steroids, GH treatment should be initiated by experienced centers. The recommended GH dosage is 0.5–1 mg/m^2/day with adjustment to maintain insulin-like growth factor-I (IGF-I) levels in the normal range. Lower doses of GH may be effective; therefore, it seems prudent to initially begin with subtherapeutic doses and to increase gradually to insure that the drug is well tolerated. Children receiving GH therapy should be monitored for thyroid dysfunction, glucose intolerance, and worsening scoliosis.

Patients with PWS often develop *anxiety and obsessive compulsive disorder and neurologic disorders including narcolepsy; seizures are less common*. Additionally, they are prone to *scoliosis* with or without growth hormone treatment. Therefore, multispecialty care with specialized consultations for management of PWS is recommended.

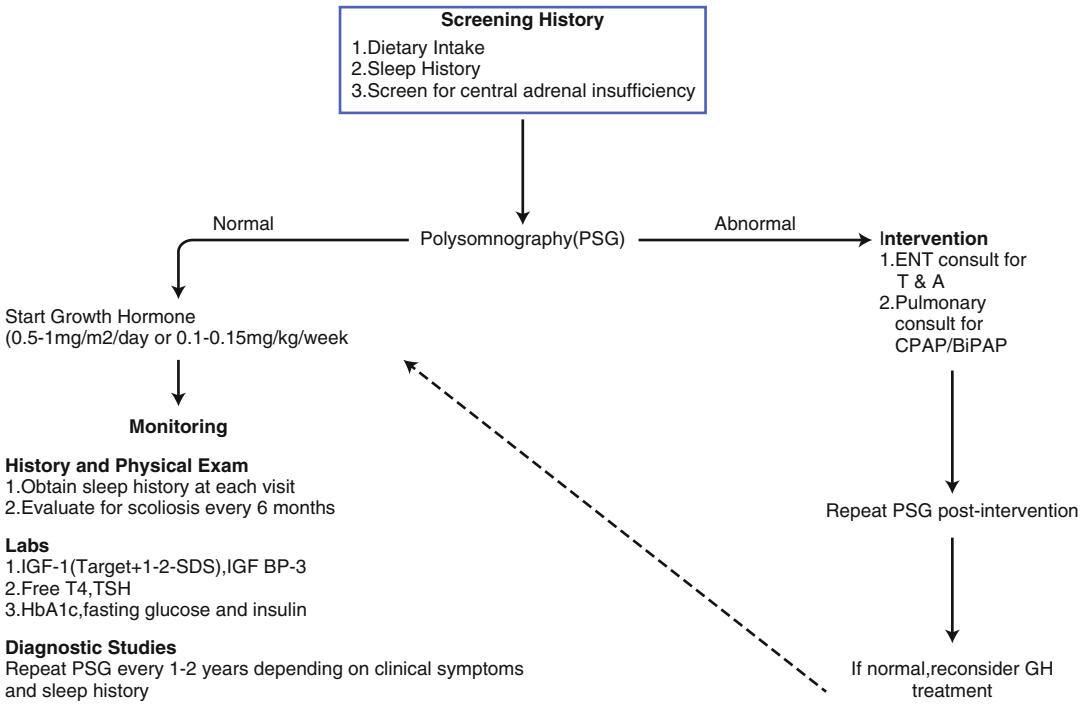

Fig. 9.3 Algorithm for initiation of growth hormone (GH) therapy in Prader–Willi syndrome (Used with permission of Elsevier from Irizarry KA, Miller M, Freemark M, Haqq AM. Prader Willi Syndrome: Genetics, Metabolomics, Hormonal Function, and New Approaches to Therapy. Adv Pediatr. 2016;63(1):47–77)

Critical Gaps in Knowledge and New Therapeutic Approaches

1. As noted previously [7, 33–35], children and adults with PWS have high fasting and postprandial levels of total ghrelin, an orexigenic peptide produced in the stomach. In contrast, total ghrelin levels are suppressed in children and adults with "exogenous" obesity or with obesity caused by mutations in leptin or the melanocortin-4 receptor [32, 60, 61]. Young PWS infants, who have not yet developed hyperphagia or obesity, have median fasting total ghrelin levels similar to age- and sex-matched controls. However, a subset (33%) of young PWS is already hyperghrelinemic [33]. The high circulating concentrations of ghrelin may be critical for the pathogenesis of weight gain in PWS because ghrelin stimulates appetite and weight gain in rodents and human adults. Octreotide treatment in children with PWS has been shown to decrease fasting ghrelin concentrations, but does not alter body weight [62–64]. Octreotide, however, is a nonspecific inhibitor of ghrelin and reduces PYY levels [65], making interpretation of its effects on food intake and weight gain difficult [35]. Strategies that specifically inhibit ghrelin action and/or increase PYY secretion or action might reduce orexigenic drive in PWS.
2. Recent studies demonstrate that agonists for the melanocortin-4 receptor (setmelanotide) can cause striking weight loss in subjects with mutations in POMC. (See Chap. 2 on Central Control of Energy Metabolism and Hypothalamic Obesity and Chap. 8 on Monogenic Obesity.) Current studies are exploring the efficacy of setmelanotide in adults with PWS.
3. PWS individuals demonstrate abnormal partitioning of body fat and lean mass. Whole-body magnetic resonance imaging (MRI) has found that PWS adults have greater fat mass relative to fat-free mass, but significantly less visceral adiposity compared to obese controls [66, 67]. Our group has also demonstrated higher total and high molecular weight adiponectin concentrations and increased ratios of HMW/total adiponectin and higher insulin sensitivity in PWS children compared to BMI-matched controls [68, 69]. The lack of visceral fat and the relative hyperadiponectinemia may protect PWS individuals against metabolic complications of obesity such as insulin resistance, type 2 diabetes, and hypertriglyceridemia [66]. Future studies are needed to understand the mechanisms that lead to abnormal partitioning of body fat in PWS and its metabolic consequences.
4. Several features of PWS – including abnormal temperature regulation, altered sleep control (excessive daytime somnolence and a primary abnormality of the circadian rhythm of rapid eye movement sleep), increased pain tolerance, and decreased salivation – suggest dysfunction of the autonomic nervous system (ANS). However, the evidence for ANS dysfunction is inconclusive. One study reported diminished parasympathetic nervous system function based on higher resting pulse rates and lesser increases in diastolic blood pressure upon standing [10]. However, when controlling for body mass index (BMI), other studies report no differences in ANS function (control of heart rate and blood pressure) in PWS subjects [70]. Interestingly, necdin-null mice have abnormal outgrowth of sympathetic neurons, predominantly from the superior cervical ganglion (the most rostral of the paravertebral sympathetic ganglions innervating the pupil, lacrimal and salivary glands, and cerebrum). Therefore, future studies examining the autonomic system in PWS will likely lead to further understanding of the autonomic nervous system's contribution to the control of energy homeostasis in PWS.
5. Finally, some preliminary evidence points to alterations in fatty acid and branched chain amino acid metabolism in individuals with PWS [69]. Future studies are needed to explore the roles of specific metabolites in the pathogenesis of obesity and insulin resistance in PWS.

Albright's Hereditary Osteodystrophy

Overview: Albright's hereditary osteodystrophy (AHO) was first described in 1942 in a child with short stocky build, round face, short metacarpals and metatarsals, and numerous areas of soft tissue calcification [71]. AHO can be an isolated finding or associated with pseudohypoparathyroidism. Pseudohypoparathyroidism is characterized by end-organ resistance to parathyroid hormone (PTH) action in the kidneys and bone, resulting in the constellation of physical findings of AHO. There may also be more generalized resistance to hormones that signal through G-protein-coupled receptors [71].

Incidence: The incidence of AHO is approximately 1:20,000 individuals.

Clinical Features: There are several forms of pseudohypoparathyroidism. Patients with pseudohypoparathyroidism type 1a (PHP type 1a) have a generalized resistance to hormones signaling through G-protein-coupled receptors (PTH, thyroid-stimulating hormone (TSH), growth hormone-releasing hormone (GHRH), and gonadotropins) and a constellation of developmental defects that is referred to as AHO. The AHO phenotype includes short stature, round face, obesity, brachydactyly, and subcutaneous calcification. Some individuals are reported to have dental and sensorineural abnormalities. Additionally primary hypothyroidism (due to TSH resistance), GH deficiency (secondary to GHRH resistance), and hypogonadism (due to gonadotropin resistance) are common [72]. Hypocalcemia associated with PTH resistance can lead to nervous excitability, cramps, tetany, hyperreflexia, convulsions, and tetanic crisis. In contrast to PHP type 1 A, individuals with pseudo-pseudohypoparathyroidism have the phenotype of AHO but have normocalcemia and lack hormone resistance [73].

Both isolated AHO and PHP type 1a can occur in the same family and are due to a functional tissue deficiency of the alpha subunit of the G-protein-coupled receptor ($G_s\alpha$). Generalized obesity develops in 50–65% of AHO patients [74]. The etiology of the obesity is thought to result from decreased energy expenditure rather than increased energy intake. Recent animal studies have shown that disruption of $G_s\alpha$ signaling in hypothalamic pathways leads to defective energy expenditure [75]. More recent clinical studies have confirmed these findings and show reduction in absolute resting energy expenditure and relative resting energy expenditure compared to obese controls [76]. Moreover, dietary data revealed these PHP1A clinical subjects consumed less than the daily allowance of calories, suggesting that reduced energy expenditure likely accounts for early-onset obesity [76].

Etiology: Autosomal dominant heterozygous inactivating mutations in the *GNAS*1 gene on chromosome 20q13.3 form the basis for $G_s\alpha$ deficiency of patients with AHO [77]. The *GNAS*1 gene consists of 13 exons and 3 alternate initial exons with different promoters, allowing for formation of four different isoforms via alternative splicing [78]. Interestingly, some mutations result in impaired expression of $G_s\alpha$ mRNA, while others result in dysfunctional $G_s\alpha$ proteins.

Several lines of evidence suggest that genomic imprinting of *GNAS*1 explains the variable phenotypes that occur with identical *GNAS*1 gene defects. First, PHP type Ia and pseudo-PHP frequently occur in the same family, but not in the same generation. Second, nearly all cases of maternal transmission of $G_s\alpha$ deficiency lead to PHP type 1a, whereas paternal transmission of the same mutation leads to pseudo-PHP [79, 80]; this suggests that variable AHO phenotypes originate from differential tissue-specific genomic imprinting.

Diagnostic Considerations: A diagnosis of AHO should be considered in an individual with functional hypoparathyroidism (hypocalcemia and hyperphosphatemia) and increased PTH concentrations or in those with clinical features of AHO such as obesity, round face, brachydactyly, and cognitive delay. It should be noted that primary hypothyroidism in PHP type 1A may be detected at an early age, before the emergence of obesity, hypogonadism, or disturbances in calcium metabolism.

Importantly, hypomagnesemia and vitamin D deficiency should be excluded, as these states can

mimic the biochemical features of AHO. Synthetic PTH [1–34] peptide is available, and various protocols exist for diagnosis of AHO based on intravenous infusion of PTH and measurement of resulting urine cAMP, phosphorus, and creatinine concentrations. *GNAS*1 gene analysis is also available through various commercial laboratories.

Treatment and Future Research: Treatment with oral calcium supplements and 1,25-dihydroxyvitamin D is needed to normalize calcium, phosphate, and PTH levels and thereby prevent hyperparathyroid bone disease. Blood chemistries and urine calcium excretion should be monitored at least twice yearly to avoid hypercalciuria and nephrocalcinosis. Although a number of defects in *GNAS*1 are responsible for AHO, the molecular mechanisms underlying hormone resistance and imprinting defects remain incompletely understood. Further characterization of novel *GNAS*1 defects will likely advance our knowledge of this disorder, and additional characterization of the obese phenotype of AHO will likely aid in our understanding of the molecular mechanisms of body weight regulation.

Bardet–Biedl Syndrome

Overview: In 1866 Drs. Laurence and Moon described four siblings with retinal dystrophy, obesity, and cognitive impairment, as well as small external genitalia and an abnormal gait in the males [81]. A similar phenotype that included polydactyly was then described by Bardet and Biedl [82, 83].

Incidence: BBS is rare; its prevalence ranges from 1 in 125,000–160,000 in Europe [84, 85] to 1 in 13,500 in the Bedouin of Kuwait [86] and 1 in 17,500 in Newfoundland, Canada [84].

Clinical Features: BBS is characterized by six primary features: progressive rod–cone dystrophy (90–100% prevalence), obesity (72–92%), postaxial polydactyly (extra digits) (63–81%), primary hypogonadism (98%), cognitive impairment (50%), and genitourinary tract malformations and progressive renal dysfunction (24%). Additional secondary features include speech delay (54–81%), behavior abnormalities (33%), hearing loss (21%), ataxia/imbalance (40–86%), type 2 diabetes (6–48%), and, occasionally, congenital heart disease (7%) [87–90]. Many of these features are not present at birth; rather, they develop over time by the second decade of life. Polycystic kidney disease and complications of obesity (type 2 diabetes, hypertension, and hypercholesterolemia) are the leading causes of premature death in BBS [88]. The obesity of BBS manifests as rapid progressive weight gain and hyperphagia in the first year of life and has been associated with reduced physical activity compared to obese controls [91]. The typical neurobehavioral profile of BBS consists of reduced IQ (mean 75.81 ± 14.01), impaired fine motor function, decreased olfaction, impaired vision, and social skills deficits [92].

Etiology: BBS is a genetically heterogeneous condition with significant intrafamilial variability. Previously BBS was determined to have autosomal recessive inheritance; however, more recent gene analysis of BBS asymptomatic gene mutation carriers suggests possible incomplete penetrance [89].

In 2003, Ansley and colleagues were the first to propose that BBS is caused by a defect at the basal body of ciliated cells [93]. DNA sequencing and whole exome sequencing technologies now implicate 19 genes in the etiology of BBS [88, 89], all of which are involved in ciliary development or intraflagellar transport. Primary cilia play central roles in cell signaling, sensing, and mediating inputs such as mechanical cues to chemical and paracrine signaling through hedgehog, Wnt, and platelet-derived growth factor (PDGF) pathways; thus, primary cilia play a key role in development to maintain cellular and tissue homeostasis [94].

BBS 1, 2, 4, 5, 6, and 8 localize to the basal body and pericentriolar region; BBS 6, 10, and 12 are likely chaperones that facilitate protein folding and account for one-third of cases. BBS 3 (a member of the Ras superfamily of small GTP-binding proteins) and BBS 11 (an E3 ubiquitin ligase) encode known proteins [95–102] (Table 9.1). Establishing genotype–phenotype correlations has been challenging. However,

studies now suggest that mutations in BBS2, BBS3, and BBS4 are associated with ocular manifestations [103]; patients with mutations in BBS16/SDCCAG8 have renal disease but no polydactyly [104]; patients with mutations in BBS6, BBS10, or BBS12 present with more severe renal disease [105].

Although not proven, the renal abnormalities seen in BBS are thought to be secondary to disordered cilia function. This is supported by features of the oakridge polycystic kidney disease mouse mutant (or^{pkd}) which exhibits dilated proximal tubules and cysts and has short and malformed cilia [106]; the mutation in this mouse maps to a gene encoding polaris, a protein required for assembly of renal cilia. Subsequent studies in cystic diseases of the kidney and BBS have illustrated that cilia in the epithelium of the renal tubules play a critical role in kidney tissue homeostasis [107, 108]. The retinal degeneration in BBS is also associated with impaired intraflagellar transport (IFT) across the connecting cilium, which links the photoreceptor inner and outer segments [109, 110]. The BBS proteins also play a role in transportation of rhodopsin to the base of the connecting cilium (CC); therefore, retinal degeneration in BBS is thought to result from both defective transport of cargo proteins to the base of the CC and defects in IFT-mediated transport across the CC [111]. Interestingly, the polydactyly of BBS is postaxial, which may result from a combination of defects in hedgehog and other signaling pathways (Wnt) [111].

Recent investigations have also evaluated the contribution of genes associated with Bardet–Biedl syndrome to the production and maintenance of pancreatic β-cells. Loss of *bbs1* or *bbs4* results in a significant increase in β-cell mass. Additionally, *bbs-1*-deficient β-cells are susceptible to apoptosis, but an increase in cell number is maintained via beta cell proliferation. This might explain the later onset of diabetes demonstrated in BBS patients; diabetes may occur eventually as a result of an inability to compensate for a high degree of β-cell death [112].

The mechanisms leading to obesity in BBS remain elusive. It is theorized that excess weight gain could result from ciliary defects in hypothalamic neurons that impair trafficking of leptin receptors and thereby reduce leptin signal transduction [113]. However, recent data suggest that leptin resistance might be a marker of obesity in BBS, rather than the causative initiating factor [114].

Recent studies in mice suggest that weight gain in BBS results from an energy imbalance. When fed the same diets, BBS mice had increased abdominal adiposity, decreased locomotion, and hyperphagia compared to control mice; this suggests that obesity in BBS reflects both increased energy intake and decreased energy expenditure [115, 116]. CNS mis-localization of G-protein-coupled receptors (GPCRs) involved in regulation of energy balance, such as neuropeptide Y2 receptor, and the brain-derived neurotrophic factor (BDNF) receptor, TrkB, may limit energy expenditure. Finally, BBS proteins play a key role in the differentiation of adipocytes, suggesting that a *defect in adipogenesis* and related abnormalities in circulating adipokines might contribute to the pathogenesis of obesity in BBS [113].

Diagnostic Considerations: Commercial labs now conduct multigene sequencing of BBS genes. However, the diagnosis of BBS is often delayed until visual deterioration manifests due to rod–cone dystrophy; night blindness typically emerges around 8 years of age, followed by loss of peripheral vision and blindness by 15 years of age [88]. Other characteristic findings that could warrant gene sequencing include postaxial polydactyly, early-onset obesity, male hypogonadotropic hypogonadism, and female genitourinary tract malformations (hypoplastic fallopian tubes and uterus, vaginal atresia, and hydrometrocolpos). Early diagnosis is important as renal disease is progressive and remains a major cause of mortality in BBS. Renal abnormalities are variable but commonly include cystic tubular disease and anatomic malformations; most patients also have a urinary concentration defect [117]. Additionally, an excess of early-onset renal cell carcinomas in obligate carriers of BBS mutations necessitates that BBS patients be carefully monitored for development of malignancies [118]. The majority of adults have obesity complicated

by hypertension, type 2 diabetes mellitus, and dyslipidemia. Some BBS patients have given birth to healthy children [88].

Treatment and Future Research: Therapeutic strategies in BBS remain supportive pending the development of novel and targeted treatments. Chronic renal dialysis or transplantation is currently the only successful mode of managing renal disease in most patients. Further studies examining long-term outcomes after renal transplantation are needed.

As improvements in gene testing have continued, new treatments have been trialed in animal studies. Gene therapy for treatment of blindness has been successful in selected mouse experiments [89]. For example, subretinal injection of the BBS gene within an adenovirus construct rescued rhodopsin and preserved eye function in mice [119, 120]. Other studies in BBS knockout mice have attenuated weight gain by administration of melanotan II, a melanocortin receptor agonist that reduced food intake [113]. Setmelanotide, a new melanocortin-4 receptor agonist, may also be beneficial in controlling weight gain in the BBS population [121].

Alstrom Syndrome (AS)

Overview: Alstrom syndrome (AS) is a rare autosomal recessive multi-organ disorder caused by mutations in *ALMS1*. It was first described in 1959 [122].

Incidence: AS has an estimated prevalence of <1:100,000 [123]. Approximately 800 cases have been described since it was first reported [124].

Clinical Features: AS exhibits much phenotypic variability, even within families. Characteristic features include progressive rod–cone dystrophy beginning in infancy and leading to juvenile blindness (90% by age 16 years), sensorineural hearing loss (89%; mean age of 5 years), early-onset childhood obesity (nearly 100%), and adult short stature (due to early rapid growth and early fusion of growth plates) [125]. Most patients have normal intelligence, although delayed fine and gross motor and language development are described in some [124].

Endocrinologic manifestations include hyperinsulinemia (92%) and acanthosis nigricans (68%), diabetes mellitus (median age of onset of 16 years; 82%), hypertriglyceridemia (nearly 100%), infertility (hypergonadotropic hypogonadism; 77%), increased androgen production and hirsutism in females, primary hypothyroidism, growth hormone deficiency, and bone–skeletal abnormalities [124, 125]. In younger patients, mortality is primarily due to cardiac failure secondary to dilated cardiomyopathy [123]. In older subjects, renal failure is the most common cause of death [124]. Advanced early-onset, non-alcoholic fatty liver diseases (NAFLD) with fibrosis (disproportionate to age, BMI and diabetes duration) are also common and lead to high morbidity/mortality in AS [126]. Fibrosis in multiple organs has been reported. Finally, a recent MRI study in AS reports a high incidence of total empty sella (34%) and partial empty sella (19%). These findings raise the importance of screening for pituitary dysfunction [127]. Note that many of the characteristic features of AS emerge as the children grow.

Etiology: The *ALMS1* gene on chromosome 2p13 was identified by two independent research groups in 2002. *ALMS1* encodes a 4169 amino acid protein that contains a large 47 amino acid tandem repeat domain [128, 129]. The function of the ALMS protein remains unknown. However, it is expressed ubiquitously and is thought to be involved in the function of centrosomes or basal bodies [130]. In support of this theory, *ALMS1* knockout mice demonstrate abnormal ciliary structure and recapitulate many features of the human syndrome including obesity, hyperinsulinemia, hypogonadism, retinal degeneration, and renal dysfunction. The phenotype is reversed by a prematurely truncated N-terminal fragment of ALMS1 [130, 131].

Until recently, approximately 80 different ALMS1 mutations, located primarily in exons 8, 10, and 16, have been implicated in AS [132]. However, the wider incorporation of automated sequencing to genotype patients with AS has now uncovered additional disease-causing mutations in *ALMS1* [133]. These are located in exons 3, 5, 8, 9, 10, 12, 14, 15, 16, 17, 18, 19, and 21 and in

introns 2, 9, and 15. Mutational hotspots for *ALMS1* occur in exons 8, 10, and 16. The majority of mutations are nonsense or frameshift abnormalities that are predicted to cause premature protein truncation; studies to date suggest no strong genotype–phenotype correlation [132]. There is phenotypic variation in visual acuity, hearing loss, cardiomyopathy, and hepatic manifestations within families. Thus, there seem to be interactions between numerous genetic modifiers, environmental or infectious exposures, and other variables leading to variations in age of onset and severity of clinical phenotype in AS patients.

Diagnostic Considerations: Diagnosis can be challenging in young children, as many of the characteristic clinical features (type 2 diabetes mellitus and hepatic, pulmonary, and renal dysfunction) do not manifest until the teenage years. Alstrom syndrome is often confused with other conditions early in life. For example, photophobia in infancy might be misclassified as Leber congenital amaurosis or achromatopsia, and childhood obesity and type 2 DM often lead to an incorrect diagnosis of Bardet–Biedl syndrome (BBS). The presence of dilated cardiomyopathy, early hearing loss, and absence of digit abnormalities are often helpful in distinguishing between BBS and Alstrom syndrome. A diagnosis of Alstrom syndrome is proven when two *ALMS1* mutations (one from each parent) are identified in a patient. However, lack of confirmation of a gene mutation does not exclude the diagnosis, and repeated clinical monitoring is recommended.

Treatment and Future Research: Currently there is no treatment that will cure Alstrom syndrome or delay or reverse the progression of disease. Management of photophobia in young children with red-tinted glasses is helpful to alleviate distress with bright lights. Total vision loss should be anticipated, and early development of Braille or other nonvisual language skills is very important. There is no specific treatment for sensorineural hearing loss; hearing aids or cochlear implants may be helpful.

Monitoring of cardiac function with echocardiography is essential in all patients. Treatment with angiotensin-converting enzyme (ACE) inhibitors is indicated in those with cardiomyopathy. Weight management and exercise are important in managing the metabolic disorders in AS. Many patients eventually require insulin sensitizers (metformin and/or thiazolidinediones) or insulin therapy. Hormonal replacement with thyroxine and/or testosterone is useful when indicated. The benefits and risks of the use of growth hormone therapy in AS are not fully understood at this time; thus, GH treatment is still considered investigational. Further elucidation of the function of ALMS1 will provide insight into the pathogenesis of AS and other uncommon forms of obesity, diabetes, and retinal disease.

Rapid-Onset Obesity with Hypothalamic Dysregulation, Hypoventilation, and Autonomic Dysregulation Syndrome (ROHHAD)

Overview: ROHHAD syndrome is a complex multisystem disorder associated with rapid onset of hyperphagia and obesity between 2 and 7 years of age. It was first described nearly 50 years ago, yet the etiology remains unknown [134, 135].

Incidence: ROHHAD is exceedingly rare; fewer than 100 cases have been reported in the literature [136]. It occurs sporadically, without any suggestive family history.

Clinical Features: ROHHAD syndrome is a complex disease with hallmark features of hypothalamic, respiratory, and autonomic dysfunction. Patients often come to attention in the preschool years due to the development of rapid weight gain of 20–30 lbs over a 3–6-month period [136]. It can be confused with other syndromes that cause early-onset obesity [134]; there is progressive accumulation of adipose tissue in the face, trunk, and breasts. Height velocity declines, mimicking the effects of the hypercortisolism of Cushing's syndrome. However, unlike classic Cushing's syndrome, there is neither facial plethora nor striae. Individuals with ROHHAD also have delayed or absent pubertal development. Interestingly, approximately one-half of patients will develop hypernatremia without true diabetes insipidus.

Major comorbidities [134, 136] include developmental delay and seizures. Autonomic dysregulation is manifest as temperature instability, GI dysmotility (constipation and chronic diarrhea most commonly), and ophthalmologic dysfunction, altered pupillary responses to light, strabismus, alacrima, and oculomotor apraxia. Most worrisome is central hypoventilation (with or without obstructive sleep apnea), which can lead to cardiopulmonary arrest [134].

One-half of patients will develop ganglioneuromas of the adrenal glands and posterior mediastinum, despite normal urine catecholamines, VMA, HVA, and plasma adrenal steroid levels [135].

Etiology: The etiology of ROHHAD syndrome is unclear. Patients with Phox 2 mutations have congenital central hypoventilation and hypothalamic dysfunction and may develop neural tumors [134] but do not have hyperphagia or obesity. Barclay and colleagues conducted whole exome sequencing (WES) on seven ROHHAD subjects, the tumors from four patients, and the unaffected monozygotic twin of one subject [136]. They discovered 13 de novo gene variants; however, no two patients had the same variants in the same gene. Further work is being done to evaluate non-exomic risk factors and possible epigenetic mechanisms of disease.

Diagnostic Considerations: Ize-Ludlow and coworkers defined the basic criteria for diagnosis of ROHHAD: (1) rapid-onset, extreme weight gain after age 1.5 years in a previously healthy, normal weight child, (2) hypothalamic dysfunction, (3) alveolar hypoventilation, and (4) autonomic dysregulation [134]. Given that ROHHAD syndrome is associated with hormonal dysregulation, diagnosis requires exclusion of other causes. The rapid-onset obesity with declining height velocity should prompt evaluation for hypercortisolism as well as growth hormone deficiency and hypothyroidism. Diurnal rhythm of plasma cortisol, 24-hour urine-free cortisol levels, and response to high-dose dexamethasone are normal. Plasma IGF-1 levels may be low in some patients, and the growth hormone response to stimulation may be submaximal [134]. There is variable hyperprolactinemia and TSH dysregulation. Patients often have delayed or absent puberty and low gonadotropins, suggesting central hypogonadotropic hypogonadism. There may also be hypernatremia without polyuria, polydipsia, or urine hypoosmolality. Leptin levels are comparable to age-matched children with similar BMI. Urine and plasma catecholamines, VMA, HVA, and plasma adrenal steroids in patients with ganglioneuromas are normal [135]. When these tumors have been resected, there have been no changes in phenotype or biochemical parameters.

A sleep study is essential to identify obstructive or central sleep apnea. Affected children often have alveolar hypoventilation during sleep with hypercarbia and hypoxemia, but do not have the expected increased rate or depth of breathing [134]. This can lead to sudden death in bed.

Treatments and Future Therapies: With an elusive etiology and complex phenotype, treatment and management are challenging. Strict diet and exercise programs have been successful in improving BMI; however, the multisystem clinical features were not improved. As previously described, patients develop growth failure with low serum IGF-1 and submaximal growth hormone response to stimulation testing. However, growth hormone treatment has not been shown to improve BMI or other clinical features. Positive-pressure ventilation should be considered when central hypoventilation is diagnosed; oxygen or tracheostomy may be required for some patients.

Overgrowth Syndromes

Infants born large for gestational age (birth weight greater than 4000 g) frequently come to the attention of primary care providers. The more common causes for fetal macrosomia are included in Table 9.3; however, macrosomia can signal underlying disease or a fetal overgrowth syndrome that may have systemic effects.

The characteristic features of several overgrowth syndromes and their associated comorbidities are outlined in Table 9.4 [137]. Generally, syndromic causes of overgrowth have several common features, including multiple

congenital anomalies, developmental delay with cognitive impairment, and predisposition toward neoplasia. Children with overgrowth syndromes have elevated birth weight that persists into postnatal life; both weight and length are increased for age. This distinguishes the overgrowth syndromes from most early-onset obesity syndromes (i.e., PWS, BBBS, AHO, ROHHAD). Children with mutations in the melanocortin-4 receptor can have relative tall stature in the presence of severe early-onset obesity, but in contrast to children with fetal overgrowth syndromes, they have normal weights at birth. Here we will focus on Sotos syndrome, Weaver syndrome, and Beckwith–Wiedemann syndromes.

Sotos Syndrome: Sotos syndrome has an estimated prevalence of 1 in 14,000 live births [137]. The etiology most commonly is due to

Table 9.3 Non-pathologic causes of fetal macrosomia

Maternal diabetes
Family history of fetal macrosomia
Maternal obesity
Excessive maternal weight gain during pregnancy
Familial tall stature

Table 9.4 Overgrowth syndromes

Syndrome	Etiology	Characteristics	Multisystemic effects
Sotos syndrome	NSD1 mutation – Autosomal dominant – De novo	**Facial appearance** – Broad, prominent forehead – Receding frontoparietal hairline – Downslanted palpebral fissures – Bitemporal narrowing with long facies – Long chin **Developmental delays** – Neonatal hypotonia – Delayed gross motor skills (walking after 15 months) – Delayed language **Overgrowth** – Large for gestational age – Length and head circumference increased for age – Advanced bone age	– Cognitive impairment – Behavioral disorders (autism spectrum, phobias) – Cardiac anomalies (ASD, VSD, PDA) – Renal anomalies (vesicoureteral reflux) – Scoliosis – Seizures – CNS abnormalities (ventricular dilatation, hypoplasia or agenesis of corpus callosum or septum pellucidum, cerebral atrophy, small cerebellar vermis) – Neoplasms (ALL, neuroblastoma)
Weaver syndrome	*EZH2* mutation – Unclear pathogenic mechanism	**Facial appearance** – Macrocephaly – Broad forehead – Flattened occiput – Large, low-set ears – Ocular hypertelorism – Micrognathia – Redundant nuchal skinfolds **Developmental delays** – Gross motor delays – Intellectual disability varies among individuals **Overgrowth** – Increased length and head circumference for age – Continued postnatal accelerated growth – Excessive adult height	– Congenital heart defects (VSD, PDA) – CNS anomalies (cerebral atrophy, pachygyria, cysts of septum pellucidum) – Neoplasms (ALL, lymphoma, neuroblastoma)

(continued)

Table 9.4 (continued)

Syndrome	Etiology	Characteristics	Multisystemic effects
Beckwith–Wiedemann syndrome	Epigonic and genomic alteration in imprinting region of chromosome 11p15	**Facial appearance** – Macroglossia – Anterior ear lobe creases – Posterior helical pits – Facial nevus flammeus **Development** – Normal cognitive development – At risk for adverse development from complications of prematurity or hypoglycemia **Overgrowth** – Large for gestational age – Pre- and postnatal length > 97th percentile – Organomegaly of the liver, spleen, pancreas, adrenal glands – Hemihyperplasia with asymmetric growth	– Abdominal wall defects (omphalocele, umbilical hernia, diastasis recti) – Neonatal hyperinsulinemic hypoglycemia – Prematurity – Renal anomalies – Cardiomegaly – High risk of embryonal tumors (most commonly Wilms' tumor; hepatoblastoma, neuroblastoma, adrenocortical carcinoma)

a heterozygous mutation of the NSD1 gene, which encodes a histone methyltransferase that catalyzes the methylation of lysine 36 on histone 3 (H3K36). The vast majority of identified patients will have de novo mutations [138]. The syndrome is characterized by three general features: characteristic facies (Table 9.4), developmental delays, and overgrowth. Infants with Sotos syndrome are large for gestational age with increased birth length and head circumference and have excessive postnatal growth in early childhood [137, 138]. Tall stature and macrocephaly persist throughout childhood but normalizes by adulthood. Commonly, the epiphyses are advanced for age, yet there are no signs of precocious puberty. Sotos syndrome may be associated with scoliosis, seizures, and renal and cardiac anomalies. *NSD1* mutations have also been identified in neoplasms including neuroblastoma, acute lymphoblastic leukemia, and sacrococcygeal teratoma [138].

Weaver Syndrome: Weaver syndrome has many similar features to Sotos syndrome, making the distinction challenging. Genetic studies have identified a heterozygous mutation in *EZH2,* a histone methyltransferase for lysine 27 on histone 3 (H3K27). Tatton-Brown and coworkers delineated the clinical features of Weaver syndrome associated with *EZH2* mutations [139]. Facial features included ocular hypertelorism, almond-shaped palpebral fissures, broad forehead, large ears, and retrognathia. In this study, only 38% of infants were large for gestational age, though infants with *EZH2* had increased birth length [139]. Children with Weaver syndrome have accelerated skeletal growth relative to epiphyseal maturation and, therefore, have increased adult height [137]. Those with *EZH2* mutations also had hypotonia, soft and doughy skin, and poor coordination. Similar to Sotos syndrome, associated neoplasms have included lymphoma, acute lymphoblastic leukemia, neuroblastoma, and sacrococcygeal teratoma [137].

Beckwith–Wiedemann Syndrome: Beckwith–Wiedemann syndrome (BWS) is the most common genetic overgrowth syndrome, occurring in approximately 1 in 10,500 births. It is characterized by distinct and recognizable features: fetal macrosomia, asymmetric overgrowth with hemihyperplasia, omphalocele or other abdominal wall defects, macroglossia, hyperinsulinemic hypoglycemia, renal malformations, organomegaly, and a high risk of neoplasms [140]. Patients have distinct facial features including prominent forehead, micrognathia, down-turned corners of the mouth, and triangular facies. The etiology of

BWS involves dysregulated imprinting of critical regions of chromosome 11p15.5 that encode insulin-like growth factor 2, cyclin-dependent kinase inhibitor 1C, and H19. BWS can be caused by loss of methylation, paternal uniparental disomy, gain of methylation, mutation of critical gene regions, or paternal duplication [140].

Children with BWS are at high risk of childhood embryonal tumors: Wilms' tumor, hepatoblastoma, neuroblastoma, ganglioneuroma, adrenocortical carcinoma, and others have been reported in the literature [137]. The risk of malignancy in BWS reaches 10% in the first decade of life [141]. Therefore, early identification of the syndrome is essential for tumor surveillance.

Recommendations for tumor screening have included ultrasounds every 3 months from infancy to age 8 years and routine measurement of alpha-fetoprotein (AFP) starting as early as 6 weeks [142]. With advanced molecular diagnostics, recent clinical studies have proposed surveillance protocols according to the molecular phenotype of BWS for improved and targeted early diagnosis [143].

SIM1 Deletion Syndrome

Overview: Human SIM1 (single-minded) deletion syndrome was first described by Holder and colleagues in a young girl with early-onset obesity, hyperphagia, and increased linear growth [144].

Incidence: Five individuals with SIM1 deletion syndrome have been reported in the literature.

Clinical Features: Subjects with SIM1 deletions exhibit features in common with Prader–Willi syndrome including hypotonia, obesity, hyperphagia, developmental delay, almond-shaped eyes, strabismus, thin upper lip, hypogonadism, and short extremities. However, patients with SIM1 deletions may have additional findings including cardiac (bicuspid aortic valve, aortic stenosis, right branch block) and neurological abnormalities (polygyria, leukomalacia, Arnold–Chiari malformation, seizures, and hearing loss). Endocrine manifestations of the condition were described in a child with a proximal interstitial 6q16.1-q21 deletion encompassing the SIM1 gene [145]. Features included hyperphagia, obesity with 60% lower resting energy expenditure, progressive linear growth failure with growth hormone deficiency, normal puberty, a "reset" osmostat with higher than normal serum osmolality and normal urine osmolality, central hypothyroidism, and partial central adrenal insufficiency.

Several groups have now confirmed rare variants in SIM1 associated with severe early-onset obesity [146, 147]. One study demonstrated 13 different heterozygous SIM1 variants in 28 unrelated severely obese patients (among 2100 severe early-onset obese patients and 1680 controls). Nine of the thirteen variants demonstrated reduced activity and co-segregated with obesity in families with variable penetrance. The affected subjects had hyperphagia, normal basal metabolic rate, and signs of autonomic dysfunction [146]. More recently, SIM1 was sequenced [148] in 283 children presenting with developmental delay and overweight; novel functional mutations (c.886A > G/p.R296G and c.925A > G/p.S309G) were found in two boys with varying degrees of cognitive delay and weight abnormalities.

Etiology: SIM1 is the mammalian homolog of the *Drosophila* transcription factor, single-minded, a member of the basic helix–loop–helix period aryl hydrocarbon receptor family of proteins. Homozygous deletion of *Drosophila* single-minded results in failure of formation of midline central nervous system structures (148). The majority of patients with SIM1 deletion syndrome have a 6q16.2 deletion. The initial patient described by Holder and colleagues had a balanced translocation between chromosomes 1p22.1 and 6q16.2 that disrupted the SIM1 gene [149]. A mouse model of heterozygous SIM1 deletion also exhibits early-onset obesity with hyperphagia, increased linear growth, hyperinsulinemia, hyperleptinemia, normal energy expenditure, and a decreased number of neurons in the paraventricular nucleus (PVN) [150]. Subsequent investigations now show that the *Sim1* gene is expressed in the supraoptic nuclei (SON) and paraventricular nuclei (PVN) of the hypothalamus, both important areas involved in the regulation of body weight [151]. More recent studies show that SIM1 is required for terminal differentiation of

the neurons in the PVN and SON nuclei and suggest that SIM1 might function downstream of the melanocortin-4 receptor to control energy balance [152]: SIM 1 was found to partially rescue the hyperphagia and obesity of agouti yellow mice (in which melanocortin signaling is defective). This suggests that the melanocortin-4 receptor signals through SIM 1 or its downstream targets to control food intake [152]. Finally, a mouse model of postnatal SIM 1 deficiency confirms that SIM 1's role in energy balance is not limited to just its role in formation of the PVN, but rather implicates changes in the leptin–melanocortin–oxytocin pathways in its regulation of body weight [153].

Diagnostic Considerations: Deletion of the 6q16.2 region and SIM1 gene deletion should be sought in patients who exhibit Prader–Willi syndrome-like features but a normal cytogenetic study of the 15q11-q12 region.

Treatment and Future Research: Several genome-wide scans in various populations have shown strong linkage of loci on chromosome 6q with obesity and type 2 diabetes-related traits [154, 155]. One association study with common single-nucleotide polymorphisms (SNPs) in the *SIM1* gene was performed in two population-based cohorts. Mutations in SIM1 were not commonly found in individuals with early-onset obesity. However, an association was found between BMI in males and in females and homozygosity for the P352T/A371V haplotype [156]. Further studies are needed to clarify the relationship between common variants of SIM1 and body weight gain.

BDNF and Tropomyosin-Related Kinase B

Overview: An 8-year-old girl with severe early-onset obesity, hyperactivity, impaired cognition, memory, and nociception due to haploinsufficiency of brain-derived neurotrophic factor (BDNF) was described in 2006 [157]. The child had a de novo chromosomal inversion 46, XX, inv. [11] (p13p15.3), a region encompassing the BDNF gene, and reduced serum concentrations of BDNF. Another report described an obese, hyperphagic tall child with impairment in memory, cognition, and nociception with a heterozygous missense mutation in the neurotrophin receptor TrkB, the receptor of BDNF [158]. Interestingly, among persons with Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation (WAGR) syndrome, BDNF haploinsufficiency is associated with lower serum BDNF concentrations and childhood-onset obesity [159]. Finally, several studies link the common single-nucleotide polymorphism (Val66Met) in the human *Bdnf* gene to a higher body mass index [160–162].

Incidence: Mutations in BDNF and TrkB are rare genetic causes of human obesity.

Clinical Features: BDNF or TrkB haploinsufficiency leads to hyperphagia, morbid obesity, and a complex neurobehavioral phenotype including impaired cognition, memory, and nociception.

Etiology: Acting through its receptor, tropomyosin-related kinase B (TrkB), BDNF regulates the development, differentiation, and survival of neurons [163]; it is expressed during developmental stages of neuronal differentiation and connectivity of synapses [163]. Therefore, BDNF plays roles in the formation of neuronal circuits in the brain, including those regulating energy homeostasis. BDNF and TrkB are expressed in areas involved in energy balance, including the ventromedial nucleus (VMN), dorsomedial hypothalamus (DMH), lateral hypothalamus (LH), arcuate nucleus (Arc), and paraventricular nucleus (PVN) [164, 165].

BDNF is implicated in energy homeostasis; hypothalamic expression of BDNF in the ventromedial hypothalamus is reduced by fasting, and BDNF administration causes weight loss in wild-type mice via reduction in food intake [164]. BDNF administration has also been shown to induce weight loss, prevent overeating, and improve glucose homeostasis in leptin- and leptin receptor-deficient mice, diet-induced obese rats, and animals with reduced melanocortin signaling [164, 166–168]. BDNF haploinsufficiency in mice leads to hyperphagia, obesity, and hyperglycemia and has been implicated in memory and various behavioral abnormalities [169, 170].

Diagnostic Considerations: BDNF or TrkB deficiency should be considered in individuals with early-onset morbid obesity and hyperphagia.

Treatment and Future Research: There is some evidence that BDNF-expressing neurons might lie downstream of melanocortin-4 (MC4) neuronal pathways, since BDNF mRNA levels are reduced in the ventromedial hypothalamus of MC4R knockout mice and levels are restored by administration of an MC4R agonist, MT-II [164]. A functional interaction between leptin and BDNF is also demonstrated by studies showing that leptin increases BDNF content in the VMN and DVC; conversely, there is reduced hypothalamic BDNF expression in leptin receptor-deficient (db/db) mice [171]. Indeed, BDNF signaling through its TrkB receptor appears to be essential for the anorexigenic effects of leptin [172].

Further research should elucidate the molecular role of BDNF and its receptor, TrkB, in the regulation of energy balance in humans. Data by Pelleymounter and colleagues provide evidence that BDNF might induce appetite suppression and weight loss via increases in hypothalamic 5-HIAA/5-HT [173]. It is possible that BDNF influences energy balance via effects on development of the hypothalamus or through modulation of synaptic plasticity in hypothalamic feeding circuits. For example, BDNF might influence rewiring of feeding circuits in response to nutritional cues to increase anorexigenic tone. Others have shown that induction of hypothalamic BDNF expression leads to selective "browning" of white fat through a sympathoneural mechanism [174]. Furthermore, BDNF is thought to play a role in the cognitive benefits (enhanced spatial learning and memory) of running and intermittent fasting [175]. Finally, the GLP-1 analogs, exenatide and liraglutide, might reduce appetite and exert beneficial neurocognitive effects, in part, through increasing BDNF production [176]. Understanding BDNF and TrkB's mechanistic role in the regulation of body weight and metabolism will likely lead to novel downstream therapeutic approaches for the treatment of human obesity.

Conclusions

Currently, syndromic obesity is managed by caloric restriction. The efficacy and durability of this approach have been severely limited in most cases. The genetics involved in these syndromes are complex, and defects in multiple genes within a pathway can lead to similar clinical phenotypes. In order to develop future effective and innovative obesity treatm.ents, it will be imperative to further unravel the molecular defects leading to the various syndromic obesity disorders.

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Editor's Question

What criteria should the clinician use to distinguish children with early-onset obesity from those who they suspect may be overfed by parents or caretakers?

Authors' Response

We suggest the following criteria to distinguish pathologic early-onset obesity from exogenous obesity:

i. Early-onset obesity occurring prior to age 5 years.
ii. Rapid rate of weight gain that is not attenuated by nutritional or exercise intervention.
iii. Hyperphagia with absent satiety signals manifest as abnormal food-seeking behavior (hiding or stealing food, eating nonfood substances, eating in excess despite abdominal pain and/or vomiting).
iv. Associated neuroendocrine abnormalities (i.e., pituitary hormone abnormalities).
v. Associated features suggesting syndromic or monogenic obesity disorders, as described in our chapter and in Chap. 9 by Marie Pigeyre and David Meyre.

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Polygenic Obesity

10

Anke Hinney and Johanna Giuranna

Polygenes for Variance in Body Weight

The term "polygene" is used for a gene or chromosomal locus known to harbor interindividual sequence variation and to account for a small fraction of the variation of a specific quantitative trait. Polygenes or polygenic loci are usually derived from genome-wide association studies (or meta-analyses thereof; GWAMA) based on single-nucleotide polymorphisms (SNP) or copy number variation (CNV), whereby a genome-wide significant SNP reaches a *p*-value $\leq 5 \times 10^{-08}$. Each polygene contains one allele predisposing to higher and the other to lower body weight. As SNPs explain only a minor proportion of the overall heritability [1], it was assumed that CNVs might explain part of the "missing heritability." CNVs are genetic variants with a minimum length of 1 kb. A relevance of CNVs for gene expression or function is easily conceivable, especially when the CNVs are located in intragenic regions [2].

We currently have identified more than 100 polygenes/polygenic loci that play a role in body weight regulation (Table 10.1) [3]. Obesity is the result of the interaction of several or many of these polygenic variants, epigenetic effects, and their combined interaction with environmental factors. Interindividual heterogeneity is most likely pronounced and implies that the specific set of polygenes predisposing to obesity in any one individual is unlikely to be the same in another randomly selected obese subject [4, 5].

In contrast to most of the initially detected genetic influences on obesity, which are conferred by a single gene with either a recessive or a dominant mode of inheritance, the effect of a single polygene is small. However, the combined effect of all polygenes involved in individual body weight regulation is substantial. Enrichment with currently known variants predisposing to obesity was analyzed in the most recent GWAMA for BMI [1]. The combined effects of lead SNPs at the 97 loci in 8164 European-descent individuals revealed an average increase of 0.1 BMI units (kg/m^2) per BMI-increasing allele; for an individual measuring 160–180 cm in height, this is equivalent to 260–320 g. Additionally, the mean BMI was 1.8 kg/m^2 higher in 145 individuals (1.78%), carrying the greatest number of BMI-increasing alleles relative to those carrying the mean number of these alleles. This translates to a difference of 4.6–5.8 kg for a person 160–180 cm in height.

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Table 10.1 List of GWAS-derived SNPs and corresponding genes associated with body mass index (BMI) or (extreme) obesity

Chrom.	SNPs	Nearest gene	Phenotype	References
1	rs657452	*AGBL4*	BMI	[1]
1	rs11583200	*ELAVL4*	BMI	[1]
1	rs17024258	*GNAT2*	Obesity	[20]
1	rs11208659	*LEPR*	Childhood obesity	[64]
1	rs2820292	*NAV1*	BMI	[1]
1	rs2815752, rs2568958, rs1993709	*NEGR1*	BMI, obesity, overweight	[17, 18, 64]
1	rs1555543	*PTBP2*	BMI	[16]
1	rs12145833	*SDCCAG8*	Childhood obesity	[22]
1	rs10913469, rs543874, rs574367, rs516636, rs591120	*SEC16B*	BMI, obesity, overweight	[18, 20, 23, 65, 68, 70]
1	rs977747	*TAL1*	BMI	[1]
1	rs1514175, rs12142020, rs1040070, rs1514174	*TNNI3K*	BMI, obesity	[16, 20, 23, 65]
1	rs17381664	*ZZZ3*	Obesity	[20]
2	rs116612809	*BRE*	BMI	[66]
2	rs17203016	*CREB1, KLF7*	BMI	[1]
2	rs11688816	*EHBP1*	BMI	[1]
2	rs7599312	*ERBB4*	BMI	[1]
2	rs887912	*FANCL*	BMI, obesity, overweight	[16]
2	rs12617233	*FANCL, FLJ30838*	BMI	[67]
2	rs1460676	*FIGN*	BMI	[1]
2	rs11126666	*KCNK3*	BMI	[1]
2	rs2890652	*LRP1B*	BMI	[16]
2	rs492400	*PLCD4, CYP27A1, USP37, TTLL4, STK36, ZNF142, RQCD1*	BMI	[1]
2	rs713586, rs6545814, rs1561288, rs6752378, rs10182181	*POMC*	BMI, obesity, overweight	[16, 20, 23, 65, 68]
2	rs6548238, rs7561317, rs2867125, rs12463617, rs4854344	*TMEM18*	BMI, obesity, overweight	[16–18, 20, 23, 64, 65, 67]
2	rs1528435	*UBE2E3*	BMI	[1]
3	rs13078807	*CADM2*	BMI, overweight	[16]
3	rs7647305, rs9816226	*ETV5*	BMI, obesity, overweight	[16, 18, 20]
3	rs2365389	*FHIT*	BMI	[1]
3	rs3849570	*GBE1*	BMI	[1]
3	rs6804842	*RARB*	BMI	[1]
3	rs16851483	*RASA2*	BMI	[1]
4	rs10938397, rs13130484, rs348495	*GNPDA2*	BMI, obesity, overweight	[16, 17, 20, 65]
4	rs11727676	*HHIP*	BMI	[1]
4	rs17001654	*NUP54, SCARB2*	BMI	[1]
4	rs13107325	*SLC39A8*	BMI	[16]
5	rs2112347	*FLJ35779*	BMI, obesity, overweight	[16]
5	rs261967, rs6232, rs6234, rs6235	*PCSK1*	BMI, obesity	[68, 69]
5	rs48361333	*ZNF608*	BMI	[16]
6	rs2206734, rs9356744	*CDKAL1*	BMI	[68, 70]

Table 10.1 (continued)

Chrom.	SNPs	Nearest gene	Phenotype	References
6	rs9400239	*FOXO3, HSS00296402*	BMI	[1]
6	rs206936	*HMGA1*	BMI	[16]
6	rs13201877	*IFNGR1, OLIG3*	BMI	[1]
6	rs9374842	*LOC285762*	BMI	[1]
6	rs13191362	*PARK2*	BMI	[1]
6	rs2033529	*TDRG1, LRFN2*	BMI	[1]
6	rs987237, rs734597, rs2272903	*TFAP2B*	BMI, obesity, overweight	[16, 20, 67, 71]
7	rs6465468	*ASB4*	BMI	[1]
7	rs9641123	*CALCR*	BMI	[1]
7	rs1167827	*HIP1, PMS2L3, PMS2P5, WBSCR16*	BMI	[1]
7	rs2245368	*PMS2L11*	BMI	[1]
7	rs6955651	*DTX2P1-UPK3BP1-PMS2P11*	BMI	[72]
8	rs4735692	*HNF4G*	Obesity	[20]
8	rs2033732	*RALYL*	BMI	[1]
8	rs17150703	*TNKS*	Childhood obesity	[22]
8	rs16907751	*ZBTB10*	BMI	[1]
9	rs4740619	*C9orf93*	BMI	[1]
9	rs6477694	*EPB41L4B, C9orf4*	BMI	[1]
9	rs11142387	*KLF9*	BMI	[70]
9	rs10733682	*LMX1B*	BMI	[1]
9	rs10968576	*LRRN6C*	BMI, obesity	[16]
9	rs1211166	*NTRK2*	BMI	[67]
9	rs1928295	*TLR4*	BMI	[1]
10	rs7899106	*GRID1*	BMI	[1]
10	rs116454156	*GRP120*	Obesity	[73]
10	rs17094222	*HIF1AN*	BMI	[1]
10	rs2116830	*KCNMA1*	Obesity	[74]
10	rs11191560	*NT5C2, CYP17A1, SFXN2*	BMI	[1]
10	rs7903146	*TCF7L2*	BMI	[1]
11	rs6265, rs4923461, rs10767664, rs2030323, rs988712	*BDNF*	BMI, obesity, overweight	[16, 18, 68, 70, 74]
11	rs12286929	*CADM1*	BMI	[1]
11	rs2176598	*HSD17B12*	BMI	[1]
11	rs10838738, rs3817334	*MTCH2*	BMI, obesity, overweight	[16, 17, 20]
11	rs564343	*PACS1*	Childhood obesity	[64]
11	rs11042023	*RPL27A*	Obesity	[20]
11	rs4929949	*TUB*	BMI	[16]
12	rs11057405	*CLIP1*	BMI	[1]
12	rs7138803, rs7132908	*FAIM2*	BMI, obesity, overweight	[16, 18, 20, 23, 71]
12	rs11109072	*RMST*	Childhood obesity	[64]
13	rs7989336	*HS6ST3*	Obesity	[20]
13	rs1441264	*MIR548A2*	BMI	[1]
13	rs9540493	*MIR548X2, PCDH9*	BMI	[1]
13	rs4771122	*MTIF3*		[16]
13	rs9568856, rs9568867	*OLFM4*	Obesity	[20, 23]
14	rs10150332	*NRXN3*	BMI, obesity	[16]
14	rs1957894	*PRKCH*	Childhood obesity	[64]

(continued)

Table 10.1 (continued)

Chrom.	SNPs	Nearest gene	Phenotype	References
14	rs11847697, rs12885454	*PRKD1*	BMI	[16] [1]
14	rs10132280	*STXBP6*	BMI	[1]
14	rs7492628	*RPS6KA5, C14orf159*	Obesity	[71]
15	rs7164727	*LOC100287559, BBS4*	BMI	[1]
15	rs2241423, rs4776970, rs997295	*MAP2K5*	BMI, obesity, overweight	[16, 20, 67, 68]
15	rs3736485	*SCG3, DMXL2*	BMI	[1]
16	rs2531995	*ADCY9*	Obesity	[20]
16	rs2080454	*CBLN1*	BMI	[1]
16	rs9939609, rs9930506, rs1121980, rs1421085, rs8050136, rs1558902, rs17817449, rs12149832, rs9940128, rs62033400, rs1421085, rs1121980, rs9936385, rs9941349, rs3751812, rs1558902, rs17817449	*FTO*	BMI, obesity, childhood obesity	[1, 8, 15–23, 64, 65, 67, 68, 70, 71, 75–79]
16	rs12597579	*GP2*	BMI	[68]
16	rs12444979	*GPRC5BB*	BMI, obesity, overweight	[16]
16	rs9925964	*KAT8, ZNF646,VKORC1, ZNF668, STX1B, FBXL19*	BMI	[1]
16	rs1424233	*MAF*	Obesity	[19]
16	rs4787491	*MAPK3, KCTD13, INO80E, TAOK2, YPEL3, DOC2A, FAM57B*	BMI	[1]
16	rs758747	*NLRC3*	BMI	[1]
16	rs2650492	*SBK1, APOBR*	BMI	[1]
16	rs7498665, rs4788102, rs7359397, rs4788099	*SH2B1*	BMI, obesity, overweight	[16–18, 20, 67]
17	rs9299	*HOXB5*	Childhood obesity	[23]
17	rs1000940	*RABEP1*	BMI	[1]
17	rs7503807	*RPTOR*	Overweight	[20]
17	rs9914578	*SMG6, N29617*	BMI	[1]
18	rs7243357	*GRP*	BMI	[1]
18	rs7239883	*LOC284260, RIT2*	BMI	[1]
18	rs643507	*LPIN2*	Obesity (asthmatic patients)	[80]
18	rs17782313, rs571312, rs12970134, rs2331841, rs6567160, rs8089364, rs7234864, rs723486, rs7227255, rs2229616, rs17782313, rs17700144, rs663129, rs571312, rs476828	*MC4R*	BMI, obesity, overweight	[15, 16, 18–20, 22, 23, 64, 65, 67, 68, 70, 71, 79]
18	rs1805081	*NPC1*	Obesity	[19]
19	rs17724992	*GDF15, PGPEP1*	BMI	[1]
19	rs2287019, rs11671664	*GIPR*	BMI	[16, 68, 70]
19	rs11084753, rs29941	*KCTD15*	BMI	[16–18]
19	rs2287019	*QPCTL*	Obesity, overweight	[20]
19	rs3810291	*TMEM160*	BMI, obesity	[16]
19	rs2075650	*TOMM40, APOE, APOC1*	BMI	[67]
19	rs11672550	*SCAMP4*	BMI	[72]
20	rs13041126	*MRPS33P4*	Obesity	[20]
21	rs2836754	*ETS2*	BMI	[1]

Gene names: *AGBL4* (ATP/GTP binding protein-like 4), *ELAVL4* (ELAV-like RNA binding protein 4), *GNAT2* (G protein subunit alpha transducin 2), *LEPR* (leptin receptor), *NAV1* (neuron navigator 1), *NEGR1* (neuronal growth regulator 1), *PTBP2* (polypyrimidine tract binding protein 2), *SDCCAG8* (serologically defined colon cancer anti-

Table 10.1 (continued)

gen 8), *SEC16B* (SEC16 homolog B, endoplasmic reticulum export factor), *TAL1* (T-cell acute lymphocytic leukemia 1), *TNNI3K* (TNNI3 interacting kinase), *ZZZ3* (ZZ-type zinc finger-containing protein 3), *BRE* (brain and reproductive organ-expressed protein), *CREB1* (CAMP-responsive element-binding protein 1), *KLF7* (Kruppel-like factor 7), *EHBP1* (EH domain-binding protein 1), *ERBB4* (erb-b2 receptor tyrosine kinase 4), *FANCL* (Fanconi anemia complementation group L), *FIGN* (fidgetin, microtubule severing factor), *KCNK3* (potassium two-pore domain channel subfamily K member 3), *LRP1B* (LDL receptor-related protein 1B), *PLCD4* (phospholipase C delta 4), *CYP27A1* (cytochrome P450 family 27 subfamily A member 1), *USP37* (ubiquitin-specific peptidase 37), *TTLL4* (tubulin tyrosine ligase-like 4), *STK36* (serine/threonine kinase 36), *ZNF142* (zinc finger protein 142), *RQCD1* (required for cell differentiation1 homolog), *POMC* (proopiomelanocortin), *TMEM18* (transmembrane protein 18), *UBE2E3* (ubiquitin-conjugating enzyme E2 E3), *CADM2* (cell adhesion molecule 2), *ETV5* (ETS variant 5), *FHIT* (fragile histidine triad), *GBE1* (1,4-alpha-glucan branching enzyme 1), *RARB* (retinoic acid receptor beta), *RASA2* (RAS p21 protein activator 2), *GNPDA2* (glucosamine-6-phosphate deaminase 2), *HHIP* (hedgehog-interacting protein), *NUP54* (nucleoporin 54), *SCARB2* (scavenger receptor class B member 2), *SLC39A8* (solute carrier family 39 member 8), *PCSK1* (proprotein convertase subtilisin/kexin type 1), *ZNF608* (zinc finger protein 608), *CDKAL1* (CDK5 regulatory subunit-associated protein 1-like 1), *FOXO3* (forkhead box O3), *HMGA1* (high-mobility group AT-hook 1), *IFNGR1* (interferon gamma receptor 1), *OLIG3* (oligodendrocyte transcription factor 3), *PARK2* (parkin RBR E3 ubiquitin protein ligase), *TDRG1* (testis development related 1), *LRFN2* (leucine-rich repeat and fibronectin type III domain containing 2), *TFAP2B* (transcription factor AP-2 beta), *ASB4* (ankyrin repeat and SOCS box containing 4), *CALCR* (calcitonin receptor), *HIP1* (huntingtin-interacting protein 1), *PMS2L3* (PMS1 homolog 2, mismatch repair system component pseudogene 3), *PMS2P5* (PMS1 homolog 2, mismatch repair system component pseudogene 5), *WBSCR16* (Williams-Beuren syndrome chromosome region 16), *PMS2L11* (PMS1 homolog 2, mismatch repair system component pseudogene 11), *DTX2P1* (DTX2 pseudogene 1), *UPK3BP1* (uroplakin 3B pseudogene 1), *HNF4G* (hepatocyte nuclear factor 4 gamma), *RALYL* (RALY RNA-binding protein like), *TNKS* (tankyrase), *ZBTB10* (zinc finger and BTB domain containing 10), *C9orf93* (chromosome 9 open reading frame 93), *EPB41L4B* (erythrocyte membrane protein band 4.1 l ike 4B), *KLF9* (Kruppel-like factor 9), *LMX1B* (LIM homeobox transcription factor 1 beta), *LRRN6C* (leucine-rich repeat and Ig domain containing 2), *NTRK2* (neurotrophic receptor tyrosine kinase 2), *TLR4* (toll-like receptor 4), *GRID1* (glutamate ionotropic receptor delta type subunit 1), *GRP120* (G protein-coupled receptor 120), *HIF1AN* (hypoxia-inducible factor 1 alpha subunit inhibitor), *KCNMA1* (potassium calcium-activated channel subfamily M alpha 1), *NT5C2* (5′-nucleotidase, cytosolic II), *CYP17A1* (cytochrome P450 family 17 subfamily A member 1), *SFXN2* (sideroflexin 2), *TCF7L2* (transcription factor 7-like 2), *BDNF* (brain-derived neurotrophic factor), *CADM1* (cell adhesion molecule 1), *HSD17B12* (hydroxysteroid 17-beta dehydrogenase 12), *MTCH2* (mitochondrial carrier 2), *PACS1* (phosphofurin acidic cluster sorting protein 1), *RPL27A* (ribosomal protein L27a), *TUB* (tubby bipartite transcription factor), *CLIP1* (CAP-Gly domain-containing linker protein 1), *FAIM2* (Fas apoptotic inhibitory molecule 2), *RMST* (rhabdomyosarcoma 2 associated transcript), *HS6ST3* (heparan sulfate 6-O-sulfotransferase 3), *MIR548A2* (microRNA 548a-2), *MIR548A2* (microRNA 548x-2), *PCDH9* (protocadherin 9), *MTIF3* (mitochondrial translational initiation factor 3), *OLFM4* (olfactomedin 4), *NRXN3* (neurexin 3), *PRKCH* (protein kinase C eta), *PRKD1* (protein kinase D1), *STXBP6* (syntaxin binding protein 6), *RPS6KA5* (ribosomal protein S6 kinase A5), *BBS4* (Bardet-Biedl syndrome 4), *MAP2K5* (mitogen-activated protein kinase kinase 5), *SCG3* (secretogranin III), *DMXL2* (DmX-like protein 2), *ADCY9* (adenylate cyclase 9), *CBLN1* (cerebellin 1 precursor), *FTO* (fat mass and obesity-associated protein), *GP2* (glycoprotein 2), *GPRC5BB* (G protein-coupled receptor class C group 5 member B), *KAT8* (lysine acetyltransferase 8), *ZNF646* (zinc finger protein 646), *VKORC1* (vitamin K epoxide reductase complex subunit 1), *ZNF668* (zinc finger protein 668), *STX1B* (syntaxin 1B), *FBXL19* (F-box and leucine-rich repeat protein 19), *MAF* (avian musculoaponeurotic fibrosarcoma), *MAPK3* (mitogen-activated protein kinase 3), *KCTD13* (potassium channel tetramerization domain containing 13), *INO80E* (INO80 complex subunit), *TAOK2* (thousand and one amino acid protein kinase 2), *YPEL3* (yippee-like 3), *DOC2A* (double C2 domain alpha), *FAM57B* (family with sequence similarity 57 member B), *NLRC3* (nucleotide-binding oligomerization domain, leucine-rich repeat, and CARD domain), *SBK1* (SH3 domain binding kinase 1), *APOBR* (apolipoprotein B receptor), *SH2B1* (SH2B adapter protein 1), *HOXB5* (homeobox B5), *RABEP1* (rabaptin, RAB GTPase-binding effector protein 1), *RPTOR* (regulatory-associated protein of MTOR complex 1), *SMG6* (SMG6, nonsense-mediated MRNA decay factor), *GRP* (gastrin-releasing peptide), *RIT2* (Ras-like without CAAX 2), *LPIN2* (lipin 2), *MC4R* (melanocortin-4 receptor), *NPC1* (NPC intracellular cholesterol transporter 1), *GDF15* (growth differentiation factor 15), *PGPEP1* (pyroglutamyl-peptidase I), *GIPR* (gastric inhibitory polypeptide receptor), *KCTD15* (potassium channel tetramerization domain containing 15), *QPCTL* (glutaminyl-peptide cyclotransferase like), *TMEM160* (transmembrane protein 160), *TOMM40* (translocase of outer mitochondrial membrane 40), *APOE* (apolipoprotein E), *APOC1* (apolipoprotein C1), *SCAMP4* (secretory carrier membrane protein 4), *MRPS33P4* (mitochondrial ribosomal protein S33 pseudogene 4), *ETS2* (ETS proto-oncogene 2, transcription factor)

It is important to realize that polygenic obesity can only ensue if an individual harbors many such variants and lives in an obesogenic environment.

Candidate Gene Analyses and Genome-Wide Approaches

Historically, two major approaches have been used for the detection of genes involved in body weight regulation.

Candidate Gene Analyses

Genes considered "candidates" for BMI variance are analyzed because prior research (biochemical, physiological, and/or clinical) implicated their roles in central or peripheral pathways controlling energy intake and expenditure. Pharmacological findings or the location of a gene within a linkage/association region can also entail its classification as a candidate gene. A large number of candidate gene-based association studies for obesity involving cases and controls or, less frequently, families comprising one or more affected children and both parents were performed. For a limited number of genes, meta-analyses are available [5].

Genome-Wide Association

Genome-wide association studies have virtually replaced candidate gene analyses; in contrast to the former approach, they have proven very successful [1, 3, 5]. Advances in DNA chip technology have made high-density SNP-based GWAS feasible and led to the identification of a number of confirmed genes for different disorders (http://www.genome.gov/26525384). Within a brief period of time, they have revolutionized the molecular genetic analyses of complex disorders. However, quite early after the first GWAS were published, a stringent *p*-value threshold of $p \leq 5 \times 10^{-08}$ was established as gold standard to correct for multiple testing. An average number of 1,000,000 analyzed SNPs were assumed for a GWAS, so that a Bonferroni correction results in this threshold [6]. This procedure is meant to reduce the chance of false-positive findings (alpha error). However, this also leads to a failure to pick up true findings (beta error). Thus, unfortunately a large number of potentially truly associated SNPs are lost due to the stringent threshold [7].

One has to bear in mind that genome-wide association "hits" identify genomic regions rather than specific genes. Hence, after a GWAS, it is the major aim of subsequent studies to detect the gene underlying the positive association. Usually at first, the gene closest to the GWAS SNP is regarded as a candidate gene for the analyzed trait. For obesity, only 2 of the 97 GWAS SNPs [1] were located in coding regions of genes. Even for these two, it is rather unlikely that the SNPs themselves are functionally relevant. The path to the discovery of the "true" GWAS gene can be exemplified by the chromosomal region harboring the *FTO* gene, the first GWAS-derived region for obesity [8]. Although the GWAS had been published already in 2007, it is still not certain if *FTO* is the gene relevant for weight regulation or not. Recent data provide solid evidence for a major importance of genes downstream, quite distant from *FTO* (see below).

Melanocortin-4 Receptor Gene (*MC4R*)

The first solidly confirmed polygenic variant with an effect on body weight regulation did not stem from a GWAS but from a mutation screen in the most relevant gene with a major effect for obesity, the melanocortin-4 receptor gene (*MC4R*). A polymorphism (Val103Ile) was shown to unexpectedly exert a weight-lowering effect (approx. −0.5 BMI units), rendering this variant as the one with the largest effect size of all known polygenic variants [9].

The MC4R has been a focus of intense investigation in obesity research. Reduced melanocortinergic tone leads to obesity. More than 160 different infrequent non-synonymous (mutations leading to an altered amino acid in the coded protein), nonsense (mutations leading to a stop codon and thus to a shortened protein), and frameshift *MC4R* mutations have been described thus far; most of these mutations were identified

in (extremely) obese individuals. *In vitro* assays showed that most of these mutations lead to total or partial loss of MC4R function. Among extremely obese individuals, combined frequencies for all functionally relevant mutations range from 2–5% [10].

As mentioned above, *MC4R* can also be considered a polygene. Large study groups had to be screened to detect the relevance of these polymorphisms because they are relatively uncommon and have small effect sizes. Heterozygosity for the 103Ile variant (Val103Ile) of MC4R is found in 2–9% of people. An effect estimate of −0.48 kg/m^2 was calculated for Ile103 carriers, which is approximately equivalent to a reduction of 1.6 kg in a 1.8 m tall individual [9]. The negative association of 103Ile with obesity was subsequently confirmed in single large epidemiological study groups [11, 12]. The polymorphism is associated with increased MC4R function, which could explain its weight-reducing effect [13]. Heterozygosity for the Ile251Leu variant of MC4R is found in 0.41–1.21% of people. A meta-analysis provided strong evidence of an obesity protective effect of MC4R-251Leu (odds ratio = 0.52) [14].

Already in 2008, a large-scale international cooperation encompassing DNA samples of over 90,000 individuals detected a SNP 188 kb downstream of the *MC4R* by a GWAS [15]. The location of rs17782313 suggests that its effect on weight regulation may be mediated through effects on *MC4R* expression and may be exerted in concert with variations in *FTO* [15]. The association result was confirmed in additional large study groups and family-based studies. Among adults, each copy of the rs17782313 obesity-risk allele (C) was associated with a difference in BMI of ~0.22 kg/m^2. A copy of the allele resulted in 8% and 12% increased risks for overweight and obesity, respectively. Interestingly, a copy of the C-allele also resulted in a higher mean height (0.21 cm), suggesting that this SNP (or the functionally relevant SNP(s) in linkage disequilibrium) influences overall adult size.

The association of the rs17782313 SNP (or SNPs in linkage disequilibrium with it) with obesity was subsequently confirmed in all GWAS of the GIANT group pertaining to BMI variation [1, 5]. Interestingly, genotyping of nearly 6000 children of the Avon Longitudinal Study of Children and Parents revealed that the effect of the C-allele was not detectable in children prior to age 7. However, in children aged 7–11, the effect size of a copy of the C-allele was twice the amount observed in adults; no effect was observed for body height. The effect on weight was disproportionately due to fat mass [5, 10].

Current Status of the Identification of Polygenes Involved in Body Weight Regulation

GWAS for BMI and Obesity in Adults

The most recent GWAMA for BMI in adults was performed in 339,224 mainly population-based individuals. A total of 97 BMI-associated loci ($p < 5 \times 10^{-8}$) were identified; 56 of these were novel. Five loci with evidence of independent associations were identified (independent secondary signals near *LINC01122*, *NLRC3-ADCY9*, *GPRC5B-GP2*, and *BDNF* and a total of three signals near *MC4R*). Evidence of heterogeneity between males and females was shown for two previously identified loci (near *SEC16B* and *ZFP64*); both effects were stronger in females. Heterogeneity between European- and African-descent samples was detected for two SNPs (near *NEGR1* and *PRKD1*) and between European and East Asian individuals for one SNP (near *GBE1*) [1].

The 56 novel loci in general had lower effect size estimates and/or minor allele frequencies than previously described loci (see below). All loci combined account for approximately 2.7% of BMI variation. Additionally, if the complete genome-wide data, not only the genome-wide significant SNPs, were used, it was estimated that common SNP variation accounts for more than 20% of BMI variation. As in the previous GWAMA of the GIANT consortium [16], it turned out that many of the target genes are likely active in the central nervous system. Significant effects for several metabolic phenotypes were

found for many of these loci. In silico pathway analyses also implicated the newly detected genes in relevant pathways (synaptic function, glutamate signaling, insulin secretion/action, energy metabolism, lipid biology, and adipogenesis) [1].

Prior to the more recent GIANT study, different groups reported obesity polygenes with small effect sizes [3, 17–19]; already in 2009, more than 150,000 individuals were analyzed in total (Table 10.1).

GWAS for Extreme BMI

It was unknown if loci relevant for general BMI distribution are also relevant for BMI extremes. Thus, a GIANT investigator group analyzed GWAS data for loci associated with the uppermost versus the lowest fifth percentiles of different phenotypes including BMI, as well as different classes of obesity. The study included 263,407 individuals of European ancestry. Seven new loci (*HNF4G*, *RPTOR*, *GNAT2*, *MRPS33P4*, *ADCY9*, *HS6ST3*, and *ZZZ3*) for obesity were identified. A substantial overlap for genetic variants between traits based on extremes and the general population was observed, while etiological heterogeneity between obesity subgroups was small [20].

GWAS for BMI and Obesity in Children and Adolescents

Right after the first GWAS on epidemiological samples in adults had been described, the first GWAS for obesity in children and adolescents emerged, with *FTO* as a single genome-wide significant locus [21]. A bit later, the first GWAMA for additional loci in extremely obese children and adolescents (GWAS data on a total of 2258 individuals) was published [22]. Results were also analyzed pertaining to their generalizability to obesity in adults and in population-based samples. In addition to previously identified loci (*FTO*, *MC4R*, and *TMEM18*), two new loci for obesity were detected (*SDCCAG8* and *TNKS/MSRA*), the latter one being limited to children and adolescents. Hence, the major common variants related to obesity overlapped substantially between children and adults [22].

The Early Growth Genetics Consortium (EGG) performed a GWAMA for childhood BMI (use of sex- and age-adjusted standard deviation scores) [23]. Among 5530 cases (≥95th percentile of BMI) and 8318 controls (<50th percentile of BMI) of European ancestry and a replication group (2818 cases and 4083 controls), two genome-wide significant loci were identified (*OLFM4* and *HOXB5*). Both loci were also associated when adding two extreme childhood obesity study groups (2214 cases and 2674 controls). Additionally the two loci yielded directionally consistent associations in a previous meta-analysis of adult BMI [16, 23].

Recently a total of 35,668 children were included in a new EEG GWAMA in the discovery phase; 11,873 children served as a replication group. Fifteen genome-wide significant loci were derived within the complete study groups. Twelve had previously been identified (*ADCY3, GNPDA2, TMEM18, SEC16B, FAIM2, FTO, TFAP2B, TNNI3K, MC4R, GPR61, LMX1B*, and *OLFM4*) as associated with adult BMI or childhood obesity. In addition, three novel loci (*ELP3, RAB27B,* and *ADAM23*) were detected. A genetic risk score for a combination of all 15 SNPs showed that each additional average risk allele among 1955 children was associated with increase in childhood BMI of 0.073 SDS (SE 0.011). Two percent of the variance in childhood BMI was explained by the risk score. Again, shared genetic background between childhood and adult BMI was detected [24].

In sum, all SNPs detected in children and adolescents were also found in adults, albeit some not genome wide significantly. Hence, the effect sizes between children and adults might be different.

Fat Mass and Obesity-Associated Gene (*FTO*)

FTO was first identified in GWAS for type 2 diabetes mellitus (T2DM) [8, 25]. By adjustment for BMI, Frayling and colleagues found that its asso-

ciation with T2DM was actually due to the higher BMI of diabetic cases in comparison to nondiabetic controls [8]. Confirmation of the BMI effect was obtained in 13 study groups comprising 38,759 adults. A meta-analysis showed that the A allele of the variant rs9939609 (intron 1 of *FTO*) was associated with a 31% increased risk to develop obesity. The 16% of adults who were homozygous for the risk allele weighed on average about 3 kg more and had a 1.67-fold increased odds for obesity when compared to individuals without risk allele.

Variations in *FTO* were also detected in the first GWAS for early onset obesity, which was performed in 487 extremely obese German children and adolescents and 442 lean controls (case-control study). Because only individuals at the opposite ends of the BMI distribution were included, this study was well powered to detect obesity polygenes despite the comparatively small sample size. Six intronic SNPs in *FTO* showed the strongest evidence for association with obesity (best SNP: rs1121980; odds ratios for obesity for heterozygosity and homozygosity for the T allele were 1.67 and 2.76, respectively) [21]. Eleven SNPs (including two *FTO* SNPs) were subsequently genotyped in 644 independent obesity families based on at least one young obese index patient. The association with early onset obesity was confirmed only for the two *FTO* SNPs**.**

There is a large body of evidence pertaining to the effect of *FTO* on body weight regulation in both humans and in rodent models. These data have recently been elegantly reviewed by Speakman [26]. Here some of the major findings are highlighted.

Effect of *FTO* Risk Alleles on Various Phenotypes

FTO rs9939609 was genotyped in a total of 17,508 middle-aged Danes. Again, the A allele was associated with overweight and obesity. Obesity-related quantitative traits such as body weight, waist circumference, fat mass, and fasting serum leptin levels were significantly increased in A allele carriers. There was an interaction between the *FTO* rs9939609 genotype and physical activity; physically inactive homozygous risk A allele carriers had an increased BMI (1.95 ± 0.3 kg/m^2) compared with homozygotes for the T allele. Low physical activity thus seemingly accentuates the effect of *FTO* rs9939609 on body fat accumulation [27]. Subsequent studies pertaining mostly to large study groups showed that the obesity risk alleles are associated with increased food intake and hunger and reduced satiety; however, resting energy expenditure or low physical activity have not (yet) been associated with these alleles in humans [26].

The obesity-risk variant of *FTO* at rs8050136 was associated with a reduced insulin effect on beta activity measured by magnetoencephalography, which implicates a lower cerebrocortical response to insulin. Since the *FTO* gene is expressed in hypothalamic centers controlling appetite (see below), this might be a mechanism by which variation in *FTO* contributes to the pathogenesis of obesity [28]. Wåhlén and colleagues suggested that *FTO* may also play a role in fat cell lipolysis, providing a functional link to body weight regulation [29].

Allelic expression ratios in five individuals heterozygous for the risk allele showed that *FTO* transcripts including the risk (A) allele at rs9939609 were more abundant than those with the T allele. Hence, the risk allele leads to an increased expression of *FTO*. This is compatible with a rodent model (see below) in which an increased *Fto* expression is associated with an increased body weight [30].

Evidence, although not genome-wide significant, was described for the involvement of the *FTO* risk alleles in, e.g., polycystic ovary syndrome [31, 32] and eating disorders [33].

Parent of Origin Effects for FTO

Most GWAS rely on unrelated individuals, so that the parental transmission of a specific allele is usually not considered in the analyses. Recently parent-of-origin effects were analyzed for 22 SNPs in *FTO* introns 1–3 under the assumption

that the transmission from mother or father has an effect on the obesity phenotype. Several of the SNPs indeed displayed different effects depending on the sex of the parent in both the original Sorb families and in 705 independent German families comprising an extremely obese patient and both parents. Thus the obesity risk of (some of) the *FTO* variants might not be independent of the parental origin of the allele [34].

Mutation analyses in the FTO gene. Although this review pertains to polygenic effects, there are a few studies dealing with mutation screens of *FTO* in humans. These studies aimed to identify genetic variants with a more profound effect on weight regulation. Based on investigations of rodent models, it was hypothesized that loss-of-function *FTO* mutations would be found in lean individuals.

The first of these studies pertains to members of a large Palestinian Arab consanguineous multiplex family. Individuals with a non-synonymous mutation (Arg316Gln) leading to inactivation of *FTO* were identified [35]. All affected individuals had postnatal growth retardation, microcephaly, severe psychomotor delay, functional brain deficits, and characteristic facial dysmorphic features. Structural brain malformations, cardiac defects, genital anomalies, and cleft palate were described in some of the affected individuals. Death occurred at 1–30 months of age; it was caused by intercurrent infection or unidentified causes.

The mutation in this family localizes to an evolutionarily conserved region of FTO and leads to inactivation of its enzymatic activity. Functional data further implied that FTO is essential for normal development of the cardiovascular and central nervous systems in humans. Detailed anthropometric data were unfortunately not available on unaffected family members. However, none of the heterozygous parents were obese nor did they show any of the clinical features detectable in homozygotes [35].

Analyses of regions of copy number variation in 985 obese and 869 lean subjects with European ancestry revealed a ~680 kb duplication at the *FTO* chromosomal locus (including *RBL2*, *AKTIP*, *RPGRIP1L*, and all except the last exon of *FTO*) in a 68-year-old male with extreme obesity. Additional family members with the same duplication were also obese and showed a distinct phenotype of increased fat distribution in the neck and shoulders. Increased expression of *RBL2* in the blood and lack of alteration in expression of *FTO* or the other genes within the region were also described in these patients. None of additional 4778 obese or lean individuals harbored this duplication, so that it cannot be a frequent cause of obesity [36].

Two studies analyzed the *FTO* gene in a total of 1629 extremely obese and 1609 lean individuals. Sequencing of *FTO* revealed that heterozygous loss-of-function mutations and other potentially dysfunctional mutations were detected in both study groups [37, 38]. Thus, surprisingly loss of one functional *FTO* copy was in humans compatible with different weight outcome [37].

Functional *in Silico* and *In Vitro* Studies Pertaining to FTO

Detailed computational analysis of the sequence and predicted structure of the protein encoded by *FTO* has been performed. Human FTO is apparently a member of the non-heme dioxygenase (Fe(II)- and 2-oxoglutarate-dependent dioxygenases) superfamily [39, 40]. Both 2-oxoglutarate and iron should therefore be important for FTO function [40].

A series of studies evaluated the functional role of FTO. Recombinant murine FTO catalyzes the Fe(II)- and 2-oxoglutarate -dependent demethylation of 3-methylthymine in single-stranded DNA. Concomitantly succinate, formaldehyde, and carbon dioxide are produced [39]. As FTO activity is dependent on 2-oxoglutarate, Speakman postulated that it could act as a sensor of the citrate acid cycle flux. However, he also points out that recent analyses suggest that FTO might rather be a sensor of circulating amino acids [26].

Murine FTO localizes to the nucleus in transfected cells, which is consistent with a potential role in nucleic acid demethylation. In wild-type

mice, *Fto* mRNA is most abundant in the brain, particularly in hypothalamic nuclei governing energy balance. In fasted mice *Fto* mRNA levels in the arcuate nucleus were reduced by approximately 60% [39]. In HEK293 cells knockdown of *FTO* had an effect on levels of transcription of genes involved in starvation response. On the other hand, overexpression affected transcription of genes related to metabolism or RNA processing. FTO transcripts were located in nuclear speckles, nucleoplasm, and nucleoli of different cell lines. Additionally loss of murine FTO had an effect on the ratios of 3-methyluridine/uridine and pseudouridine/uridine in total brain RNA [41].

Thus, FTO level seem to have multiple effect on the transcriptome and on RNA modifications [41]. The steady-state levels of several miRNAs were shown to be affected by knockdown of the m6A demethylase FTO. Additionally, m6A was found in a significant fraction of miRNAs. Consensus sequences discriminating between methylated and unmethylated miRNAs were identified. These data imply that epigenetic modification of an epigenetic modifier increases the complexity of the posttranscriptional regulation of expression of genes [42].

FTO in Rodent Models

Complete (homozygous knockout) loss of *Fto* in mice leads to postnatal growth retardation and a significant reduction in adipose tissue and lean body mass. The leanness of *Fto*-deficient mice results from increased energy expenditure and systemic sympathetic activation despite decreased spontaneous locomotor activity and relative hyperphagia. *Fto* expression in heterozygous $Fto^{+/-}$ mice was reduced; this led to reduced weight gain after 12 weeks. These observations suggest that the effects of *Fto* on energy homeostasis are mediated, at least in part, through the control of energy expenditure [43]. Compatible with these data, overexpression of *Fto* in mice led to increased food intake and adiposity, with no impact on energy expenditure [26, 44].

Is FTO the Target Gene of the GWAS Studies?

Recently Claussnitzer and colleagues questioned the role of FTO in body weight regulation. They showed that a FTO obesity-risk allele represses tissue autonomously mitochondrial thermogenesis in adipocyte precursor cells. This variant (rs1421085) disrupts a conserved repressor motif (ARID5B), so that a potent pre-adipocyte enhancer is no longer repressed, which leads to increased expression (doubling) of *IRX3* and *IRX5* in early adipocyte differentiation. This in turn results in a developmental shift from energy-dissipating beige (brite) adipocytes to energy-storing white adipocytes, thereby reducing mitochondrial thermogenesis and increasing lipid storage considerably (factor 5). Reduction of Irx3 in adipose tissue in mice reduced body weight and increased energy dissipation. Physical activity and appetite were unchanged. Knockdown of either *IRX3* or *IRX5* in primary adipocytes from human carriers of the risk allele restored their thermogenesis. The opposite effect was shown for overexpression of these genes. When the ARID5B motif in primary adipocytes was repaired, repression of *IRX3* and *IRX5* was restored. The authors concluded that manipulation of the pathway for adipocyte thermogenesis, which involves ARID5B, rs1421085, *IRX3*, and *IRX5*, could have pronounced effects on obesity development [45]. Recent studies describe increased adipocyte-specific expression of *IRX3* and *IRX5* in lean children with a *FTO* risk haplotype, but not in comparable obese controls. This might be regarded as a defense mechanism to protect body weight in lean children [46].

In summary, complete *Fto* disruption leads to growth failure, with reductions in adipose tissue and lean body mass. Conversely, *Fto* overexpression leads to the opposite phenotype. These effects appear to be mediated, at least in part, through central-dependent increases in energy expenditure. The association of obesity with intronic polymorphisms in *FTO* suggests that the polymorphisms may increase FTO activity, which was also suggested by an allele-specific expression study [30].

Gene-Environment Interactions

A gene-by-environment interaction is exemplarily shown by a study that recently revealed the relevance of a *FTO* risk SNP (rs1421085) for a number of lifestyle and environmental factors. Interactions between the *FTO* risk allele and the following phenotypes were detected: frequency of alcohol consumption; deviations from mean sleep duration; overall diet, including added salt; and physical activity [47]. However, in a meta-analysis of eight eligible randomized controlled trials comprising 9563 individuals, the response to weight loss intervention (changes in BMI, body weight, and waist circumference) was not dependent on *FTO* genotypes [48].

Composite Phenotype, Cross-Phenotype, and Cross-Disorder Analyses

The analyses of GWAMA for single traits were successful for BMI (Table 10.1) and obesity-related traits. However, recently these GWAMA data were included in combined analyses either for (i) obesity or body weight-related traits (composite phenotypes) or (ii) for traits associated with altered body weight regulation (e.g., eating disorders, ADHD, bipolar disorder, schizophrenia, Alzheimer's disease, i.e., "cross-phenotype, cross-disorder" analyses). The following paragraphs summarize the current major findings.

Composite Phenotypes

Large meta-analyses of GWAS for single traits, like BMI, were recently included in combined analyses of different, related phenotypes. Genetic variants were analyzed with an effect on body shape as a composite phenotype representing a combination of six anthropometric traits (body mass index, height, weight, waist and hip circumference, waist-to-hip ratio). Six novel loci were identified (*LEMD2*, *CD47*, *RPS6KA5/C14orf159*, *GANAB*, *ARL15,* and *ANP32*) for the composite phenotype. The authors [49] stress the value of the use of multiple traits to define complex phenotypes, as these help to detect variants that were not identified by single-trait analyses. These might well shed light onto new biological pathways. Several previously identified loci were associated with more than one anthropometric trait. Interestingly, the BMI-increasing allele of the *MC4R* locus was also associated with increased height [15], whereas the BMI-increasing allele at the *POMC/ADCY3* locus was associated with reduced height. Hence, some loci might be associated with a more complex body shape phenotype that is not captured by the current GWAS on single phenotypes [49].

Cross-Phenotype and Cross-Disorder GWAMA Analyses

Recently, a new method was established to estimate genetic correlation from GWAS summary statistics. The method eliminates the need to use individual-level genotype data and at the same time reduces the problem of overlapping data in different meta-analyses. The new technique (cross-trait LD Score regression, LDSC) is not biased for overlapping samples. The method was used to estimate 276 genetic correlations for 24 traits including anorexia nervosa (AN), schizophrenia, obesity, and educational attainment [50]. The LDSC technique was subsequently applied to various other diseases. Across 23 psychiatric and neurological brain disorders (n = 842,820), the extent of shared genetic contributions was analyzed. For psychiatric versus neurological disorders, substantive differences in the specificity of genetic etiology were suggested. Interestingly, significant sharing of genetic influences between anthropometric measures (e.g., BMI, height) and brain disorders (e.g., major depressive disorder and neuroticism personality score) were detected [51]. A GWAS for educational attainment (discovery: 293,723 individuals, replication: 111,349 individuals) recently identified 74 genome-wide significant loci associated with the number of completed years of schooling. Overall SNPs associated with an increased school attainment were associated with lower BMI [52].

Look-Up Studies

In addition to these general approaches including GWAS summary statistics, a number of "look-ups" of GWAS hits for one trait (e.g., BMI) in GWAMA data were cross-checked for related traits (e.g., anorexia nervosa) and vice versa in order to find shared genetic variants. The results are compatible with the genetic overlap between traits as shown in the studies above. Cross-disorder analysis for Alzheimer's disease and obesity implied a SNP (rs10838725) at the locus *CELF1* that is genome-wide significant for both traits [53]. For ADHD and obesity as well, two genomic loci seemed to be shared albeit the results were not genome-wide significant for ADHD [54]. Recently, the look-up of the best (lowest *p*-value) 1000 GWAS SNPs for AN (no genome-wide significant SNP in the study) [55] in the GWAMA for BMI [1] revealed three genomic regions seemingly relevant for both. A locus on chromosome 10 seems especially interesting because the association with underweight was mainly driven by females [56]. A look-up of the 74 SNPs for educational attainment (see above) revealed that two were associated with lower BMI and one with higher BMI [52]. Here, again the cross-phenotype/trait analyses revealed genetic loci that had been missed by the single-GWAMA analyses.

Epigenetics

Epigenetic mechanisms might play an important role in obesity. It remains unclear if epigenetic marks are trans-generationally heritable and if they might explain part of the "missing" heritability related to excess weight gain. A total of 46 epigenetic studies in human obesity have recently been reviewed [57]. Technological improvements also led to an increasing number of chip-based epigenome-wide studies. As environmental exposures early in life [58] can have a major effect on the epigenome, the relevance of these modifications might be of paramount importance for weight regulation. The majority of epigenetic association studies pertain to DNA methylation pattern either globally, site specific (candidate regions), or genome wide [57]. Consistent evidence for association between global methylation and obesity was not derived, whereas multiple obesity-associated differentially methylated sites, mainly in blood cells, were identified [57]. As methylation patterns are highly cell type specific [59], the use of whole blood is highly questionable.

The first large genome-wide methylation analysis for BMI was published in 2014 [60]. Whole blood DNA from a total of 479 individuals of European descent was analyzed (HumanMethylation450 array) for the discovery phase. Replication was performed in two independent study groups (339 plus 1789 individuals). Methylated sites linked to BMI in analysis of whole blood were also analyzed in adipose tissue (n = 635) and skin (n = 395). Expression analyses ensued. Differential methylation was found at three sites (cg22891070, cg27146050, and cg16672562), which were all located in intron 1 of *HIF3A*. Two SNPs (rs8102595 and rs3826795) not associated with BMI showed associations with methylation at cg22891070 in all study groups.

In sum, increased BMI was associated with increased methylation at the *HIF3A* locus both in the whole blood and in adipose tissue. These results imply that disturbances of pathways involving the hypoxia inducible transcription factor might have a role in the response to increased weight in humans [60].

More recently additional, albeit rather small, epigenome-wide association studies have been published. Differential DNA methylation was analyzed in saliva from 50 lean and 50 heavy adolescent females. The ten CpG sites/regions most strongly associated with BMI overlapped with obesity- and insulin-related genes (e.g., *MC2R*, *IGFBPL1*, *IP6K1*, and *IGF2BP1*) [61].

Cross-disorder epigenome analyses were also performed. EWAS data (27,589 CpG sites) for BMI on 871 women (replication in 187 women) from a study of breast cancer were analyzed. Four CpG sites were genome-wide significant (false discovery rate $q < 0.05$) in discovery and replication sets. The adjacent genes have previously been related to obesity and obesity-related chronic diseases. Thus obesity-related epigene-

tic alterations are detectable in blood and might be related to risk of chronic disease [62].

Metastable Epialleles

"Metastable epialleles" had been described in mice; these are inherited epigenetic variants that could in principle explain part of the "missing heritability" [63]. Recently, a study in humans provided evidence that methylation at a variably methylated region (VMR) within the pro-opiomelanocortin gene (*POMC* in postmortem human laser-microdissected neurons) is associated with BMI. Methylation of the POMC VMR is established in the early embryo. Interestingly methylation in the offspring correlated with the paternal somatic methylation pattern. Additional association with levels of maternal intake of one-carbon metabolites at conception was identified. Methylation was stable during postnatal life. In sum, these human data provide evidence that the POMC VMR may represent a human metastable epiallele with influence on body weight regulation [63].

Conclusions and Perspectives

Initially, molecular genetic studies led to the identification of a small number of major genes for human obesity. The relevant mutations have a profound influence on the development of excess body weight, but they are rare. The majority of confirmed genes involved in the predisposition to obesity are of polygenic nature. The contribution of any single polygene to the development of obesity is small; detection and confirmation of such variants requires screening of thousands of individuals.

In 2007, a variation in exon 1 of *FTO* was shown to be associated with obesity. Within a short period of time, it became evident that *FTO* represents a major polygene in populations of European, African, and Asian descent. Clinical and experimental observations confirm its importance in energy homeostasis. More than 100 other polygenes for body weight regulation have been reported since then. The minor allele at the Val103Ile variant of the *MC4R* is of interest as it confers protection from obesity. Other *MCR4* variants also contribute to obesity risk. Thus, genetic variation of genes expressed in the CNS plays a prominent role in BMI variation. This is not surprising, given the role of the brain in behavior and energy balance.

Given that twin studies suggest that genetic variation accounts for 50–70% of the variance in human BMI, we have far to go; only about 3% of BMI variance is explained by the currently known polygenes. Realistically, we might assume that the currently detected variants represent the tip of the iceberg; effect sizes of variants detected in the future may be even smaller. Obviously, sample sizes have to be very large to detect these signals and to confirm them independently. If BMI heritability results from the effect of hundreds of alleles, many of which account for less than 50 grams, we would have substantial genetic heterogeneity among obese individuals. Assuming this scenario to be true, simplistic ideas of genotype-phenotype correlations would have to be dismissed. Cross-trait/-disorder analyses have revealed new genetic loci that had been missed by the analyses of single traits only. Additionally the genetic correlation between different traits (e.g., a negative correlation between AN and obesity) was detected by analyses of the complete GWAMA data sets. Epigenetic studies are likely to identify genomic regions that might respond to environmental factors.

In light of the low BMI variance explained by the polygenes detected in recent GWAMA, we can speculate that infrequent alleles with stronger effect sizes, not readily detected in GWAS, may explain a larger part of the variance of BMI. Another disconcerting idea pertains to genotype-environment interactions. These may be rather specific, based on the genotype of an individual. While formal genetic studies have taught us that nonadditive factors play a prominent role in BMI heritability estimates, the currently known variants seemingly act in an additive manner only. Future analysis of genetic factors involved in body weight regulation will substantiate our understanding of the mechanisms leading to obesity and, we hope, lead to improved therapeutic approaches.

Editor's Comments and Questions

Much of the research on genetic determinants of obesity has focused on gene variants that predispose to weight gain. Yet we all know people who are able to eat whatever they seem to like and yet maintain a lean phenotype. We are also quite familiar with children who seem to have little interest in food and have trouble gaining weight. In this regard, the genetic variants in the MC4R that appear to protect against obesity are particularly interesting.

1. Are these variants associated with increased energy expenditure and/or decreased appetite, or might they modulate the development and/or differentiation of white or brown adipose tissue?
2. Genetic variants that promote weight gain might provide adaptive advantages under conditions of food scarcity. Is there any reason to think that gene variants that defend against weight gain might be disadvantageous under certain conditions (e.g., prematurity, illness, aging, etc.)?

Authors' Responses

1. Activation of MC4R results in repression of food intake and an increase in energy expenditure in mice[a]. Obesity in *Mc4r* null mice is associated with increased food intake (hyperphagia) and decreased energy expenditure [b,c]. In humans, mutations leading to a reduced receptor function and with it to an altered MC4R signaling are not only associated with increased linear growth but also with increased bone mineral density[d] and increased hunger for fat[e].

Two MC4R variants (103Ile and 251Leu) are associated with a slightly reduced body weight[f,g,h]. There are some studies related to the phenotypic consequences of these two polymorphisms in humans:

(a) An analysis of Val103Ile in 1173 consecutive patients undergoing cardiac catheterization showed reduced triglyceride levels in heterozygous carriers of the 103Ile allele, suggesting a positive effect of MC4R activity on triglyceride levels in cardiovascular patients[i]. Supportingly, Mc4r knockout mice have elevated triglyceride levels in the plasma, liver, and intestine[j]. It had been suggested that MC4R plays a role in a peripheral, local gut signaling mechanism that regulates intestinal triglycerides and controls intestinal lipid absorption[j]. Very recently, it had been described that the melanocortinergic system directly influences lipid metabolism[k].

(b) In a study of 7888 adults of a population-based cross-sectional study, the 3.7% who were carriers of the MC4R 103Ile variant did not show differences in blood pressure but displayed a significantly decreased waist circumference, decreased glycosylated hemoglobin, and increased HDL cholesterol. It was more unlikely for carriers of the MC4R 103Ile allele to show features of the metabolic syndrome than for noncarriers[l]. A trend toward association of this genetic variant with carbohydrate assimilation could underlie the association of MC4R 103Ile with leanness. Hence, the data provided evidence that this polymorphism could have an influence on other parameters of the metabolic syndrome due to its function on appetite regulation that also affects BMI[l]. However, another study demonstrated that carriers of the 103Ile variant exhibited significantly increased daily energy and carbohydrate intakes than noncarriers[m].

(c) A study on patients undergoing bariatric surgery implied that carriers of the infrequent allele at Ile251Leu have a better clinical outcome, reduced risk of type 2 diabetes, and increased weight loss after diet or surgical interventions[n]. This finding could subsequently not be confirmed[o].

(d) The infrequent alleles at both Val103Ile and Ile251Leu were associated with reduced BMI in white (Val103Ile nominal $p = 0.01$ and Ile251Leu nominal $p = 0.03$), but not in black females, respectively. In the black women, nominal association ($p = 0.02$) between the 251Leu allele and higher abdominal visceral fat was reported[p].

In sum, phenotypic data pertaining to the influence of the two weight-lowering polymorphisms in MC4R are scarce and partly contradictory. An influence of the central melanocortinergic system on brown adipose tissue function had been described in the mouse model[q]. However, for humans carrying the weight-lowering MC4R alleles, an effect on the development and/or differentiation of white or brown adipose tissue has not been described yet.

2. It has not been studied in depth if weight-lowering variants could be disadvantageous under certain environmental exposures. Neel proposed in 1962 already the "thrifty gene hypothesis." This suggested that genes (gene variants) that are relevant for hunger and energy storage are thought to confer a selective advantage in times of food scarcity[r]. In modern times of abundance of energy-dense food, these thrifty genes become disadvantageous.

In recent years, the "thrifty gene hypothesis" was viewed controversially. For instance, Speakman[s] points out that famine was too infrequent in former times and not the main reason of mortality. In addition, there is no evidence that individuals with obesity survived famines better than lean people. So if these thrifty genetic variants would have been very important for survival, nearly everybody would have accumulated these variants nowadays and as consequence would be obese. As this is not the case, an alternative hypothesis was introduced. The "drifty gene hypothesis" suggests that the genetic variants influencing energy storage emerged rather through genetic drift than through genetic selection[s]. This hypothesis was recently confirmed by the analysis of 115 genes associated with obesity. Of these genes, only four provided evidence for selection that benefits obesity[t]. Additionally, it is well conceivable that gene variants that defend against weight gain might be disadvantageous under certain conditions (e.g., prematurity, illness, aging).

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Part V

Pre- and Peri-natal Determinants of Childhood Obesity

11 Maternal Determinants of Childhood Obesity: Maternal Obesity, Weight Gain and Smoking

Jenna Hollis, Hazel Inskip, and Siân Robinson

Prelude

A predisposition to gain excess weight in childhood may in part be the consequence of influences acting during foetal life. At present, the developmental influences on obesity are poorly understood, although epidemiological evidence shows links between maternal factors that influence the intrauterine environment and offspring body composition. The causal mechanisms to explain how factors acting in foetal life influence later risk of obesity in humans are poorly understood. Some of the factors which have been investigated include maternal pregravid obesity, weight gain in pregnancy and maternal smoking. This chapter examines some of the epidemiological and intervention evidence that links these three factors with adiposity in childhood.

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Maternal Obesity

There is considerable evidence of a strong association between maternal pregravid adiposity and overweight and obesity in childhood [1, 2]. For example, a meta-analysis of four studies found that children of mothers who were overweight or obese prior to conception were nearly twice as likely to be overweight (Odds Ratio (OR), ... OR, 1.95; 95% CI, 1.77, 2.13) and three times more likely to be obese (OR, 3.06; 95% CI, 2.68, 3.49; $p < 0.001$) than children born to mothers who were of normal weight prior to pregnancy [2]. This finding is consistent with the elevated odds ratios found in seven of the eight other studies included in the review but not pooled in the meta-analysis [2] and in another systematic review investigating a broad range of risk factors for childhood obesity during infancy [3]. In two studies [4, 5] that described an association between maternal pre-pregnancy overweight or obesity and relative odds of being overweight or obesity in childhood, estimates were 1.37 (95% CI, 1.18, 1.58) at 3 years [4] and 4.25 (95% CI, 2.86, 6.32) at 7 years [5].

The association persists at later ages in childhood, with one study identifying maternal obesity as the strongest predictor of obesity at all ages in childhood [6]. In the National Longitudinal Survey of Youth, children of mothers who were obese (body mass index (BMI) ≥ 30 kg/m^2) prior to pregnancy were nearly three times more likely

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to be overweight (OR, 2.89; 95% CI, 2.02, 4.15) [7], and the association between maternal and child obesity became more marked with increasing age of the children. These findings suggest that the effect of maternal obesity on childhood overweight may be due to an early propensity to gain weight which is perpetuated as the child ages [7].

One of the main issues with understanding the association between mother and offspring obesity is separating the influences of the intrauterine environment from the shared postnatal environment [8], making it challenging to decipher whether the identified association is due to the factors acting in the prenatal period or in early childhood. This question can be explored by comparing the direct effects of maternal obesity on the offspring with the effects of paternal obesity. If the influences of maternal obesity are acting in the prenatal period, then the association between the BMI of the mother and child should be greater than that of the father and child. However, a meta-analysis of seven prospective cohort studies comparing the associations of maternal and paternal obesity with obesity in the offspring did not find consistent results [9]. While a couple of studies reported strong maternal influences [5, 10], overall the evidence was inconclusive [11–13] and made more challenging as few studies made formal comparisons of the magnitude of effects between maternal and paternal obesity. Paternal obesity appears to act in concert with maternal obesity to increase the risk of childhood weight gain.

A novel study that provides some insight into the direct effects of maternal obesity examined the prevalence of obesity in 2–18-year-old children who were conceived and born to 113 obese mothers before and after undergoing weight loss surgery [14]. The prevalence of overweight and obesity among 45 children born prior to surgery was 60%, compared with a prevalence of 35% among 172 children who were born after surgery [14]. These findings indicate that surgery, and a consequent reduction in maternal adiposity, may have helped to prevent the transmission of adiposity to the offspring. The study provides strong evidence to support a direct influence of maternal obesity acting on the intrauterine environment that has long-term effects on the offspring and their regulation of body weight. However, the prevalence of obesity in the offspring of surgically treated mothers remains higher than expected (35%), highlighting the role of shared genetic modifiers as well as the obesogenic postnatal environment.

Many potential causal mechanisms to explain the association have been proposed, including through (1) genetic mechanisms; (2) dysregulation of glucose, insulin, lipid and amino acid metabolism [15]; or (3) a shared familial environment (e.g. similar food preferences, physical activity levels or sedentary time) [16]. Recent investigation of offspring epigenome-wide DNA methylation in the Avon Longitudinal Study of Parent and Children (ALSPAC) suggests that epigenetic modification may be a plausible mediating mechanism to explain the relation between maternal and offspring obesity [17]. The results showed some evidence of an association between maternal underweight with lower offspring adiposity and maternal obesity with greater offspring adiposity, through varied DNA methylation of the neonatal epigenome [17]. Offspring methylation was more strongly associated with maternal rather than paternal obesity, highlighting the importance of the prenatal environment [17]. Further high-quality research is needed to understand the effects of maternal obesity and whether a predisposition to gain excess weight in childhood is, at least in part, a consequence of influences acting during foetal life.

Gestational Weight Gain

Although the optimal pattern of weight gain in pregnancy is unknown, greater gestational weight gain (GWG) has consistently been associated with increased obesity in the offspring [18–22]. For example, among 1044 mother-child dyads

studied in Project Viva in the United States (US), greater GWG was associated with a 30% increased odds of overweight in children at 3 years of age for every 5 kg of total weight gained during pregnancy (OR, 1.30; 95% CI, 1.04, 1.62) [23]. The association changed little after adjustment for potential confounding influences [23]. In another study examining the association between GWG and childhood obesity among infants born of normal birth weight in 24,141 mother-offspring pairs, greater GWG was also associated with childhood obesity [24]. The study found that GWG above 18.1 kg was associated with both overweight (>85 percentile) and obesity (>95 percentile) during the first decade of life, and the effects remained after adjustment for confounders, including maternal age, parity and pre-pregnancy BMI [24]. In this study excess GWG was estimated to account for 16.4% (95% CI, 9.4, 23.2) of the risk of developing obesity [24], highlighting its potential contribution to obesity in childhood.

The majority of studies investigating an association between GWG and obesity in childhood have examined GWG using the US Institute of Medicine (IOM) categories of recommended weight gain in pregnancy, defined as *inadequate*, *adequate* and *excess* weight gain according to maternal pre-pregnancy BMI [25]. Using the IOM categories, studies have shown that the offspring of women who gain *excess* weight during pregnancy are more likely to be obese in childhood, in comparison with the offspring of women who gain *adequate* weight [18, 19]. For example, two meta-analyses found that children born to mothers who gained *excess* weight during pregnancy had 33% (OR, 1.33; 95% CI, 1.18–1.50) [22] and 38% (OR, 1.38; 95% CI, 1.21–1.57) [20] greater odds of being overweight. In another meta-analysis of 12 studies, the likelihood of obesity in the offspring was 1.4 times greater (95% CI, 1.23–1.59) [19]. The relationships were similar when stratified by life stage (<5 years, 5–18 years, 18+ years), suggesting that *excess* GWG is associated with offspring obesity from childhood to adulthood [19].

The majority of studies have used BMI as a measure of adiposity, despite the known limitations of interpreting child BMI measures [26]. However, two studies involving UK prospective pregnancy cohorts have examined the relationship between GWG and childhood obesity using direct measures of body composition and have shown similar associations. In the ALSPAC cohort [27] and Southampton Women's Survey (SWS) [28], children born to mothers who had gained *excess* weight in pregnancy had greater fat mass as measured by dual-energy X-ray absorptiometry (DEXA), in comparison with children born to women with *adequate* weight gain. In the SWS, children born to women with *excess* GWG had 7, 4 and 10% greater fat mass at birth, 4 and 6 years, respectively [28]. The findings from these cohorts provide strong evidence of an association between GWG and adiposity in childhood, although a causal relationship cannot be inferred due to the observational nature of the studies and the potential for residual confounding.

The association between *inadequate* GWG and risk of obesity is less clear. Some studies have found a U-shaped association between the GWG categories and risk of obesity, whereby either *excess* or *inadequate* GWG according to the 2009 IOM GWG guidelines was associated with increased risk of obesity in childhood compared with *adequate* GWG [28, 29]. In contrast, two meta-analyses have shown a small "protective effect", such that the offspring of women who gained *inadequate* gestational weight were 14% (relative risk, 0.86; 95% CI, 0.78–0.94) [19] and 9% (OR, 0.91; 95% CI, 0.85–0.98) [20] less likely to be obese than the offspring of women who gained *adequate* weight. The findings from the two reviews support the concept that the relationship between GWG and risk of obesity is not linear [20]. The majority of studies investigating the link between GWG and adiposity have focused on examining the impact of *excess* GWG; more research is needed to confirm whether *inadequate* GWG also predisposes children to later adiposity.

There is some evidence that the timing of the mother's weight gain during pregnancy may influence the risk of obesity in her offspring. While not conclusive, preliminary studies suggest that *excess* GWG in early and mid-pregnancy may be an important factor for determining later risk of adiposity [18]. Evidence from the Project Viva cohort showed that greater GWG in the first and second trimester was associated with higher BMI z-score and fat mass in mid-childhood (median 7.7 years old), whereas GWG in the third trimester was not associated with childhood adiposity [30]. Associations were strongest among women who were obese prior to pregnancy [30]. In another longitudinal cohort study of 977 mother-child pairs, for each 200 g/week increase in weight gained during the first trimester of pregnancy, children were 1.25 (95% CI: 1.09, 1.42) and 1.15 (95% CI: 1.05, 1.25) times more likely to be overweight and obese at 2 and 4 years of age, respectively [31]. Greater weight gain in the first trimester was also associated with other measures of adiposity at 4 years, including an increased risk of a larger waist circumference (relative risk, 1.13; 95% CI, 1.04, 1.23) and greater skinfold thickness (relative risk, 1.15; 95% CI, 1.02, 1.29) [31]. Conversely, greater weight gain during the second and third trimester was associated with higher birth weight (relative risk, 1.22; 95% CI, 1.02, 1.45) but not with subsequent measures of adiposity at 4 years [31]. The findings highlight the importance of monitoring GWG early in pregnancy, which may be challenging for unplanned pregnancies or when routine prenatal care is not sought until the end of the first trimester.

Much of the evidence that links GWG with offspring adiposity is observational, although a number of intervention studies that directly aim to limit GWG and reported the interventions' effects on adiposity in childhood are ongoing. The Lifestyle in Pregnancy and Offspring (LiPO) randomised control trial (RCT) is aimed to determine the effects of a lifestyle intervention during pregnancy on offspring metabolic risk factors [32]. Obese, pregnant women (n = 360) were randomised to either a lifestyle intervention (dietary advice, coaching and exercise) or a control group (routine obstetric care) [32]. Although the study did not directly target GWG, women receiving the lifestyle intervention gained less gestational weight compared with the control group (7.0 and 8.6 kg, respectively, p = 0.01) [33]. However, the study found no intervention effect on BMI z-score, BMI or body composition measured by DEXA in children at 2.8 years [32]. The authors hypothesised that the lack of findings may be due to the limited impact that the lifestyle programme had on reducing GWG in intervention participants or due to the poor retention rate and the study being underpowered at follow-up [32]. The timing of the intervention, commencing at 10–14 weeks gestation, may have also reduced any potential intervention effect [32] since there is some evidence to suggest that GWG in the first trimester is important [31]. Similar results were found in the follow-up of another RCT in which obese mothers participated in a weight gain restriction programme or a control group [34]. Although the study was effective in limiting GWG in the intervention (mean 8.7 kg, SD 5.43) compared with the control group (mean 11.1 kg, SD 5.7, $p < 0.001$), the follow-up of children at 5 years of age found no difference in BMI or BMI z-score [34]. New intervention studies that recruit women prior to conception are effective at monitoring and managing GWG through the entire pregnancy, and measures of body composition in children at follow-up are needed to understand the effects of excess GWG on childhood obesity.

Maternal Smoking

Observational cross-sectional and cohort studies show a clear and consistent association between maternal smoking during pregnancy and an increased likelihood of the offspring developing overweight and obesity in childhood. Two meta-analyses [35, 36] found similar adjusted odds ratios, with children born to

mothers who smoked during pregnancy 1.50 (95% CI: 1.36, 1.65) and 1.52 (95% CI: 1.36, 1.70) times more likely to be overweight and/or obese than children born to mothers who did not smoke during pregnancy. Although smoking tends to be associated with a host of sociodemographic and lifestyle factors, such that smokers tend to have less healthful diets and lifestyles, the association remained after adjustment, suggesting that the effects of the measured confounding influences cannot fully explain the association [35].

One issue that has been raised is the challenge of interpreting findings from meta-analyses that pool data from studies including both preterm infants (<37 weeks' gestation) and those born at "term" [37], as children born prematurely may have different growth trajectories [38, 39], and stratification by preterm and term births may be needed. A more recent meta-analysis of published and unpublished literature that pooled data from 39 studies, and included 236 687 children restricted to those born at "term" from Europe, North and South America, Australia and Asia, examined the association of smoking with childhood overweight and obesity separately. The review found that the adjusted odds ratio of childhood obesity (1.55, 95% CI: 1.40, 1.73) was slightly greater than that for overweight (1.37, 95% CI: 1.28, 1.46) [37]. The adjustment for confounding variables in the included studies varied, although generally they included a measure of socioeconomic status, parental education and breastfeeding [37]. As the pooled data from the studies used the lowest smoking exposure measured at the earliest available prenatal time point in pregnancy, the findings are likely to be a conservative estimate of the association between maternal smoking and childhood obesity [37]. There was some evidence of a dose-response association; eight studies reported a greater effect on overweight in childhood with an increased number of cigarettes smoked each day or continued smoking throughout pregnancy [37], although this was not consistent across all studies. The majority of studies were conducted in Western, high-income countries, highlighting an important gap in the global health smoking research from middle- and lower-income countries [37]. Although causality cannot be demonstrated due to the observational design of the included studies and the likelihood of unmeasured residual confounding, the findings do add to the mounting body of evidence for an association between foetal smoking exposure and childhood obesity.

The importance of prenatal exposure has also been confirmed in studies comparing the association between child obesity and maternal smoking in pregnancy, with paternal or household smoking. In a meta-analysis of 12 studies that mutually adjusted for maternal and paternal smoking exposure, the offspring (n = 108,939 children, aged 3–18 years old) of mothers who smoked in pregnancy had higher odds of both overweight (1.33; 95% CI, 1.23, 1.44) and obesity (1.60; 95% CI, 1.37, 1.88), as compared with the pooled odds ratio for offspring of fathers who smoked at any time (overweight 1.07; 95% CI, 1.00, 1.16; and obesity 1.23; 95% CI, 1.10, 1.38) [40]. Similar odds ratios were found when comparing maternal smoking during pregnancy (overweight 1.35; 95% CI, 1.20, 1.51; and obesity 1.28; 95% CI, 1.07, 1.54) with general household smoking at any time in pregnancy and childhood (overweight 1.22; 95% CI, 1.06, 1.39; and obesity 1.31; 95% CI, 1.15, 1.50), which likely reflects an overlap in continued maternal smoking in both pregnancy and postnatal period (measured in the household environment) [40]. The higher effect estimates in the mutually adjusted models for maternal smoking in pregnancy compared with those for paternal smoking suggest that foetal intrauterine exposure, rather than family lifestyle factors associated with smoking, is likely to be more influential in predisposing offspring to obesity [40, 41].

The causal mechanisms to explain the effect of prenatal smoking on risk of obesity in the offspring are not fully understood, although a number of plausible biological mechanisms have been proposed. Prenatal smoking has been associated with low birth weight, possibly through

the vasoconstrictive action of nicotine leading to foetal hypoxia [37]. It has been hypothesised that this may affect infant growth patterns leading to a higher risk of obesity [37], although some studies have found that the association between maternal smoking in pregnancy and obesity in childhood is not mediated by patterns of growth in childhood [42]. It has also been proposed that increased adiposity in childhood may result from foetal exposure to nicotine, which has been shown to have long-term effects on programming the regulation of appetite and the control of food consumption [42–44]. There is also some evidence of a time-dependent association, such that smoking in the first trimester appears to be more relevant to an offspring's risk of obesity [45, 46], while smoking in the final trimester is associated with low birth weight [47, 48]. Evidence of a dose-response association in some studies [37, 44, 49] adds to the evidence that the relationship between prenatal smoking and obesity in children is causal.

Intervention studies examining the effects of smoking cessation in pregnancy on obesity in childhood are sparse [50]. In a RCT on smoking cessation during pregnancy, 1853 pregnant, smoking women were allocated to either an antismoking educational intervention (leaflet and one clinician-led discussion on quitting smoking) or usual care [51]. While the intervention reduced the prevalence of maternal smoking during pregnancy and increased birth weight, there were no differences in weight or height in the offspring at 9-year follow-up [51]. Unfortunately, the RCT did not report weight for height, body fat or BMI as measures of obesity. Longer follow-up of smoking cessation intervention trials that collect detailed body composition data is needed to understand the effects of maternal prenatal smoking on childhood obesity.

Summary

The prevalence of obesity in childhood is increasing and is recognised as a major global health problem. Strong evidence indicates that the prenatal environment may be a critical period when the long-term regulation of energy balance is permanently "programmed" [5]. However, distinguishing between the influence of the intrauterine environment, shared genetic traits and postnatal influences such as living in an obesogenic environment is challenging. Observational evidence supports an association between prenatal factors and childhood obesity, although high-quality intervention evidence confirming causal mechanisms are lacking. Approaches to test whether the effects are mediated by epigenetic mechanisms are currently being developed, and preliminary evidence is promising. Better characterisation of these influences will help to identify opportunities to intervene to prevent childhood obesity.

Three modifiable early-life risk factors discussed in this chapter have been shown to be independent predictors of adiposity in childhood, but to understand the potential public health impact, insight can be gained by evaluating their combined effect. In a UK birth cohort, these three risk factors (maternal pre-pregnancy obesity, excess GWG according to the 2009 IOM guidelines and smoking during pregnancy) and further two risk factors (low maternal vitamin D status and short duration of breastfeeding) were examined in relation to the risk of developing overweight or obesity [52]. Children with four or five risk factors were 3.99 (95% CI, 1.83, 8.67) and 4.65 (95% CI, 2.29, 9.43) times more likely to be overweight or obese at 4 and 6 years, respectively, than children who had no risk factors ($p < 0.001$) [52]. Behavioural interventions that simultaneously address these modifiable early-life risk factors could make a significant impact on the prevention of childhood obesity.

Future research should focus on preventative efforts prior to and during pregnancy as a potential window of opportunity to reduce childhood obesity. Policies and primary prevention initiatives that support young women of child-bearing age and encourage them to stop smoking and have a healthy body weight prior to pregnancy are needed, both for their own health and that of their children.

Editor's Comments and Question

It may not be possible to fully distinguish the relative roles of the intrauterine environment, shared genetic traits and postnatal environment because they are strongly interrelated. For example, the study of offspring of women prior to and following bariatric surgery suggests important roles for maternal weight gain and metabolic function prior to and during pregnancy. However, the prevalence of obesity in the offspring of surgically treated mothers remains higher than expected (35%), arguing for roles of shared genetic modifiers as well as the obesogenic postnatal environment. It should also be noted that paternal obesity appears to act in concert with maternal obesity to increase the risk of childhood weight gain.

Your review suggests that the health and metabolic status of women *prior to*, *during and after* pregnancy has critical impacts upon the health and well-being of their offspring. If you had to target limited resources to prevent childhood obesity, where in that cycle would you devote most effort?

Authors' Response

Waiting until pregnancy to intervene may be too late. For example, rapid weight reduction is not recommended for women who are already obese on entering pregnancy, and, although many women give up smoking, this may not occur in the early weeks before they are aware that they are pregnant. Successful interventions to prevent childhood obesity may therefore be best targeted towards women in the period before conception, particularly to encourage healthy diets and body weights and to promote smoking cessation. However, as young women rarely access public services, the teenage years may be the period in the life course in which to devote most effort. This is a time when children are developing their health behaviours, offering potential to improve their own lifelong health, as well as that of the next generation. The challenges of changing health behaviours are considerable. But, as highlighted by the evidence presented in this chapter, for women who go on to become pregnant, the impact of these changes on offspring health could be very significant.

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Fetal and Infancy Growth

12

Ken K. Ong

Introduction

The secular trends towards increasing prevalence of overweight and obesity are detectable even in very young preschool-aged children. Globally, the World Health Organization estimated that the prevalence of childhood overweight and obesity in children below the age of 5 increased from 4.2% in 1990 to 6.7% in 2010 [1]. Estimates were higher in developed (11.7%) rather than developing countries (6.1%), although the relative change in prevalence in the last decade has been higher in developing countries [1]. Such findings indicate that our attention to the aetiology, prediction, and prevention of obesity should start very early on in life to include even antenatal and early infancy factors.

In contrast to body weight in early childhood, there is little evidence that average birth weight has changed appreciably over time, at least in North America and Western Europe [2]. Birth weight is positively associated with later BMI in most epidemiological studies, and therefore larger babies are more likely to become obese [3]. However, BMI is an inaccurate marker of adiposity, and in studies that use more accurate measures of body composition, it is evident that larger babies are more likely to have greater lean body mass but not greater fat mass as children, adolescents, and older adults [4]. Rather, it appears that low birth weight babies, born following intrauterine growth restriction, are more likely to become more adipose and have higher risks for obesity-related diseases in later life, an observation that was originally reported by David Barker and colleagues and which led to the eponymous "Barker hypothesis" described below.

It should be noted here that, as well as fetal growth-restricted infants, infants who are born macrosomic (birth weight >4000 g) may also be at high risk for later diabetes and other obesity-related diseases. Particularly in countries that experienced rapid developmental transition, the rising prevalence of maternal obesity and gestational diabetes has led to a rising incidence of macrosomic births [5]. Obesity risk in such offspring will be described in a following chapter.

The Barker Hypothesis

The observation that low birth weight is associated with higher risk of cardiovascular disease was prompted by the strong geographical association between areas in England and Wales with the highest infant mortality rates in 1921–1925 and the highest ischaemic heart disease mortality rates in 1968–1978 [6]. Barker and Osmond

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proposed that the transition from poor nutrition in early life to a subsequent affluent diet might increase the susceptibility to obesity-related disease. Over the following decade, those authors and others established the epidemiological associations between small size at birth and various adulthood disease risks, including cardiovascular disease, hypertension, type 2 diabetes, and stroke [7]. Other low birth weight associations include ageing, ovarian hyperandrogenism, and menstrual irregularities [8]. The persistence of such associations after exclusion of preterm infants and adjustment for gestational age meant that reduced or restricted fetal growth was the implicated exposure, although preterm-born individuals also have higher risks for type 2 diabetes [9]. The continuum in disease risks across the whole spectrum of birth weights indicates that these associations reflect the effects of common determinants of fetal growth, rather than maternal disease or severe placental dysfunction.

These findings have not been unchallenged. Meta-analyses have shown that, as with many other associations, the initial reports tended to report far greater effect sizes than subsequent larger studies [10]. A more concerning challenge has been that these associations might be due in part to inappropriate statistical adjustment, particularly for current body size, which creates an artifactual statistical effect known as "collider bias" or the "reversal paradox" [11]. In many studies, the association between birth weight and later disease was not apparent until after adjustment was made for adult body weight or BMI [10].

While it is difficult for traditional observational studies alone to resolve the question of statistical artefact, recent population genetic studies provide strong support for a true continuous relationship between birth weight (and implied fetal growth rate) and later obesity-related disease. A recent study identified 60 genomic loci where common variation in fetal genotype was robustly ($P < 5 \times 10^{-8}$) associated with birth weight [12]. Furthermore, strong inverse genetic correlations were found between birth weight and systolic blood pressure ($r_g = -0.22$, $P = 5.5\times10^{-13}$), type 2 diabetes ($r_g = -0.27$, $P = 1.1\times10^{-6}$), and coronary artery disease ($r_g = -0.30$, $P = 6.5\times10^{-9}$). Notably, in contrast to those inverse correlations with disease outcomes, there were positive genetic correlations between birth weight and BMI ($r_g = 0.11$, $P = 7.3\times10^{-6}$) and waist circumference ($r_g = 0.18$, $P = 3.9\times10^{-10}$) [12]. Hence, the mechanisms that promote greater fetal growth and birth weight may also promote a "metabolically healthy" state of higher adult BMI and obesity. Conversely, mechanisms that restrict fetal growth and lower birth weight confer higher risks of metabolic disease despite lower BMI. Despite their "protection" against high BMI, low birth weight individuals may have metabolically adverse fat patterning [13], and if they were to become overweight or obese, it is possible that their disease risks may be amplified.

The Developmental Origins of Health and Disease Hypothesis

The Developmental Origins of Health and Disease Hypothesis (DOHaD) arose in the early 2000s from findings of epidemiological studies that analysed information on infant and childhood growth. Furthermore, instead of "collider bias" (see above), a more constructive interpretation of the analyses of "birth weight adjusted for adult body size" was made by Lucas and colleagues who pointed out that "early size adjusted for later size" is a measure of change in size between the earlier and later measurements [14]. Having started with a focus on birth weight as a marker of fetal growth, the search for the early origins of health and disease now encompasses the full range of childhood growth and development and has spawned its own subdiscipline named "life course epidemiology".

Indeed, in many studies the associations with childhood size appear to be stronger than those with birth weight alone. For example, in a study of men with birth and school records in Helsinki, Finland, the risk of death from coronary heart disease increased by 14% for each unit (kg/m^3) lower ponderal index at birth and by 22% for each unit (kg/m^2) higher childhood BMI [15]. Such observations supported the original postulate of Barker

and Osmond that adult disease might be a consequence of poor prenatal nutrition followed by improved postnatal nutrition [6].

With regard to early postnatal growth, epidemiological studies have described a very consistent association between rapid weight gain during infancy and higher likelihood of being overweight or obese in childhood or adult life. A recent systematic review found that 45 of 46 studies, performed in various countries, reported a positive association between infant weight or infancy weight gain and childhood overweight or obesity [16]. Such observational findings are supported by evidence from a few randomised controlled trials in preterm and small for gestational age infants [17]. Regarding the shape of association, a pooled individual-level meta-analysis across ten studies found a largely linear positive association between infancy weight gain and childhood obesity but a substantially higher risk of obesity in those infants whose weight crossed upwards through >2 centile bands (equivalent to >1.33 Z-scores) [18] (Fig. 12.1). Therefore, there may be potential benefits on later obesity risk for both population-wide and also targeted high-risk preventive strategies starting in early life. Furthermore, the risk of childhood obesity related to rapid infant weight gain appears to be the same for both breastfed and formula milk-fed infants and for both normal birth weight and low birth weight infants [18].

In addition to obesity risk as defined by BMI thresholds, rapid infancy weight gain is also positively associated with measures of central adiposity, insulin resistance, childhood adrenal and gonadal sex steroid concentrations, and earlier timing of puberty during adolescence [19]. In turn, males and females with earlier pubertal timing have higher risks for type 2 diabetes, cardiovascular disease, various reproductive cancers, and all-cause mortality [20, 21]. Therefore, rapid infancy weight gain may indicate a whole life course trajectory of faster growth and development that leads to accelerated ageing and death.

However, while the epidemiological disease associations may appear to be stronger with postnatal growth rather than fetal growth, in such observational studies, it may be difficult to disentangle the effects of antenatal from postnatal exposures. Low birth weight infants who were growth restrained in utero are much more likely

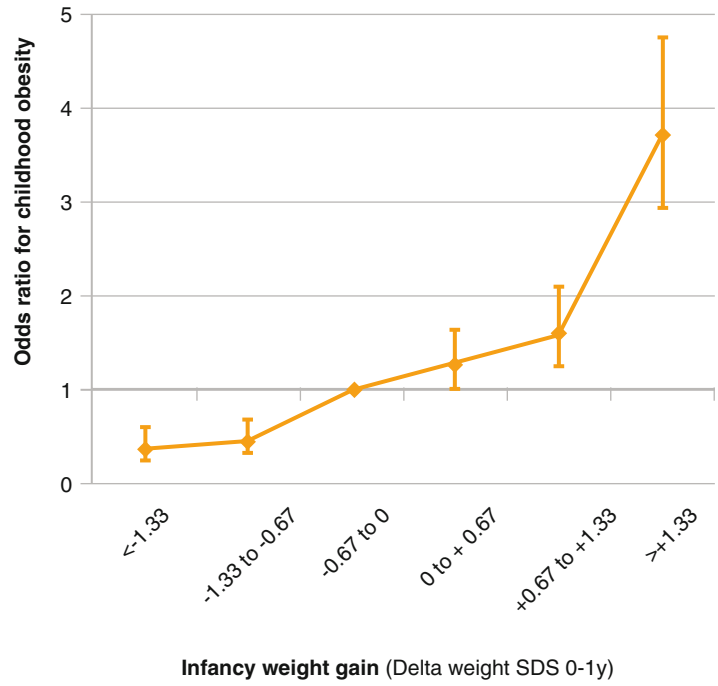

Fig. 12.1 Odds ratio for childhood obesity by rate of infancy weight gain between birth and 1 year old. Individual-level meta-analysis of data from around 45,000 participants (Used with permission of John Wiley and Sons from Druet C, Stettler N, Sharp S, Simmons RK, Cooper C, Smith GD, et al. Prediction of childhood obesity by infancy weight gain: an individual-level meta-analysis. Paediatr Perinat Epidemiol. 2012;26(1):19–26)

than other infants to show rapid postnatal growth, often termed "catch-up" growth as it compensates for the earlier growth deficiency [22]. Alternatively the two factors might lie on the same causal pathway to later disease, and their effects may be additive. Efforts to identify and quantify the relative contributions of antenatal and postnatal factors are needed in order to inform preventative strategies.

Antenatal Mechanisms: Animal Models

A variety of animal models have demonstrated that fetal growth restriction leads to increased blood pressure, hyperinsulinaemia, and impaired glucose tolerance [23]. Intrauterine growth restriction may be achieved by a variety of techniques including bilateral uterine arterial ligation, protein restriction, caloric restriction, or glucocorticoid exposure. There is some evidence that the embryo and developing fetus may exhibit particular sensitivity to nutrient deficiencies. For example, maternal periconceptional B vitamin and methionine status may influence offspring insulin resistance and blood pressure in sheep [24]. It has been suggested that long-term brain and cardiovascular function may be most sensitive to the influences during the embryonic period, renal outcomes during maximal placental growth and development, and adipose tissue and muscle outcomes during the fetal growth phase during late pregnancy (Fig. 12.2) [25]. Changes in tissue structure following fetal growth restriction have been reported in the kidney [26] and endocrine pancreas [27].

There is much interest in the potential role of epigenetics, stable gene expression regulating marks that are independent of genomic DNA sequence, as a mechanism that could explain how short-term discrete exposures during early life may have very long-lasting effects on metabolism and disease risks in later life [28] and even on the transmission of these changes to future generations [29, 30]. DNA methylation has been well studied, as a mechanism that results in stable yet diet-sensitive changes in gene expression, but histone modifications and microRNAs are also potent regulators of gene expression [23]. Early-life insults may also predispose to later disease susceptibility by

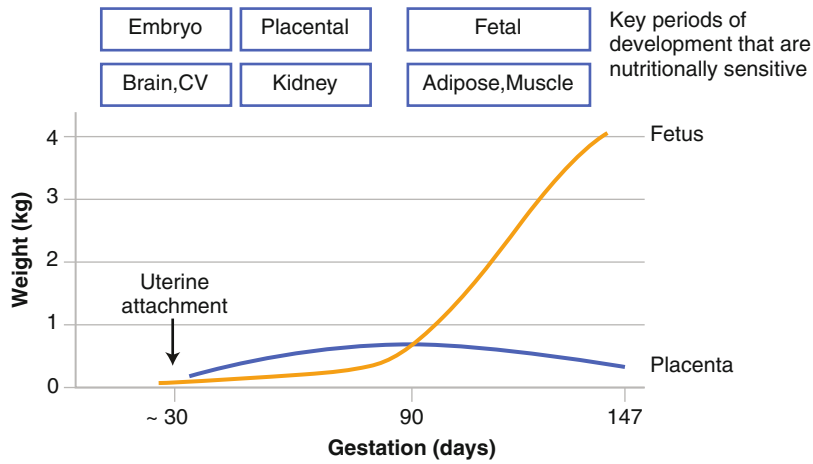

Fig. 12.2 Summary of the main developmental windows during the reproductive period in sheep during which manipulation of the maternal diet significantly modulates placental and fetal development. *Upper bars* represent windows of developmental plasticity with respect to individual organs. CV, cardiovascular system (Used with permission from Symonds ME, Stephenson T, Gardner DS, Budge H. Long-term effects of nutritional programming of the embryo and fetus: mechanisms and critical windows. Reprod Fertil Dev. 2007;19(1):53–63. Proceedings of the Annual Conference of the International Embryo Transfer Society, Kyoto, Japan, 6–10 January 2007. Copyright IETS 2007. Published by CSIRO PUBLISHING, Melbourne Australia. http://www.publish.csiro.au/nid/45/issue/3364.htm)

promoting accelerated cellular ageing. Specific mechanisms include reduced length of telomeres, which protect the ends of chromosomes from deterioration and abnormal fusion with neighbouring chromosomes [31], and diminished capacity of cells to withstand oxidative stress [23].

As well as fetal undernutrition, there is increasing evidence that susceptibility to later life disease may also be programmed by fetal overnutrition, whether directly, e.g. by giving pregnant mothers diets rich in simple sugars and saturated fat, or indirectly, e.g. through maternal or paternal preconception overnutrition [32]. As has been reported for undernutrition [29, 30], parental overnutrition may have transgenerational effects on the fetus, mediated through heritable epigenetic marks. Notably, a chronic high-fat diet in Sprague-Dawley rat fathers altered the expression of 642 pancreatic islet genes and programmed β-cell dysfunction in female rat offspring [33].

The identification of such long-lasting effects of discrete exposures during critical early developmental periods of life has led to many interesting hypotheses as to why it may be beneficial for an individual organism to make very long-term decisions on metabolism or organ function. Barker and Hales coined the "thrifty phenotype" hypothesis to describe how the observed structural and physiological responses to early nutritional insults might enhance fetal survival [34]. For example, during settings of overall fetal growth restriction, the development in the fetus of peripheral resistance to insulin or insulin-like growth factor-I (IGF-I) could beneficially divert sparse nutrients towards essential head or longitudinal growth. This hypothesis has been further developed in arguments that promote adaptive developmental plasticity as a mechanism that evolved to enhance survival and reproductive success [35].

Antenatal Mechanisms: Human Studies

With regard to antenatal nutritional restriction, the limited studies in humans provide some confirmation of the results of animal models. Ravelli and colleagues reported that infants exposed to the Dutch famine of 1944–1945 during the first half of pregnancy had higher obesity rates at 19 years of age; in contrast, famine exposure during the last trimester of pregnancy and the first months of life led to lower obesity rates [36]. These findings are broadly consistent with a long-term effect of early nutritional deprivation on later regulation of weight gain and adiposity. The precise mechanisms by which this effect is mediated are unclear, but epigenetic events may play a role. For example, periconceptional famine exposure has been associated with reduced DNA methylation of the imprinted insulin-like growth factor-II gene [37]. Comprehensive "epigenome-wide" assessment of DNA methylation has identified numerous prenatal malnutrition-associated differentially methylated regions that occur preferentially at regulatory regions and implicate genes that link birth weight to lipid metabolism and insulin sensitivity [38]. However, the Dutch famine studies do not explain why lighter babies at birth are at greater risk of disease, as early gestation famine exposure was associated with slightly larger rather than lower birth weight. Furthermore, studies of other famines, such as the Leningrad Siege, did not confirm these findings, and in rural Gambia, food supplementation increased birth weights only during the wet season when women had negative energy balance due to food shortages and high agricultural workload, but not during the dry season when energy intakes were still only 60% of the recommended dietary allowance [39]. Such findings suggest that human fetal growth is relatively protected against all except very extreme changes in macronutrient intakes. Maternal micronutrient (such as in vitamin B12 and folate) deficiencies may play a greater role in the early determination of fetal growth and childhood insulin resistance [40].

Non-nutritional factors could link low birth weight to later risks of obesity-related disease. Fetal growth may be restrained due to maternal smoking, primiparity, maternal disease, such as gestational diabetes or pre-eclampsia, or by less severe increases in blood pressure [41]. Elegant animal models of glucocorticoid administration, or genetic modification of cortisol metabolism, demonstrate that increased glucocorticoid activity

can link low birth weight to later insulin resistance and associated disease risks [42]. However, in humans the role of the hypothalamic-pituitary-adrenal axis in explaining the epidemiological associations with low birth weight and obesity is yet unclear [43, 44].

Repeated high-dose maternal corticosteroid therapy is now well established for the prevention of neonatal respiratory distress syndrome following preterm labour and also for in utero prevention of genital abnormalities in female infants with congenital adrenal hyperplasia. These treatments appear to have good safety profiles, modest impact on reducing birth weight, and no adverse effects on growth or health in early childhood [45]; however, long-term follow-up of such children is clearly needed.

The recent insights into the genetics of birth weight identified several biological pathways that regulate fetal growth and plausibly also contribute to adult disease risk, including insulin signalling, glycogen biosynthesis, cholesterol biosynthesis, IGF signalling, and chromatin remodelling. Specific overlaps were also found between genetic determinants of birth weight and those of blood pressure, steroidogenesis, insulin processing, and insulin secretion [12]. It should be appreciated that results of population genetic studies yet explain only small proportions of the observed natural variation. Rather than claiming to provide gene-centric explanations for disease, according to the Mendelian randomisation approach, these genetic findings may also have much to tell us about the causal effects of modifiable or environmental influences [46].

Early Postnatal Mechanisms: Animal Models

Several of the original animal models of antenatal nutritional growth restriction were accompanied by postnatal overnutrition. For example, offspring of pregnancy diet-restricted mice were more susceptible than controls to the excess weight gain induced by postnatal weaning onto a hypercaloric diet, accompanied by profound adult hyperphagia [47]. In contrast, postnatal low-protein-restricted mice are resistant to the excess weight gain from a highly palatable diet, indicating that the early environment has long-term consequences for weight gain [48]. The combination of antenatal growth restriction and postnatal growth acceleration also leads to a shortened lifespan in mice; this contrasts with the increased longevity in mice with limited growth during the suckling period [49].

The early postnatal period may therefore represent a specific window of opportunity to reset the antenatal "metabolic programme" established in response to fetal growth restriction [35]. The clearest evidence for a very specific window comes from studies of the postnatal leptin surge in rodents. Leptin increases fivefold to tenfold during the second postnatal week independent of fat mass, before declining again after weaning. It is thought that this leptin surge may have neurotrophic effects on the maturing neuroendocrine axis. Rats that received injections of leptin between days 3 and 10 showed a transient reduction in weight gain. The effects were more marked in rats that had been severely undernourished in utero (their mothers received 30% of ad libitum intakes); in this group postnatal leptin administration also completely blocked their predisposition to adiposity, insulin resistance, and other adverse metabolic parameters [50]. However, in male rats of normal pregnancies, the same neonatal leptin treatment increased diet-induced weight gain, hyperinsulinaemia, and total body adiposity, indicating a complex interdependency between the effects of these antenatal and early postnatal signals.

Early Postnatal Mechanisms: Human Studies

The following section considers the impact of infant feeding patterns on rapid infancy weight gain. When considering the determinants of infancy weight gain, it is important to recognise that infant feeding involves the interaction between the mother and infant [51]. Mothers recognise and respond to their infant's feeding signals, as in other species, and this interaction may be disrupted by mode of infant milk feeding and other external factors, with adverse consequences on growth and development [52]. Genetic studies have begun to shed light on the

intrinsic mechanisms that determine infant feeding behaviours. However, few studies have yet examined the potential bidirectional relationship and interaction between parental feeding patterns and infant feeding behaviours on infancy weight gain and subsequent obesity risk.

Infant Feeding and Weight Gain

Infant formula milk feeding is highly prevalent worldwide and has a substantial influence on infant growth and weight gain. In high-income countries, formula-fed infants show a faster trajectory of growth and weight gain compared to breastfed infants [53]. Indeed, this difference underlies the rationale for the World Health Organization (WHO) 2006 Growth Standards for children aged 0–5 years. Previous growth references were based on predominantly formula milk-fed infants in Western countries, and they therefore inadvertently promoted a rapid trajectory of infancy weight gain. By contrast, the WHO Growth Standards are based on predominantly breastfed infants in high socio-economic settings [54]. Hence, healthy breastfed infants track along the WHO Growth Standard's mean weight-for-age Z-score but appear to falter on previous growth references, and the WHO Growth Standard identifies more children as being overweight [54].

The influence of the faster weight gain trajectory of formula milk-fed infants on their risks for obesity remains debated. Higher obesity prevalence is clearly observed in formula milk-fed than breastfed groups; however, the strong possibility of confounding by socio-demographic factors and other healthy behaviours limits the simple assumption of a causal effect of formula milk. Some commentators highlight as key experimental evidence the lack of effect on childhood BMI of breastfeeding promotion in the large randomised PROBIT trial [55]. However, in that Belarus setting, breastfeeding promotion led to higher rather than lower weight during the first 12 months, possibly by reducing the high prevalence of gastrointestinal and respiratory infections [56]. Therefore, that trial would not indicate the protective effect of breastfeeding on obesity mediated by slower infancy weight gain, as seen in more developed eras and settings.

Several explanations have been posited for the rapid infancy weight gain of formula milk-fed infants, typical of western settings, including differences in milk nutrient composition or diminished signalling of infant satiety. There is good evidence that high protein content infant milk formulas promote rapid infancy weight gain [57], and in recent years, the protein contents of most formula milk preparations have been lowered [58]. The nutrient composition of human breast milk is highly variable, and recent observational studies support a positive association between milk protein content and infant weight and also suggest a potential weight-limiting role of milk fat content and fat intakes, possibly due to its higher effect on satiation [59, 60].

Total energy intake in formula milk-fed infants is positively associated with infancy weight gain and childhood BMI [61]. This may be particularly relevant for childhood obesity, as energy intakes in infants and young children are high compared to the estimated average requirements [62]. While the solution may appear straightforward to limit infant intakes, to implement effective strategies requires careful consideration of parents' understanding of infant growth and sensitive education and support. Parents often report familial and cultural pressures in favour of "chubby" children, possibly influenced by fears of food insecurity [63]. Targeted support may also be needed for parents of infants who have high intrinsic levels of appetite.

Earlier age at the introduction of complementary (solid or semi-solid) foods has been associated with a higher risk for obesity. However, there is little evidence that this association reflects a causal effect. In some studies, the association is weakened after adjustment for socio-economic factors and infant milk feeding [16]. Furthermore, several studies have reported evidence for "reverse causality", because the rapid infant weight gain preceded the introduction of solids [64]. Therefore, it appears that many parents may respond to larger infant size, faster weight gain, or other signals of increased nutritional demand, by introducing solid foods earlier than recommended [64].

Infant Regulation of Infancy Weight Gain

Rare deleterious mutations in around a dozen genes have been identified as the monogenic causes of severe early-onset obesity. Individuals affected by such disorders display extremely high and insatiable appetites ("hyperphagia") as infants and young children. Functional studies of those genes have uncovered a hypothalamic network that closely regulates appetite and weight gain [65]. While such monogenic disorders are rare, milder interindividual differences in gene function appear to contribute to the wide normal variations in eating behaviours, postnatal weight gain, and long-term obesity risk. Twin studies have reported that the estimated heritability of BMI in young children is 70% or higher [66]. Genome-wide association studies (GWAS) aim to efficiently assess the contributions of common and low-frequency genetic variants that contribute to heritability. Such GWAS for BMI have been performed in hundreds of thousands of adults and report ~100 common variants that are highly robustly associated with adult BMI [67]. While similar GWAS in children are unfortunately an order of magnitude smaller, the genetic signals for adult BMI have remarkably stronger influences on weight gain during infancy and childhood than on adult weight gain [68]. The associations are seen across the spectrum of weight gain, in that the genetic variants that predispose to rapid infancy weight gain and childhood overweight are protective against "inadequate" infancy weight gain [69]. These adult BMI-related variants are also associated with puberty timing, type 2 diabetes, and cardiovascular disease; hence, they indicate mechanisms that underlie the Developmental Origins of Health and Disease Hypothesis.

The GWAS adult BMI-related variants are located in or near to genes that are expressed in the central nervous system, particularly the hypothalamus and pituitary gland. Those findings indicate a predominantly "central" genetic regulation of BMI, as suggested by the studies of rare monogenic obesity. Stable and heritable eating behaviours, corresponding to appetite and satiety, are measurable from early life and play an important role in infancy weight gain and later obesity risks. Furthermore, in both children and adults, eating behaviours appear at least partially to mediate the effects of genetic variants on BMI [70]. Therefore, genetic factors that act centrally in the brain contribute to the wide interindividual differences in infant appetite, food intake, and weight gain, and they provide biological links between early growth and feeding behaviours to puberty timing and adult disease risks.

Future Strategies: Healthy Catch-Up Growth?

Significant short- and long-term benefits of rapid postnatal catch-up growth, on resilience to infection and avoidance of stunting particularly in developing settings [71], contrast with the increased risks of future obesity-related disease. This risk-benefit balance for the fetal growth-restrained infant has been termed "the catch-up dilemma". In SGA children who remain short, there is evidence that growth hormone therapy may achieve the beneficial gains in long-term height and even cognitive function, but without the increased adiposity and metabolic disadvantages normally associated with early spontaneous, appetite-driven, catch-up growth [72]. While a pharmaceutical approach in all SGA children should not be contemplated, those studies illustrate the potential for different pathways of postnatal catch-up growth leading to differences in future disease risks (Fig. 12.3).

Firstly: to catch-up or not? One might rephrase this question as "how much catch-up is best?" The authors of one large prospective study proposed that for SGA infants, catch-up to around the 30th weight percentile in the first postnatal months and to around the 50th percentile by 7 years old was optimal for both short-term infection and longer-term metabolic and cognitive outcomes [73]. For normal birth weight infants in developed settings with high prevalence of rapid weight gain and childhood obesity, preventive strategies need to start very early in life to avoid excess nutrient intakes and weight gain. Such strategies should consider both population-wide and targeted high-risk group approaches.

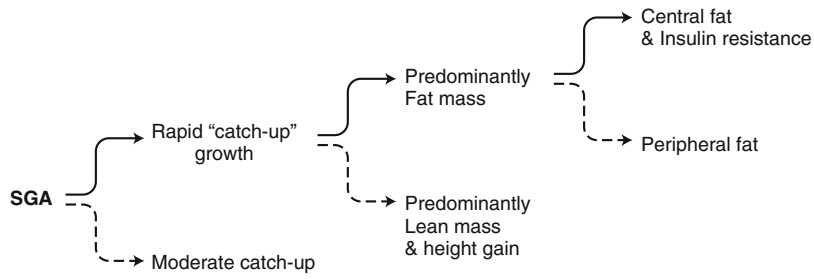

Fig. 12.3 Schematic diagram of the common SGA pathway of rapid postnatal catch-up weight gain leading to increased total and central adiposity (*bold arrows*). Alternative putative pathways to healthy catch-up growth are shown by the *dotted arrows* (Used with permission of Wolters Kluwer Health Inc. from Ong KK. Catch-up growth in small for gestational age babies: good or bad? Curr Opin Endocrinol Diabetes Obes. 2007;14(1):30–4)

Secondly: might it be possible to promote catch-up growth in healthy tissues (lean mass and statural growth) rather than in total and central fat mass? Differential gains in infancy adiposity versus lean mass may occur due to genetic or endocrine regulators. For example, IGF-I may regulate a more favourable partitioning of infant weight gain into greater statural growth rather than adiposity [74]. However, the long-term health relevance of body composition in infancy is unknown. Body composition changes markedly during infancy. Percent body fat rises markedly from birth to around 8 months of age and then declines until the adiposity rebound at age 4–7 years old. While it may appear logical to assume that infants with higher relative adiposity may be at higher long-term risk of obesity and obesity-related diseases, the data are yet sparse. Conversely, formula milk-fed infants have greater lean mass than breastfed infants during infancy [75], and genetic variants associated with adult obesity risk promote symmetrical gains in fat mass and lean mass during infancy [76]. Therefore, rapid infancy gains in body length and lean mass are not necessarily reassuring for later obesity risk.

In the future, it is possible that microbiome, metabolomics, and lipidomic biomarkers might guide healthy trajectories of early postnatal growth [77, 78]. As is the case for infant body composition, their relevance to future health will require long-term follow-up studies, although in the interim, comparisons between infants at low versus high genetic susceptibility to later obesity may be informative. To achieve such healthy growth trajectories during infancy, both population-wide and targeted high-risk group approaches may be complementary. Both approaches will need to consider ways to encourage parents to aim for healthy infant growth trajectories rather than rapid weight gain and will need to consider how to identify and support parents of infants with high levels of intrinsic food-demanding behaviours.

Editor's Comments

The general health and nutrition of the mother and the growth and function of the placenta have profound effects on fetal growth and metabolic homeostasis[a]. Maternal obesity and diabetes mellitus predispose to fetal adiposity and increase the risks for childhood and adult obesity, insulin resistance, and type 2 diabetes mellitus. (See Chap. 11 by Dr. Hollis and colleagues and Chap. 13 by Drs. Dabelea and Sauder.) As noted here by Dr. Ong, fetal growth restriction also predisposes to obesity and metabolic dysfunction if there is rapid catch-up weight gain during childhood (see also Chap. 1 by Dr. Freemark).

The pathogenesis of metabolic dysfunction following intrauterine growth restriction (IUGR) is poorly understood. In animal models, maternal malnutrition or exposure of the fetus to high levels of glucocorticoids[b,c] reduces skeletal muscle mass, pancreatic beta-cell mass, and the number of renal nephrons[a,d,e]. This favours the accumulation

of fat relative to lean body mass and may predispose to type 2 diabetes, hypertension, and the metabolic syndrome.

In humans, IUGR resulting from maternal malnutrition or placental dysfunction is associated with fetal hypoinsulinaemia, low levels of IGF-1 and IGF BP-3, hypoleptinaemia, and hyperghrelinaemia[d,f,g]; cord blood cortisol levels are also elevated in infants with reduced rates of fetal growth, at least in some studies[f]. Fetal hypercortisolaemia may result from premature activation of the hypothalamic-pituitary adrenal-axis[h] and/or decreased expression or dysfunction of placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HDS2), which converts maternal cortisol to its inactive metabolite cortisone. Placental 11β-HSD2 activity is decreased by malnutrition, hypoxia, catecholamines, and inflammatory cytokines[b]. Low levels of leptin and high levels of ghrelin and cortisol in the perinatal period may facilitate catch-up weight gain through increases in food intake and may thereby predispose to childhood obesity. And yet repeated exposure to betamethasone in utero has variable and inconsistent effects on long-term metabolic function[i,j]. Given the importance of this field, much work remains to be done.

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Intrauterine Exposure to Maternal Diabetes and Childhood Obesity

13

Dana Dabelea and Katherine A. Sauder

Introduction

The prevalence of obesity has increased dramatically in the United States over the past decades in each race/ethnic group, in both men and women, and in adults as well as children [1]. According to NHANES 2011–2012 data, 17.7% of children age 6–11 years are obese (BMI > 95th percentile) [1], compared to 4.0% of children in 1971–1974 [2]. Among youth aged 12–19 years, prevalence of obesity increased from 4.6% in 1963–1970 to 20.5% in 2011–2012 [1, 2]. Moreover, the distribution of body mass index (BMI) has shifted in a skewed fashion, such that the heaviest children have become even heavier and more adipose over time [3, 4]. Overweight is now present at increasingly younger ages, indicating that risk factors for this condition start operating early in life [1]. As in adults, obesity in childhood and adolescence is associated with adverse short- and long-term chronic outcomes, such as the insulin resistance syndrome, type 2 diabetes, hypertension, cardiovascular disease, and increased cardiovascular mortality [5, 6].

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Fetal life is considered one of the critical periods when an exposure may have lifelong effects, through biological programming, on the structure or function of organs, tissues, and body systems. These early effects may be modified by later-life exposures (through biological interaction) to determine future chronic disease risk [7]. Determining which and how early life factors operate among youth to promote the development of obesity is the first step toward prevention of both childhood and adult obesity.

Fetal Programming: A Conceptual Framework

The notion that inadequate "nutrition" at critical periods of development in fetal life is a key determinant of childhood and adult health has important implications [8–10]. The hypothesis of fetal overnutrition or fuel-mediated teratogenesis [11] proposed in the 1950s by Pedersen postulates that intrauterine exposure to hyperglycemia causes permanent changes in the fetus of a woman with diabetes in pregnancy, leading to malformations, macrosomia, and an increased risk of developing obesity and type 2 diabetes later in life. In the 1980s this hypothesis was broadened to include the possibility that other fuels, such as free fatty acids, ketone bodies, and amino acids, also increase fetal growth [11].

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Most studies of fetal overnutrition have focused on maternal diabetes. Recent evidence, however, suggests that exposure to maternal diabetes represents the extreme of a distribution of altered maternal fuels to which the fetus is exposed in pregnancies complicated by obesity.

Consequences of Exposure to Diabetes During Pregnancy

Exposure to altered glucose-insulin metabolism (or frank diabetes) in utero predisposes to fetal macrosomia and may increase the risks for obesity and metabolic consequences of obesity later in life, including during childhood and adolescence [12].

Fetal Growth

Infants of diabetic mothers display excess fetal growth (birth weight >90th percentile for gestational age), often, but not always, resulting in macrosomia (birth weight >4000 g) [13]. This increases the risks for cesarean delivery, traumatic birth injury, need for ventilation, and neonatal mortality [14]. Excess fetal growth is thought to be caused by increased substrate availability, including but not necessarily limited, to glucose. While maternal glucose freely crosses the placenta to the fetus, maternal insulin does not [11]. As a result, the fetus receives excess nutrients, and the fetal pancreas responds by producing increased insulin to meet the excessive glucose load. Insulin acts as an anabolic hormone in the fetus, promoting adiposity and, to a lesser extent, linear growth.

There is evidence that increased adiposity is already present at birth in infants of mothers with gestational diabetes. Catalano and colleagues [15] studied a group of 195 infants of mothers with gestational diabetes and 220 infants of mothers with normal glucose tolerance and found that fat mass, but not birth weight or fat-free mass, was 20% higher in the infants exposed to diabetes in utero. These results have been confirmed by a recent meta-analysis of 35 studies [16]. Catalano and colleagues reported that maternal fasting glucose level measured during the oral glucose tolerance test was the strongest correlate of infant adiposity, supporting the hypothesis that the degree of hyperglycemia determines the metabolic effects on the neonate [15]. More recently in the Healthy Start study from Colorado, among 804 mother-neonate pairs, Crume and colleagues reported that maternal fasting glucose, insulin resistance (HOMA-IR), and glycated hemoglobin during pregnancy were each significant independent predictors of increased neonatal adiposity, even among women without gestational diabetes [17]. In contrast, fasting cholesterol (total and HDL), free fatty acids, and triglycerides during pregnancy were not related to neonatal adiposity [17]. These findings suggest that, even in the absence of macrosomia or clinical hyperglycemia, the exposure to the diabetic intrauterine milieu causes alterations in fetal growth patterns, which likely predispose to neonatal overweight.

Childhood Growth and Obesity

The role of exposure to diabetes in utero on subsequent infant and childhood growth, obesity, and type 2 diabetes has been prospectively examined in several studies, including the Pima Indian Study, the Diabetes in Pregnancy Study at Northwestern University in Chicago, and the Exploring Perinatal Outcomes in Children (EPOCH) study in Colorado. The offspring of Pima Indian women with preexistent type 2 diabetes and gestational diabetes were larger for gestational age at birth, and, at every age, they were heavier for height than the offspring of prediabetic or nondiabetic women [12, 18, 19]. Even in normal birth weight offspring of diabetic pregnancies, childhood obesity was still more common than among offspring of nondiabetic pregnancies [20].

Researchers at the Diabetes in Pregnancy Center at Northwestern University have reported excessive growth in offspring of women with diabetes during pregnancy [21]. By age 8 years, the children were, on average, 30% heavier than

expected for their heights. In this study, amniotic fluid insulin was collected at 32 to 38 weeks of gestation. At the age of 6 years, there was a significant positive association between amniotic fluid insulin levels and childhood obesity, as estimated by the symmetry index (calculated as relative weight [measured weight divided by National Center for Health Statistics {NCHS} median weight for age] divided by relative height [measured height divided by NCHS median height for age]). The amniotic insulin concentrations in children who had a symmetry index of less than 1.0 (86.1 pmol/L, 14.4 uU/mL) or between 1.0 and 1.2 (69.9 pmol/L, 11.7 uU/mL) at 6 years of age were only half of those measured in the more obese children who had a symmetry index greater than 1.2 (140.5 pmol/L, 23.4 uU/mL, $p < 0.05$ for each comparison). Thus, this study demonstrated a direct correlation between one measure of the altered diabetic intrauterine environment and the degree of obesity in children and adolescents.

Data from the EPOCH study in Colorado demonstrated that BMI growth trajectories of children exposed or unexposed to diabetes in utero were similar from birth to 27 months [22]. However, from 27 months to 13 years, exposed offspring had a significantly greater BMI and accelerated growth velocity compared to unexposed offspring, with the most notable difference in growth velocity occurring from 10 to 13 years. Exposed offspring also exhibited a more centralized fat distribution pattern (assessed by abdominal MRI), although these associations were largely attenuated to non-significance after adjustment for maternal pre-pregnancy BMI [23]. The majority of the children in this study were prepubertal (Tanner stage 1) at the time of assessment, and it is possible that the effects of exposure to diabetes on childhood growth and adiposity may become more pronounced as children transition through puberty, as is suggested by the greater growth velocity observed predominately at older ages. Notably, the effect of gestational diabetes on accelerated growth trajectories was attenuated among exposed children who were breastfed for ≥6 months, suggesting that breastfeeding may be a postnatal exposure that can mitigate risk conferred by intrauterine exposures [24].

Other studies provide evidence for an association between exposure to maternal diabetes in utero and childhood adiposity. Project Viva [25] and an Indian study [26] demonstrated that children exposed to gestational diabetes had significantly greater skinfold thicknesses at 3 and 9 years, respectively. Similarly, a longitudinal cohort at Kaiser Permanente Northern California reported that girls born to mothers with gestational diabetes were significantly more likely to be in the top quartile of percent body fat (assessed by bioimpedance) at 6–12 years compared to mothers with glucose values <90 mg/dL at the 24–28-week 50 g, 1 h glucose screening test [27]. The above findings were all independent of maternal pre-pregnancy BMI; however, some other studies have reported that associations of gestational diabetes with offspring obesity/adiposity are attenuated after adjustment for maternal pre-pregnancy BMI [28–30]. Given that pre-pregnancy BMI is a risk factor for gestational diabetes, inclusion of pre-pregnancy BMI in the analytic model may represent overadjustment. The inconsistencies in these results could also be partly explained by differences in exposure prevalence across populations studied. The rates of obesity and diabetes (including diabetes in pregnancy) in Pima Indians exceed those of nearly all other populations. Additional studies are needed to evaluate the effect of intrauterine diabetes exposure on fetal and childhood growth, independent of maternal obesity, among different ethnic groups and among populations with milder degrees of hyperglycemia.

Abnormal Glucose Tolerance and Risk for Type 2 Diabetes

For more than 30 years, Pima Indian women have had routine oral glucose tolerance tests approximately every 2 years as well as during pregnancy [18]. Women who had diabetes before or during pregnancy were termed diabetic mothers; those who developed diabetes only after pregnancy were termed prediabetic mothers. By age 5–9 and 10–14 years, type 2 diabetes was present almost exclusively among

the offspring of diabetic women. In all age groups, there was significantly more diabetes in the offspring of diabetic women than in those of prediabetic and nondiabetic women, and there were much smaller differences in diabetes prevalence between offspring of prediabetic and nondiabetic women [31]. Recently, the SEARCH Case-Control (SEARCH CC) study provided novel evidence that intrauterine exposures to maternal diabetes and obesity are important determinants of type 2 diabetes in youth of other racial/ethnic groups (non-Hispanic white, Hispanic, and African American), together contributing to 47% of type 2 diabetes in the offspring [32]. Exposure to gestational diabetes is also associated with metabolic abnormalities in childhood and adolescence that are precursors to type 2 diabetes, including insulin resistance [26, 33], impaired β-cell function [34, 35], and reduced oral disposition index [35, 36].

Cardiovascular Abnormalities

Animal studies have shown that exposure to diabetes in utero can induce cardiovascular dysfunction in adult offspring [37, 38]. Studies in humans have reported increased systolic blood pressure in offspring of diabetic pregnancies at 3 years [25], 5 years [39], 7–11 years [40], and 10–16 years [41], independent of the child's current obesity (BMI, BMI z-score) or adiposity (percent body fat). Higher concentrations of markers of endothelial dysfunction (ICAM-1, VCAM-1, E-selectin), as well as increased cholesterol-to-HDL ratio, were reported among offspring of mothers with type 1 diabetes compared with offspring of nondiabetic pregnancies, also independent of current body mass index [42]. Children exposed to gestational diabetes who were born large-for-gestational age were significantly more likely to have developed metabolic syndrome by 11 years compared to unexposed children or those born appropriate-for-gestational age [43]. These data suggest that in utero exposure to diabetes confers risks for the development of cardiovascular disease later in life that are independent of adiposity and may be exerted in concert with genetic predisposition to diabetes or cardiovascular disease.

Does Maternal Diabetes Type Matter?

Several studies have found that the effects of exposure to diabetes in utero on future obesity and insulin resistance are similar for pregnancies complicated by preexisting type 1, type 2, or gestational diabetes [12, 21, 44, 45], although other studies disagree. Wroblewska-Seniuk and colleagues compared anthropometrics and glucose metabolism in offspring of women with pregestational diabetes (type 1 or type 2), gestational diabetes, or women without diabetes [46]. At 4–9 years of age, offspring exposed to gestational diabetes had significantly higher BMI z-score and homeostatic model of insulin resistance (HOMA-IR) compared to the other two groups; however, the prevalance of severe insulin resistance was similar between all three groups. Similarly, Boerschmann and colleagues found that the prevalence of overweight (BMI >90th percentile) among offspring exposed to gestational diabetes was significantly greater at 2 years compared to unexposed offspring and significantly greater at 8 and 11 years compared to both unexposed offspring and those exposed to maternal type 1 diabetes [47]. Offspring exposed to gestational diabetes also had significantly greater HOMA-IR at 11 years compared to both groups. However, neither of these studies adjusted for potential confounders, including maternal prepregnancy BMI.

In a study of impaired glucose tolerance in the offspring of mothers with type 1, type 2, and gestational diabetes, Silverman and coworkers found that the risk of impaired glucose tolerance was not different by type of maternal diabetes [48]. Rather, impaired glucose tolerance was closely related to the amniotic fluid insulin levels, which are indicative of the degree of fetal hyperinsulinemia. Sobngwi and colleagues also confirmed that impaired glucose tolerance and defective insulin secretory responses in adults are

associated with exposure to pregestational type 1 diabetes in utero [49]. The control population in this study was a group of adult offspring of fathers with type 1 diabetes; in theory, this controls for confounding by genetic susceptibility. These results further support the conclusion that hyperglycemia and other fuel alterations in pregnancies complicated by diabetes, and not the etiology of the mother's diabetes, are the important factors influencing risk of obesity and glucose metabolism abnormalities in the offspring.

In the Pima Indian population, Franks and colleagues found that maternal glucose levels are associated with excess fetal growth and later risk of diabetes even among women with normal glucose tolerance [50]. Birth weight was found to increase significantly with each standard deviation increase in maternal blood glucose level, and the risk of type 2 diabetes in the offspring increased 30% with each standard deviation increase in maternal glucose level. In a study of 951 mother-offspring pairs, Shapiro and colleagues reported that neonatal adiposity was positively associated with increasing maternal mid-pregnancy fasting glucose levels and insulin resistance, even within normal range [51]. The presence of excess risk of metabolic abnormalities in offspring even in glucose-tolerant mothers suggests that exposure to hyperglycemia is a continuous risk factor, and prevention of long-term consequences in the offspring may require improvement in glycemia even in pregnancies uncomplicated by diabetes.

Programming of Fetal Growth and Adiposity by Maternal Obesity

Much less is known about whether and how fetal programming is driven by exposure in utero to maternal obesity in the absence of diabetes. Multiple factors have been associated with fetal growth, in addition to maternal glucose intolerance: age, parity, race/ethnicity, weight, weight gain, smoking status, and fetal gender [52, 53]. Black race, female infant gender, and younger maternal age are associated with risk of fetal growth restriction [54–56], while advancing parity and higher maternal body size are associated with larger babies [56]. Interestingly, paternal contribution to fetal growth seems less important [52]. Maternal height and "frame size," regarded as markers of lifelong nutritional status, are important determinants of fetal growth [57]. Birth weight was shown to increase linearly with increasing pre-pregnancy BMI and with increasing weight gain during pregnancy [58–60].

An important question is whether exposure to maternal obesity during pregnancy in the absence of frank diabetes is also associated with increased obesity in the offspring, above and beyond genetic susceptibility. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study reported that offspring born to mothers with a BMI >22.6 kg/m^2 were 2–3 times more likely to have a birth weight and percent body fat (measured by skinfolds) >90th percentile compared to offspring born to mothers with a BMI <22.6 kg/m^2, independent of prenatal glucose levels [61]. Among 826 infants in the Healthy Start study not exposed to maternal diabetes, maternal pre-pregnancy BMI and gestational weight gain were each independent predictors of neonatal fat-free mass, fat mass, and adiposity (based on air displacement plethysmography) at birth [60]. Further analyses indicated that mid-pregnancy maternal fasting glucose and insulin resistance (HOMA-IR) mediated 21% of the association between maternal BMI and neonatal adiposity, even among women without gestational diabetes, while other fuels (triglycerides, nonesterified fatty acids) were not mediators [17]. These data support the hypothesis that obesity-induced insulin resistance influences neonatal body composition even in the absence of frank diabetes, through specific intrauterine effects. Increased adiposity (based on skinfolds) with increasing maternal pre-pregnancy weight and gestational weight gain was also reported by Vohr and colleagues at birth [62] and 1 year of life [63] among both infants of mothers with gestational diabetes and infants of control mothers. It has also been reported that children exposed to maternal obesity, in the absence of gestational diabetes, are at increased risk of developing the metabolic syndrome during adolescence [43]. Collectively,

these data suggest that metabolic factors that affect fetal growth and perinatal outcomes are present in obese mothers who do not fulfill the diagnostic criteria for gestational diabetes. Similarly, in SEARCH CC, exposure to maternal obesity in utero was associated with 2.8-fold increased odds for type 2 diabetes in multiethnic youth, independent of exposure to diabetes during pregnancy [32].

Genetic, Familial, or Specific Intrauterine Effects?

It is clear that the above associations are partly due to increased genetic susceptibility to obesity and diabetes inherited by offspring from their mothers. Shared genes certainly account for some of the similarity in maternal and offspring weight and risk for type 2 diabetes [64]. However, there is also strong evidence that excess growth experienced by offspring of diabetic mothers is not due to genetic factors alone. First, obesity is no more common in the offspring of women in whom diabetes developed after delivery than in those of nondiabetic women [12, 65]. Second, obesity and diabetes in the offspring of diabetic women cannot be accounted for by maternal obesity [12, 20, 32]. Third, the excessive growth seen in the offspring of diabetic mothers is not found in offspring of diabetic fathers in either the Joslin clinic or the Pima Indian series [66].

While these findings provide evidence that genetic confounding does not explain all of the effects of maternal diabetes during pregnancy on the risks of obesity and type 2 diabetes in the offspring, there are genetic mutations which have been shown to cause obesity and type 2 diabetes and are maternally transmitted [67]. Therefore, the ideal way to remove possible confounding by genetic predisposition is to examine sibling pairs in which one sibling is born before and one is born after the onset of their mother's diabetes [68]. The Pima Indian studies have examined the effect of intrauterine exposure to diabetes on risk for obesity among discordant siblings [68]. The mean body mass index in the 62 Pima Indian nondiabetic siblings born after the onset of the mother's diabetes, i.e., the offspring of the diabetic woman, was significantly higher (mean BMI difference, 2.6 kg/m^2) than among the 121 nondiabetic siblings who were not exposed to diabetes in utero, e.g., born before the onset of the mother's diabetes. In contrast, there was no significant difference between siblings born before or after their father was diagnosed with type 2 diabetes (mean BMI difference, 0.4 kg/m^2) [68]. These data support the hypothesis that exposure to diabetes in utero has effects on offspring body size that are distinct from, or act in concert with, genetic susceptibility to obesity. They point toward the role of altered maternal fuels, especially hyperglycemia, as mediators of fetal growth and risk of obesity in offspring exposed to maternal diabetes in utero.

The Growing Up Today Study [29], on the other hand, found that the 40% increased odds of being overweight among 9–14-year-old offspring of mothers with gestational diabetes was no longer significant when adjustment was made for birth weight and reported maternal BMI; the latter is considered a surrogate for genetic susceptibility for obesity. These findings suggest that either shared adverse lifestyle habits among mothers and daughters or maternal transmission of susceptibility genes accounts for part of the increased risk of obesity among offspring of mothers with gestational diabetes in addition to the intrauterine exposure to diabetes per se.

Alternatively, since insulin resistance in the mother spares glucose, amino acids, and fatty acids for placental-fetal transport [57, 69], it can be hypothesized that obese or diabetic pregnant women, who have severe insulin resistance, transport an excess of nutrients to the fetus. This results in fetal adiposity [57]. This hypothesis is entirely compatible with the original "fuel-mediated teratogenesis" hypothesis [11], as long as the metabolic pathways responsible for the abnormal fetal growth and development are also associated with an increased risk of later-life chronic disorders such as obesity, type 2 diabetes, and cardiovascular disease. Data in rats [70] show that pregestational obesity induced by

overfeeding leads to obesity, metabolic alterations, and increased adipose tissue cellularity in the offspring. Importantly, in these models, the process is independent of inherited genetic influences.

Possible Mechanisms Responsible for the Intrauterine Effects

Despite the evidence from animal and human studies that exposure to maternal diabetes and obesity in utero may have long-term programming consequences on the offspring, the specific mechanisms responsible for these effects are not fully understood.

Dysregulation of the Adipo-Insular Axis

One of the proposed mechanisms is a resetting of the adipo-insular axis in exposed newborns. The adipo-insular axis is a bidirectional feedback loop involving leptin released by adipocytes and insulin released by pancreatic β cells [71]. As body fat stores increase, leptin levels increase, which in turn reduce insulin production. Increased levels of insulin stimulate the biosynthesis and secretion of leptin from adipocytes [71]. This feedback loop found in animal studies [72, 73] is now also supported by human data (71).

Several studies suggest that the adipo-insular feedback loop may be programmed in utero [74–76]. Elevated cord blood leptin concentrations were found in infants of mothers with type 1 diabetes (24.7 ng/mL) and of mothers with gestational diabetes (29.3 ng/mL), as compared with controls (7.9 ng/mL) [77], even after controlling for differences in birth weight. This suggests a direct influence of maternal hyperglycemia on fetal fat mass and leptin levels. In two other studies, exposure to gestational diabetes was associated with both hyperleptinemia and hyperinsulinemia in the newborn [74, 78]. This suggests that fetal overnutrition by exposure to maternal diabetes and obesity in utero may lead to increased insulin secretion and adiposity in the offspring despite an increase in plasma leptin concentrations, which are unable to control the release of insulin and the increase in fetal adiposity [74]. Induction of leptin resistance in utero may therefore be hypothesized as a potential mechanism for later development of obesity in offspring exposed to overnutrition in utero. Inefficient leptin action programmed in utero may lead to hyperphagia, decreased fat oxidation, increased tissue triglyceride levels, insulin resistance, and obesity later in life [71, 73, 79].

Fetal Malprogramming of Hypothalamic Neurons: "Functional Teratogenesis"

An interesting hypothesis relating hormonal changes present at birth in offspring exposed to diabetes in utero has been formulated by Plageman and colleagues [80]. When present in increased concentrations during critical ontogenetic periods, hormones (such as insulin and leptin) can act as "endogenous functional teratogens" [80]. As example, untreated diabetes in pregnant rats leads to "malprogramming" of hypothalamic neuropeptidergic neurons in offspring, leading to increased orexigenic neuropeptide Y and agouti-related peptide, which could contribute to hyperphagia and later development of overweight. Islet transplantation in pregnant rats with gestational diabetes normalizes blood glucose and prevents these acquired alterations [81].

Defective Insulin Secretion in Offspring Exposed to Maternal Diabetes

In Goto-Kakizaki (GK) rats, the diabetic syndrome is produced by streptozotocin injection or glucose infusion**.** These rats do not have any genetic predisposition for diabetes**,** nor can their diabetes be classified as type 1 or 2. In these studies, hyperglycemia in the mother during pregnancy leads to impairment of glucose tolerance and decreased insulin action and secretion in adult offspring [82, 83].

Impaired insulin secretion has also been observed in human studies [84]. Among 104 normal glucose-tolerant Pima Indian adults, the acute insulin response was 40% lower in offspring of diabetic versus prediabetic mothers [85]. In a different population, Sobngwi and colleagues [49] showed that adult offspring of women with type 1 diabetes during pregnancy had a significantly decreased insulin secretory response to glucose when compared with offspring of type 1 diabetic fathers, while there were no differences between groups with respect to insulin action. Lastly, in a longitudinal study of obese adolescents, Holder and colleagues reported that the oral disposition index, which reflects insulin secretion adjusted for insulin resistance, was significantly lower at 12 and 15 years of age among adolescents exposed to gestational diabetes compared to unexposed adolescents [35]. These results remained significant even after adjustment for current BMI, suggesting that the β cells of the exposed offspring were impaired and unable to compensate for increasing insulin resistance, regardless of adiposity. Based on the observations made in rats and supported by the human findings, it may be hypothesized that exposure to hyperglycemia during critical periods of fetal development "programs" the developing pancreas in a way that leads to a subsequent impairment in insulin secretion. This, coupled with an increased risk for obesity, resulting from overnutrition in utero, may lead to an early onset of type 2 diabetes, especially in individuals at high genetic risk.

Epigenetics and Intergenerational Transmission of Risk

Epigenetics refers to changes in gene expression via DNA methylation, histone modification, and noncoding RNA gene silencing that do not affect the DNA sequence but can be passed from generation to generation. In mouse models, maternal hyperglycemia has been reported to alter DNA methylation, subsequent expression of insulin-like growth factor 2 (IGF-2), and islet cell function in offspring [86, 87]. Emerging data from human studies indicate that exposure to maternal hyperglycemia in utero alters DNA methylation of placental leptin and adiponectin genes, as well as thousands of other genes in umbilical cord tissue and blood that have been implicated in metabolic disease pathways [88]. While such findings hold promise of understanding the mechanisms driving the effects of maternal diabetes for offspring health, the fields of epigenetics and related "omics" (metabolomics, proteomics, nutrigenomics, etc.) are still in the early stages and rapidly evolving. As new technologies become widely available and methodologies are standardized across laboratories, these initial results must be replicated and expanded upon to fully understand how fetal programming influences the intergenerational transmission of obesity and chronic disease risk.

Interventions to Improve Offspring Outcomes

Given the adverse health outcomes associated with intrauterine exposure to maternal diabetes for offspring in observational and animal studies, it is important to know whether successful management of maternal hyperglycemia improves health outcomes in offspring. In a multicenter trial of 958 pregnant women with mild gestational diabetes, Landon and colleagues reported that treatment of mild gestational diabetes with dietary intervention, blood glucose self-monitoring, and (if needed) insulin therapy resulted in significantly lower mean birth weight and fat mass, the proportion of large-for gestational age infants, and the need for cesarean delivery [89]. Similarly, the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial reported that macrosomia occurred in only 5.3% of pregnancies receiving treatment for mild gestational diabetes

compared to 21.9% in the untreated group [90]. However, in both of these studies, the neonatal effects did not persist into childhood: by 4–10 years of age, there was no difference between groups for offspring BMI, overweight/obese status, or metabolic outcomes [90, 91]. These findings are limited by the population enrolled, as it is possible that successful management of more severe maternal hyperglycemia would have more persistent effects on offspring. Additional follow-up studies are needed to better understand the long-term effects of treatment of gestational diabetes on offspring.

There is also a need to understand the degree to which gestational diabetes can be prevented in high-risk women, and whether prevention has beneficial effects on offspring. This has been the subject of dozens of clinical trials in recent years, although few have examined offspring outcomes beyond neonatal complications or birth weight. The majority of clinical trials have been conducted during pregnancy and have emphasized lifestyle modification (dietary changes, physical activity, or both) to prevent gestational diabetes. The largest trials to date, LIMIT (Australia) and UPBEAT (United Kingdom), which collectively enrolled almost 4000 overweight/obese pregnant women, had no effect on the incidence of gestational diabetes or large-for-gestational age infants [92, 93]. In a recent meta-analysis of 29 clinical trials, Song and colleagues concluded that prenatal interventions can reduce the risk of gestational diabetes up to 20% when they begin prior to 15 weeks gestation, while interventions that begin after 15 weeks gestation are ineffective [94]. However, effects of prenatal interventions on offspring health beyond birth outcomes are still unknown. Given the early timing of the potential mechanisms responsible for the intrauterine effects of diabetes exposure, and the challenges to commencing an intervention early in pregnancy, it is likely that interventions that reduce diabetes and obesity risk in women prior to conception have the greatest potential for improving offspring health outcomes. This approach has been largely underutilized to date, and studies that develop and evaluate effects of a preconception intervention on short- and long-term health outcomes for offspring are needed.

Clinical and Public Health Implications

The long-term effects of exposure to maternal diabetes during childhood and over the life course have been described as a vicious cycle [95]. Children whose mothers had diabetes during pregnancy are at increased risk of becoming obese and developing diabetes at young ages. Many of these female offspring already have diabetes or abnormal glucose tolerance by the time they reach their childbearing years, thereby perpetuating the cycle. A remaining research need is to derive risk estimates for childhood obesity, impaired glucose tolerance, and type 2 diabetes that are attributable to exposure to maternal diabetes in utero, in various racial/ethnic groups.

If maternal obesity during pregnancy drives fuel-mediated teratogenesis, the public health consequences are enormous, since obesity is widespread and increasing. Studies are needed to disentangle the relative contributions of various fuels to the long-term effects on childhood risks for obesity and impaired glucose metabolism in offspring of obese pregnant women.

Finally, more information is needed to determine the most effective strategies and interventions to address the risk of chronic metabolic diseases in the infant of the diabetic mother. However, it is increasingly clear that public health efforts to prevent obesity and type 2 diabetes should focus not only on adult lifestyle risk factors but also on prenatal exposure to hyperglycemia and obesity in utero. Reduced obesity in women of reproductive age and prevention of excessive weight gain during pregnancy may not only decrease the risk of gestational diabetes in the mother but will likely also reduce the risk of excess fetal growth, future obesity, and type 2 diabetes in the offspring.

Editor's Comments and Question

Given that insulin stimulates white adipogenesis as well as lipogenesis, the excess adiposity of infants of diabetic mothers could in theory reflect an increase in white adipocyte number and/or size. In theory, an increase in adipocyte number (hyperplasia) could provide a larger pool of cells for future triglyceride accumulation; on the other hand, an increase in adipocyte size (hypertrophy) can be associated with adipocyte dysfunction and impaired lipolysis, which could also facilitate development of obesity.

Studies performed long ago[a] found an increase in the size of subcutaneous white adipocytes in stillborn infants of diabetic mothers; adipocyte volume appeared to correlate with maternal blood glucose concentrations. Adipocyte hypertrophy has also been demonstrated in the offspring of obese and diabetic rodents and sheep[b]. Whether or not adipocyte number is also increased in the offspring of obese or diabetic pregnant mothers is currently unclear.

The distribution of adipose tissue has important effects on insulin sensitivity and insulin secretion and modulates the risks of glucose intolerance and fatty liver disease.

Do we know anything about the relative distribution of visceral and subcutaneous fat in offspring of diabetic mothers at birth or later in childhood?

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Authors' Response

Several studies have reported that children exposed to maternal diabetes or increased glucose levels in utero are more likely to have central obesity, measured by waist circumference[a–e], waist-to-height ratio[f], and dual X-ray absorptiometry (DXA)[g]. Few studies have specifically measured visceral and subcutaneous fat by magnetic resonance imaging (MRI), with conflicting results. The Exploring Perinatal Outcomes in Children (EPOCH) study reported an increase in both visceral and subcutaneous fat (measured by MRI) and a more centralized fat distribution (higher ratio of subscapular to triceps skinfold thickness) in 461 children aged 6–13 years exposed to gestational diabetes compared to unexposed children[h]. In contrast, a longitudinal study of 210 Latino children aged 8–13 years reported no differences in visceral or subcutaneous fat among exposed versus unexposed children[i], although all children were overweight. Thus, while it appears that children exposed to gestational diabetes do indeed have increased central versus peripheral adiposity, it is not clear whether this observation is due specifically to increased visceral adiposity. Further work is needed to understand how fat distribution may change in exposed children as they grow and progress through puberty, a period during which visceral adiposity begins to increase in all children[j].

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Endocrine Disruptors as Obesogens

14

Leonardo Trasande and Bruce Blumberg

Introduction

Substantial effort has been devoted to explaining secular trends in childhood obesity and metabolic risks to unhealthy diet and physical activity. It is plausible, for example, that a child who ingests 50 calories more per day would gain an additional 5 pounds as fat over a year, if that intake is not matched with an increase in energy expenditure [1]. If a similar dietary change has occurred over the cohort of American children, then dietary changes would account for a significant portion of the increase in childhood obesity.

While data from the National Health and Nutrition Examination Survey suggest that adult caloric intake increased over the period between 1971–1975 and 2003–2004 [2], the Bogalusa Heart Study found no such increase across the 10-year-old cohorts they followed from 1973 to 1994 [3], and more recent studies suggest that BMI is 2.7 points higher now than in 1986 at the same levels of caloric intake and energy expenditure [4]. Ecologic data from the Youth Risk Behavior Surveillance System provide somewhat stronger support for the notion that changes in physical activity patterns may explain the observed increases in obesity. Enrollment in physical education classes declined among high school students from 42% to 28.4% over the period 1991–2003. From 1977 to 2001, walking to school decreased from 20.2% to 12.5% (as a proportion of total trips) [5]. More recent data, however, reduce the likelihood of this secular trend contributing to changes in adolescent obesity [6].

While these and other studies are suggestive, the major conclusions drawn are that increased caloric intake and decreased exercise levels may have a partial role in the pathogenesis of obesity and metabolic risks. Since it is unlikely that the human genome has changed significantly in a single generation to have generated an increased susceptibility to excess weight gain in early life, we are left with the reality that factors in addition to diet and exercise represent important risks for obesity and metabolic disorders—environmental influences are among these important factors. In contrast to diet and physical activity, which can require intensive attention, effort, and costs to modify through behavioral and other interventions, government action can fundamentally transform the environmental influences to prevent disease and disability. The costs of regulations to limit environmental obesogens can also be much lower than the benefits to society.

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The notion that synthetic chemicals in the environment can disrupt metabolism was first and most definitively described with tributyltin (TBT), a fungicide used to prevent fouling of the hulls of ships [7–9]. In laboratory studies, TBT selectively activates peroxisome proliferator-activated receptor (PPARy) and its heterodimeric partners, the 9-cis retinoic acid receptor (RXR) [10]. PPARy has long been known as a target for pharmaceutical drugs intended to treat diabetes, adding to the plausibility that synthetic chemicals created for other purposes can influence these master receptors that organize carbohydrate and lipid metabolism [8]. In animal studies, TBT exposure in utero has produced adiposity in mice, with effects that can be transmitted transgenerationally, such that the "great-grandchildren" of mice exposed during pregnancy to TBT can become obese without additional exposure [11, 12].

Over the past two decades, rapidly accumulating scientific evidence has expanded this mechanistic framework to recognize that multiple pathways can be influenced by an even broader array of synthetic chemicals, with characteristic metabolic disruption across multiple endocrine organs and tissues [13, 14]. PPARs such as PPAR-gamma require heterodimerization with RXRs, binding together on target DNA to activate the expression of downstream genes [15]. Sex steroid pathways have also been proven to produce sex-specific effects on body mass [16].

The remainder of this chapter focuses on three categories of chemicals for which the evidence in laboratory, animal, and human studies is the most convincing: phthalates, bisphenols, and persistent organic pollutants. For each, we describe pathways of exposure and methods to limit exposure. We then close with a discussion of the disease burden and costs that can be traced to chemicals that contribute metabolic risks and opportunities for policy action to reduce exposures to the most hazardous chemicals that may contribute.

Phthalates

Phthalate esters have a diverse array of uses in consumer products, and they can be classified into two categories. Low molecular weight (LMW) phthalates are frequently added to shampoos, cosmetics, lotions, and other personal care products to preserve scent [17], whereas high molecular weight (HMW) phthalates are used to produce vinyl plastics used in many applications ranging from flooring, clear food wrap, and intravenous tubing [18]. Within the HMW category, di-2-ethylhexylphthalate (DEHP) is of particular interest because industrial processes to produce food frequently use plastic products containing DEHP [19], and its metabolites are often considered as a subcategory.

Mono-(2-ethylhexyl)phthalate (MEHP), a DEHP metabolite, increases expression of peroxisome proliferator-activated receptor (PPAR)-gamma [20] which plays key roles in lipid and carbohydrate metabolism, providing biological plausibility for the potential influence of DEHP metabolites in childhood obesity and insulin resistance. Laboratory studies have found that metabolites of phthalates promote release of interleukin-6, a pro-inflammatory cytokine [21], and oxidant stress [22]. This is important because oxidant stressors appear to diminish insulin-dependent glucose transport activity [23] and to modify the endothelial relaxant nitric oxide, promoting vasoconstriction, platelet adhesion, and release of inflammatory cytokines such as interleukin-1 [24, 25]. In experimental models and patients with primary hypertension, there is increased release of oxidant free radicals by endothelial cells throughout the body [26]. Emerging animal evidence also suggests that DEHP may produce arrhythmia [27], change metabolic profiles, and produce dysfunction in cardiac myocytes [28]. This raises the possibility of phthalates as a contributor to cardiovascular risk, independent of obesity.

Of the three cross-sectional studies in children and adolescents, one found no associations of urinary phthalate concentrations in 1209 children and adolescents in 1999–2002 NHANES with

unstandardized measurements of BMI (body mass index) or WC (waist circumference) [29] although patterns of association varied by age and gender. The second, in a population of largely Latino, New York City (NYC) children [30], examined urinary phthalates measured in 6–8-year-olds and associations with BMI and WC 1 year later, stratifying models to examine for effects within overweight/normal BMI subpopulations. While whole-sample associations were not observed, Teitelbaum and coworkers identified positive relationships with body mass measures in relationship to log-transformed phthalate metabolites for monoethyl phthalate, or MEP, and the sum of all LMW phthalate metabolites (MEP, mono-n-butyl-phthalate or MBP, mono-isobutyl phthalate or MiBP, and mono-(3-carboxypropyl) phthalate or MCPP). Finally, in the third study, analyses of NHANES 2003–2008 identified increases in odds of overweight, obese, and BMI Z-score associated with log-transformed LMW metabolites among non-Hispanic Blacks in stratified, multivariable models, but not in other subpopulations. Longitudinal studies exploring the relationship between prenatal phthalates and childhood growth discovered different results in males and females, predominantly resulting in negative associations with growth in males [31–33]. One limitation of all studies was the infrequency of phthalate measurements during pregnancy. This is important because pharmacokinetic studies in adults suggest that phthalates have a half-life in the range of 12–48 h, respectively [34], and fat deposition may disrupt kinetics as well [35].

Bisphenols

Bisphenol A (BPA) is used to manufacture polycarbonate resin and is a breakdown product of coatings that prevent metal corrosion in food and beverage containers [36]. A comprehensive, cross-sectional study of dust, indoor and outdoor air, and solid and liquid food in preschool age children [37] suggested that dietary sources constitute a major source of BPA exposure. Given the mild estrogenic activity of BPA [38], and the known association of obesity with increased estrogen levels in males [39], potentially gender-specific increases in weight gain are plausible. BPA also reduces the function of adiponectin, which protects against oxidant stress, insulin resistance, and heart disease [40]. BPA has been documented to trigger the differentiation of preadipocytes into adipocytes; to increase the quantity of stored fat [41]; to disrupt pancreatic β-cell function in vivo [42], producing insulin resistance and glucose intolerance [43]; and to affect glucose transport in mouse adipocytes. Disruption of these metabolic and hormonal processes has been documented in environmentally relevant doses [40, 41, 44].

To date, the epidemiologic evidence for the role of BPA in childhood obesity has been chiefly cross-sectional. The first study leveraged NHANES 2003–2008, identifying relationships of quartile and logarithm-transformed urinary concentrations with BMI Z-score and obesity. Controlling for race/ethnicity, age, caregiver education, poverty/income ratio, gender, serum cotinine, caloric intake, television watching, and urinary creatinine, children in the lowest BPA quartile had a lower estimated prevalence of obesity (10.3%; 95% CI, 7.5–13.1) than those in the second, third, or fourth quartiles (20.1%, 95% CI, 14.5–25.6%; 19.0%, 95% CI, 13.7–24.2%; and 22.3%, 95% CI, 16.1–27.9%, respectively). Obesity was not associated with exposure to other environmental phenols commonly used in other consumer products, such as sunscreens and soaps. However, explanations of the association could not rule out the possibility that obese children ingest food with higher BPA content or that obese children have greater adipose stores of BPA [45].

Three more recent longitudinal studies have yielded positive, albeit not completely consistent results, although these studies were all limited by infrequent measurements of BPA in pregnancy [46–48]. This is important because pharmacokinetic studies in adults suggest that BPA has a short half-life in the range of 4–43 h [34], and fat deposition may disrupt kinetics of BPA elimination [49]. Studies with serial BPA measurements have

identified Pearson correlation coefficients in the range of 29–56% over 1–6-month periods [50–52]. Similarly, data from Generation R, a prospective, longitudinal multiethnic birth cohort study which has longitudinally followed 9778 pregnancies and children born between 2002 and 2006, suggest that reliability of a single urine specimen as a marker of pregnancy-wide BPA exposure is modest, as estimated by the intraclass correlation coefficient (0.32) in 80 women in which samples were analyzed at <18, 18–25, and >25 weeks gestation. While we note that weak indices of early exposure should bias estimates of association toward the null [53–55], this post hoc justification has limits. There remains a need for studies of individual subjects with biospecimens from time points when BPA and phthalate exposure could more plausibly and permanently disrupt metabolic and/or endocrine homeostasis, producing chronic caloric imbalance.

The "thrifty phenotype" hypothesis first described by Barker and coworkers [56, 57] suggests that early-life adaptations to poor in utero nutritional conditions can produce a profile of maladaptation after birth in which the ability to acquire energy results in increased adiposity beginning in childhood and cardiovascular risks later in life. A recent association of phthalates with low birth weight (LBW), as well as data associating increases in BPA with reductions in estimated fetal weight, would be consistent with this idea, although the thrifty phenotype hypothesis remains largely unexplored. Most typically, studies have examined risk factors for obesity insofar as they affect the trajectory of postnatal growth; however, this approach fails to recognize the different trajectories of fetal growth and potentially more impactful moments of exposure. Increasingly precise ultrasonographic approaches to estimating fetal weight at different periods in gestation now permit comparison of estimated fetal weight against optimal fetal weights customized by individual profiles and detection of health consequences of different nutritional and chemical exposures [58, 59].

Persistent Organic Pollutants

Persistent organic pollutants (POPs) are a diverse class of chemical contaminants, which degrade slowly and are widely distributed in the environment [60]. We focus here on four categories of POPs for which exposures persist at levels relevant for possible disruption of developmental metabolic processes.

Organochlorine pesticides (OCPs) such as dichlorodiphenyltrichloroethane (DDT), chlordane, and lindane have been banned through the Stockholm Convention [61], and concentrations of DDT and its main metabolite, dichlorodiphenyldichloroethylene (DDE), are reported to be decreasing in the environment [62]. However, current levels of DDE are known to be antiandrogenic [63], raising the possibility of sexually dimorphic effects on body mass, in addition to the estrogenicity of DDT [64], and effects on adipocyte differentiation [65].

Polychlorinated biphenyls (PCBs) were banned by the US Environmental Protection Agency in 1979, yet exposures continue in the United States due to latent environmental contamination of food (fish in particular) [66], soil [67], and water [68]. Low levels of PCB have long been known to inhibit thyroid hormone [69], which plays a critical role in human metabolism. Dioxin-like PCBs are also potent aryl hydrocarbon receptor (AhR) agonists, inducing xenobiotic metabolizing enzymes that can augment generation of reactive oxygen species [70], which are well known as major mechanisms underlying cardiometabolic risks.

Polybrominated diphenyl ethers (PBDEs) are structurally similar to PCBs and have been extensively used as flame retardants in household products, such as textiles, foam, and electronic devices [60, 71, 72]. Although California and other states have banned penta- and octa-brominated PBDEs, deca-PBDEs remain in use and are found in computers, television sets, mobile phones, construction materials, polyurethane foam mattresses, cushions, carpets, and draperies. Deca-PBDEs are readily metabolized into lower-brominated forms, and one such compound, PBDE 47, increases adipocyte differentiation in a dose-dependent manner [73]. Rats perinatally exposed to PBDEs displayed similar responses upon stressful stimulation in later life, including increased systolic BP and cardiovascular reactivity [74]. PBDE exposures in animal studies have induced oxidative stress-mediated hepato- and nephrotoxicity [75], in addition to decreased vasopressin levels, which

indirectly impact BP via regulation of blood volume, plasma osmolality, and water retention [76].

Perfluoroalkyl compounds (PFCs) are fluorine-based halogenated hydrocarbons with powerful surfactant and water-repelling properties. PFCs are used as surfactants and stain-resistant coatings on many products, including upholstery, carpet, food packaging, and nonstick cookware, among others [77]. Four longer-chain PFCs (≥8 carbon) were scheduled to be phased out at the end of 2015 [78], yet numerous PFCs continue to be used, and effects of past longer-chain PFC exposures remain relevant given the 7–15-year half-lives of these chemicals. A study of PFC use trends between 1996 and 2010 in Sweden reported increases (11%/year) in perfluoroalkylbutane sulfonate (PFBS), a four-carbon substitute for the longer-chain PFOS. PFBS is increasingly being identified as a food contaminant, suggesting that diet may be a relevant route of exposure [79]. PFCs are reported to activate the nuclear receptors, PPAR-alpha and PPAR-gamma, which play key roles in lipid and glucose metabolism, providing biological plausibility for PFC-induced childhood obesity and insulin resistance. In cell cultures using the 3T3-L1 preadipocyte system, multiple PFCs increased cell number, increased total triglyceride, and altered expression of genes associated with adipocyte differentiation and lipid metabolism [79, 80]. Developmental PFC exposures in mice have also been found to increase leptin and insulin levels in midlife [81]. Microvascular endothelial cell culture studies have also shown that PFC exposure increases reactive oxidative species and induces endothelial permeability [82], which plays a critical role in ischemic renal injury [83].

Epidemiologic studies of POPs have yielded results suggesting substantial contribution to obesity and other metabolic outcomes in youth. Pooled analyses of multiple European birth cohorts have associated prenatal PCB-153 (but not DDE) with decreased birth weight [84] and DDE with accelerated infant weight gain [85]. While associations of prenatal OCP/PCB exposures were absent in the Collaborative Perinatal Project [86], increases in obesity among Mexican-American boys in the CHAMACOS study were associated with DDT and DDE levels in pregnancy [87]. Prenatal DDT exposure has been associated with hypertension diagnosed in women <50 in the California-based Child Health and Development Studies [88].

Few studies have examined PBDE early-life exposures in relationship to postnatal body mass and cardiovascular outcomes. A small cross-sectional study of 43 children found that serum PBDE levels were related to increased cardiovascular stress responses [89]. The CHAMACOS cohort identified positive associations of maternal PBDE with BMI Z-score in boys, with negative associations in girls, as well as an inverse association of PBDE at age 7 with simultaneously measured BMI Z-score [90].

Perfluorooctanoic acid (PFOA) levels in pregnant women have been associated with increases in pregnancy-induced hypertension [91–93]. There is also some evidence that PFCs may impact birth weight and early life growth trajectories [94, 95]. Infants in the Norwegian Mother and Child Cohort Study (MoBa) with higher levels of PFCs in utero were found to have slightly lower birth weight than those exposed to lower levels [94]. Danish infants exposed in utero to PFCs tended to weigh less at 5 and 12 months of age than less exposed children, and this effect was more pronounced in boys [95]. More research is required to elucidate these effects and whether they are related to long-term impacts on BMI [96, 97]. However, the relationship between altered fetal growth, early-life growth restriction, and CVD in adulthood has been widely accepted, due to the work from the Dutch Winter Hunger Study and, more recently, the Biafran famine [98, 99]. Although longitudinal studies of a population exposed to PFCs due to emissions from a chemical plant did not associate antecedent PFC exposure with increases in obesity [100], these antecedent exposures may not reflect effects in the general population, and were modeled from resident address and water measurements, which have modest predictive value in children (62%) [101].

Prevention of Obesogenic Exposures

While uncertainty exists about mechanisms of effect as well as timing of exposures that may contribute to early-life adiposity, there are

safe and simple steps that practitioners can take to advise families to reduce exposure. Choosing personal care products labeled as "phthalate-free" has reduced urinary levels of MEP by 27% in young girls in one study [102]. A fresh food intervention has produced even larger reductions in exposure [103]. Consumption of a diet according to World Health Organization recommendations has been associated with lower levels of PFCs and PCBs [104, 105].

Ultimately, policy action to regulate endocrine-disrupting chemicals could produce more rapid reductions in childhood obesity and net economic benefits to society. While the FDA recently banned its use in baby bottles and sippy cups, it recently declined to ban BPA in other food uses [106]. Natural and synthetic alternatives to BPA exist, and a recent estimate suggests that naturally derived oleoresin linings cost 2.2 cents more than those derived using BPA [107]. If 100 billion aluminum cans are produced annually [108], then the incremental cost of replacing BPA with oleoresin would be $2.2 billion. In one scenario based on reduction of BPA, 6200 cases of childhood obesity and $748 million in annual associated costs could be prevented by substitution of BPA with an alternative free of health effects [109].

It should be noted that endocrine-disrupting chemicals have a broad array of effects across the life course, and there are additional benefits to protecting against chemical obesogen exposures insofar as these exposures have other associated health effects. Recent studies suggest that the costs of EDCs annually are €163 billion in Europe and $340 billion in the United States [110, 111]. Of these costs, metabolic effects comprise €15 billion and $5 billion, respectively. These are likely to be underestimated because the researchers examined less than 5% of known EDCs (for which the most data were available), and only a subset of medical conditions linked to these EDCs, and did not include costs of suffering and other indirect consequences of conditions downstream of obesity.

Editor's Comments and Question

Experiments done many years ago at the National Institute of Environmental Health Sciences[a] demonstrated that neonatal treatment with diethylstilbestrol (DES) causes obesity in rodents. Bisphenol A (BPA) has structural similarities to DES, exerts adipogenic effects in vitro, and induces weight gain in rodents treated in the perinatal period. These findings suggest that exposure to BPA during a critical developmental window may "program" the development of obesity, insulin resistance, and possibly type 2 diabetes, at least in rats and mice. This has been more difficult to prove in humans, in part because (a) a critical window for toxic exposure in humans has not yet been defined and (b) longitudinal studies have not yet confirmed the hypothesis that exposure of human infants to BPA in pregnancy programs weight gain in childhood [46 and 47].

Nevertheless, the ubiquity of BPA and other endocrine disruptors, and their potential ramifications for reproductive development and malignancy[b], has for good reasons raised concerns among the public. In response, manufacturers have in some cases replaced BPA in their products with bisphenol S or related compounds. Are these compounds any safer than BPA?

Additional References for Editor's Comments and Question

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Authors' Response

In the absence of regulatory action to limit BPA exposure, BPA is already being replaced with synthetic alternatives that have been identified in paper products [57] and human urine [58], including bisphenol S (BPS). The current regulatory framework does not require comparison of newer chemicals such as BPS for similarity in structure-function relationships and potential toxicity to BPA [59]. Much less is therefore known about BPS than BPA regarding public health consequences of exposure.

The few studies that have had the opportunity to study BPS have identified similar genotoxicity and estrogenicity to BPA [60–65] and greater resistance to environmental degradation than BPA [66, 67]. Substitution of BPA with BPS may therefore yield the same consequences for obesity and cardiometabolic conditions. Regulatory agencies should consider the potential toxicity of as-yet untested substitutes for BPA in deciding how to further restrict BPA in food uses.

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Part VI

The Roles of Diet and Energy Expenditure in Obesity Pathogenesis and Complications

Early Feeding Practices and Development of Childhood Obesity

15

Megan H. Pesch and Julie C. Lumeng

Introduction

Early feeding practices are believed to be an important contributor to obesity risk in early childhood. Feeding practices can be considered to encompass both what and how caregivers, usually parents, feed their children. In this chapter, we will review the evidence to support links between feeding practices and the development of childhood obesity. We will begin by reviewing the evidence linking infant feeding practices and obesity, including breastfeeding, formula composition, the timing of introduction of solid foods, and bottle use.

Next, we will move on to consider the evidence for associations between parent feeding practices in toddlerhood and beyond with child obesity. Specifically, we will review the main constructs typically used to conceptualize parental feeding practices, including pressure, monitoring, restriction, promotion of autonomy, repeated exposure, modeling, and teaching. We will also briefly consider the beliefs about child obesity and feeding that often underlie these practices. We will consider the home feeding environment with a focus on the role of television, family mealtimes, and timing of eating in childhood obesity. We will consider the composition of food served, including dietary variety.

Finally, we will consider the role of the child in shaping the parent's feeding behavior. Children are not "blank slates", but rather active participants in the parent-child interaction around feeding. Just as parents may shape children's obesity risk, children's individual traits and behavior shape parenting practices. We will consider children's food preferences, eating in the absence of hunger, responsiveness to hunger and satiety, emotional or stress eating, and temperament as predictors of parent feeding practices. We will close by considering directions for future research.

It is important to note that the vast majority of research on this topic to date has focused on mothers. Future work should include fathers and father figures, as they also play critical roles in parenting and shaping a child's obesity risk. In addition, much of the work on early feeding practices has occurred in US or European populations of children, most of whom are white and relatively well resourced. Future work should consider whether the findings are generalizable to other populations of children. Finally, understanding feeding practices is complicated

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by challenges in measurement. The vast majority of studies have gathered data via maternal self-report on questionnaires, which has inherent bias. A growing body of work has employed videotaped observation, though this approach has its own limitations. Ultimately, capturing feeding practices requires a multi-method approach that can consolidate, and facilitate interpretation of, available evidence.

Feeding in Infancy and Childhood Obesity Risk

Infancy is a critical period for obesity risk. The rate of weight gain in infancy is associated with future obesity, and food preferences and feeding practices established in infancy often track into later childhood and adulthood. Parents of infants may also be particularly responsive to interventions designed to shape feeding practices, as behaviors may not yet be firmly established. We review here the evidence linking breastfeeding, formula composition, and introduction of complementary foods with childhood obesity.

Breastfeeding

Breastfeeding promotion as a target for obesity prevention in infancy and early childhood has received substantial attention and a great deal of study. A major motivator for this focus has been the low rates of breastfeeding in low-income and minority populations with high obesity risk, which has led interventionists to suspect a causal relationship. Mechanisms involving improved satiety responsiveness and metabolic programming related to breast milk composition have been posited. Support for the breastfeeding-obesity link grew as observational cohort studies repeatedly showed small protective effects. More recent work, however, has called into question the association of breastfeeding and obesity prevention and particularly whether the association is causal. Specifically, large observational cohort studies that have been able to more robustly attend to residual confounding have not detected an independent association [1]. Most recently, no effect of breastfeeding on obesity risk at middle childhood was found in a large randomized controlled trial. The Promotion of Breastfeeding Intervention Trial involved more than 17,000 healthy newborns with more than 80% retention to age 11 years and found no statistically significant effect of breastfeeding on children's body mass index [2]. In summary, although breastfeeding has many critical benefits, focusing on breastfeeding promotion for the purpose of obesity prevention is unlikely to be effective.

Formula Composition

Formula-fed infants are larger than breastfed infants by the end of the first year of life [3]. It has been proposed that the composition of infant formula may be a critical contributor to the rate of weight gain in infancy. A key proposed mechanism for this effect is the protein composition of infant formula. In one study, infants consuming protein hydrolysate formula, as compared to those fed cows' milk formula, were satiated sooner and had more normative (less excessive) rates of weight gain [4]. There are several hypotheses for the mechanism of this effect. Free glutamate, which is abundant in human breast milk, is thought to act as a satiety signal. Conversely, high levels of ingested protein may promote production or secretion of hormones that increase infant weight gain and growth: circulating levels of insulin and insulin-like growth factor 1 (IGF-1) are lower in infants fed breast milk or low-protein formula than in those fed higher-protein formula. The effect of protein on infant growth rates has been demonstrated in a randomized controlled trial design. Specifically, among more than 1000 infants randomized to low- versus high-protein infant formula, those consuming the lower-protein formula, which is most similar in protein content to breast milk, had lower rates of weight gain up to age 6 years [5]. In summary, infant formula composition, particularly with regard to protein content, may be a valuable strategy for shaping infant weight

gain trajectories. Importantly, however, the long-term effects on growth, obesity risk, and other important outcomes remain unknown.

Complementary Foods: Timing of Introduction and Composition

Complementary foods, also known as "solids," are the foods given to infants besides formula or breast milk. Parents often introduce complementary foods earlier than the recommended age of 6 months because they perceive the infant to be hungry and presume that these foods increase satiety more than formula or breast milk alone. This practice is more common in lower-income and racial/ethnic minority groups with the highest risks of obesity, which has led to the hypothesis that the early introduction of solid foods could increase the risk of excess weight gain. Advising against the early introduction of solid foods is therefore frequently included in intervention trials designed to prevent obesity. However, systematic reviews find no consistent association between the timing of introduction of complementary foods and risk of obesity [6].

While the majority of research on complementary foods has focused on the timing of their introduction, few studies have examined their composition. The limited available data suggest that greater rate of weight gain in infancy is linked with higher dietary protein, but not with dietary fat. Future work might consider focusing on the macronutrient composition of complementary foods as opposed to the timing of their introduction.

Feeding Behaviors, Practices, and Styles

Parents' feeding behaviors, practices, and styles are generally considered to be the approaches parents take to achieve a certain dietary intake or growth pattern in their child. *Behaviors* are generally considered to include pressuring or restricting intake. In contrast, *practices* comprise the specific approaches employed, such as bribing a preschooler or spoon-feeding a toddler to pressure intake. Finally, *styles* are generally conceptualized as the tone that pervades these behaviors and practices. For example, pressure can be delivered with varying degrees of sensitivity. Feeding style is generally defined similarly to the classic categorization of parenting styles. Specifically, very sensitive parents (e.g., those who are attuned and responsive to their child's cues and needs) but who also impart many rules and a great deal of structure are considered *authoritative*. Less sensitive parents with many rules and a great deal of structure are considered *authoritarian*. Sensitive parents with fewer rules and less structure are considered *permissive or indulgent*. Finally, less sensitive parents with fewer rules and less structure are considered *neglectful*.

The measurement of feeding behaviors, practices, and styles is methodologically challenging [7]. Specifically, most studies rely on parent self-report questionnaires, which have the benefit of capturing patterns over extended periods of time, but may be influenced by social desirability bias. Other studies have used videotaped mealtime observations, which may offer different information than questionnaires but also are limited by social desirability as well as being only a brief window into the feeding interaction. Methods employing ecological momentary analysis, which allows a research participant to report on affect and behavior close in time to the experience, or emerging technologies such as continuous audio or video recording may hold promise for capturing feeding practices that occur outside of mealtime and therefore may constitute a substantial amount of the parenting that occurs around feeding. A major limitation of the available literature is that few studies have examined feeding approaches and weight status longitudinally, making inferences about causation very challenging.

As we will review below, the literature for each feeding approach remains equivocal regarding whether a given feeding approach causes excess weight gain or is a response to a child's weight or eating behavior. The associations are in all likelihood bidirectional and transactional. In

other words, while parental feeding approaches may shape a child's weight, parents also likely change their feeding practices in response to a child's weight and eating behaviors. Despite the limited evidence for a causal relationship with obesity, interventions and practice guidelines continue to recommend that parents avoid excessive pressure or restriction and promote children's autonomy. We will review below the strength of evidence for these recommendations for each feeding approach below.

Pressure

Pressuring feeding approaches consist of strategies parents use to encourage children to eat more food or certain types of food. Some have theorized that these strategies contribute to increased obesity risk because they override a child's ability to attend to and respond to physiologic satiety cues. Children who are repeatedly pressured to eat beyond their own internal satiety cues may learn to ignore these cues and ultimately develop patterns of overeating and obesity. Pressuring feeding approaches are also thought to emanate from some parents' beliefs that a heavier child is a healthier child and their desire for their child to have a heavier body type. This parent belief and resulting pressuring behavior is theorized to peak in early childhood at the time of adiposity rebound, i.e., the period when children's adiposity reaches its lowest point. As children's adiposity naturally declines to a low point between ages 4 and 7 years, parents may pressure children to eat more to prevent this decline in adiposity, which they view as unhealthy.

Although these theoretical models are logical and often compelling explanations for obesity in young children, the data linking pressuring feeding approaches and obesity risk are actually remarkably equivocal. Specifically, pressuring feeding approaches have been positively [8], negatively [9], and not [10–14] associated with risk of childhood obesity. In summary, although there may be some parent-child dyads in which excessive pressuring of children to eat beyond satiety may cause excessive weight gain and obesity, the evidence does not support a robust effect for most children.

Monitoring

Monitoring refers to the extent to which parents keep track of their children's food intake, generally with regard to both quality and quantity. Monitoring at its most fundamental level is simply the parent being aware of and attending to their child's intake. For example, parents who make note of how many glasses of milk their child drank that day already, or how many cookies their child takes from the platter at a party, are monitoring their child's intake. Although one would hypothesize that parents who monitor intake more would have children who are less likely to be obese, monitoring has been inconsistently associated with risk of obesity, eating behaviors, and dietary intake [15]. These associations may be inconsistent because parents are likely to monitor intake of children who they perceive to be too thin, as well as those they perceive to be too heavy. In addition, the inconsistent associations may reflect bidirectional relationships, in that parental monitoring may increase in response to voracious child eating behaviors and obesity.

Restriction

Restriction can refer to restricting the quantity, quality, or timing of a child's intake. For example, parents may limit portion size of dessert, limit their child's intake of processed food, or limit snacking to a predetermined snack time. Restriction can be practiced with sensitivity, manifesting with gentle guidance, or with harshness, manifesting as critical and negative comments about a child's intake. Restriction can also occur overtly, with explicit comments and articulation of household rules, or covertly, with parents making choices not to purchase certain foods to avoid having them in the house. Parents are advised against "overly restricting" children's

intake [16] due to concerns about promoting unhealthy weight control behaviors as well as the potential for overriding children's physiologic hunger cues, thereby leading to future overeating. However, the data linking restrictive feeding with obesity is conflicting. Restrictive feeding approaches have been associated with both heavier [17–20] and thinner [21] child weight status, while still other studies find no associations [22, 23]. This conflicting literature may be due to a lack of specificity in research to date on restriction. Specifically, prior work on restriction has often not differentiated extreme versus moderate restriction, sensitive versus harsh restriction, or overt versus covert restriction. In the current obesity-promoting food environment, it is likely that parents will have to educate their children about the need for self-restraint. Future research should consider how parents can communicate restriction to children in adaptive, healthy ways.

Promotion of Autonomy

Promotion of autonomy in eating is defined by supporting the child's presumably innate ability to recognize and appropriately respond to physiologic hunger and satiety cues. A number of interventions have sought to train children to accurately recognize hunger and satiety, which seems to be achievable at least in the short term [24]. These approaches, however, are predicated on the notion that children adhering to their physiologic hunger and satiety cues will promote healthy weight status in all children. Although this may be true in the short term [25], it is not clear that relying on physiologic hunger and satiety cues is a viable method of obesity prevention for all individuals. Specifically, some individuals may have inborn or acquired drives that limit satiety and therefore predispose to obesity. Overall, the correct behavioral approach for obesity prevention likely needs to be tailored to the individual. Some children may be able to achieve a healthy weight if parents simply reduce intrusion and control and allow the child to attend to and follow his or her own physiologically driven hunger and satiety cues. However, other children provided no guidance regarding portion size, food choice, and frequency of eating may develop obesity if they rely only on physiologically driven hunger and satiety. The correct parenting approach likely needs to be tailored to the behavioral phenotype of the individual child.

Repeated Exposure

Parents of young children are often advised to offer new foods repeatedly to increase food tolerance and enjoyment. This feeding recommendation is based on the goal of expanding dietary variety and increasing children's intake of vegetables. Indeed, young children typically require up to ten repeated tastes of a new food in order to develop increased liking for and acceptance of the food [26, 27]. Of note, however, although increased dietary variety may have a number of health benefits, links between dietary variety and weight status in young children are mixed, with greater dietary variety possibly even conferring greater risk for obesity [28]. Thus, although a focus of feeding advice is often to encourage children to try new foods by offering them repeatedly, the current state of the science does not support this approach as an effective strategy for obesity prevention.

Modeling

Children's diets tend to be very similar to their parents' diets [29], which has led to recommendations that parents role model healthy eating to prevent obesity [16]. The scientific evidence to support this recommendation is limited, however. For example, although modeling is very effective in persuading children to sample a new food [30], it has a less robust effect on actually changing a child's food preferences or increasing intake. In addition, there are very few data regarding whether modeling restraint (i.e., not eating junk food or limiting portion size) has robust effects on children's intake or weight status. Finally, as with all research linking parent and child behavior, it is

very difficult to disentangle the effects of nurture versus nature. Specifically, a significant proportion of the variance in food preferences and picky eating behaviors is accounted for by genetics. When children like the same vegetables their parents like, at least part of this behavior may be due to shared genetic inheritance as opposed to parental modeling. Compared to other feeding behaviors, the role of parental modeling in preventing childhood obesity has received relatively little research attention and will be an important direction for future work.

Teaching

A relatively small body of research has focused on how to most effectively teach children about healthy eating, and whether this sort of teaching actually changes children's dietary intake and obesity risk. As is true with many types of health behavior, knowledge is necessary but not sufficient to achieve behavior change. Providing children health information about a food has not had strong effects on intake, food tolerance, or food appreciation [31] with one study even showing that when children are told a food is healthy, their liking for the food declines [32]. Research in developmental cognitive psychology is generating important new insights into how children understand and learn about the world around them, as well as how this information influences their behavior [33]. Future work should consider bringing these insights to nutrition education efforts with the goal of enhancing intervention effectiveness.

Beliefs About Feeding

Parents' choices about how to feed their children are embedded in complex belief systems influenced by culture and personal experience. Qualitative studies have described parents' skepticism about definitions of childhood obesity and whether these definitions apply to their children [34]. In fact, parents (even of obese or overweight children) often conceptualize child obesity as due to inept or neglectful parenting [35]. If parents believe that childhood obesity is due to "bad parenting," it is therefore not surprising that they may reject a label of "obese" for their own child. The balance between attributing obesity to societal and biological factors versus personal responsibility (i.e., parenting) is a critical consideration in working with families. While achieving behavior change requires internalization of personal responsibility, attributing obesity to personal "failure" is also the root of the intense stigma that obese individuals experience. Particularly in the context of the very mixed evidence linking parenting behaviors and obesity, interventionists should try to avoid implying that a child is obese due to inadequate parenting. The belief that many parents have internalized from pervasive societal messaging that childhood obesity is caused by "bad parenting" may be one reason why it is difficult for clinicians to engage parents around childhood obesity interventions.

The Home Feeding Environment

The structure of the home feeding environment can be considered to include the family's use of media, structured family mealtimes, the timing of eating, and the composition of meals served. Specific feeding approaches occur within this overall context, and certain approaches may not be necessary if structural changes are made. For example, parents may not need to exert as much restriction if the family routine is to only eat at certain times and junk food is kept out of the house. Thus, structural elements of the family's home and routine are important to consider as contributors to child obesity and may either strengthen or attenuate the impact of specific feeding behaviors or practices on children's obesity risk.

Media

More hours of television has been linked to a greater prevalence of childhood obesity in multiple studies over the past 30 years. This association is

well recognized, and screen time is one of the most robust risk factors for child obesity and therefore a frequent intervention target. The mechanism of effect, however, is less well understood. Although reduced physical activity has been theorized to be the key mechanism, this hypothesis has not been supported in meta-analysis [36]. Instead, the evidence has suggested an important role for television commercials in shaping children's food requests and preferences [37, 38]. Yet, in the last decade, the manner in which young children consume media has changed substantially, such that they tend to watch more television shows that do not include commercials. Therefore, the role of television commercials for unhealthy foods in shaping young children's eating behavior may be declining. Another mechanism via which screen time or television may shape children's eating behaviors is through snacking. Young children tend to snack more while watching television as compared to when not watching it [39], and the foods that are eaten while the television is on tend to be less healthy than when it is off [40, 41].

Finally, in the last 5 years, mobile devices have become ubiquitous. To our knowledge, no studies have examined if parents' or children's use of mobile devices is associated with child obesity risk and, if so, if this risk occurs only in the context of certain ways of using the device (i.e., watching videos vs. playing games vs. texting). Research studies are needed to determine if mobile devices constitute a new risk factor for obesity, and if so via which mechanism. Overall, it is possible that the role of television, which was a robust and well-evidenced risk factor for 30 years, may be declining as the role of television in families' homes changes. Research into links between media exposure and child obesity should reconsider this association in the context of the rapidly changing media landscape.

Family Mealtimes

Family mealtimes are recommended as a key strategy for childhood obesity prevention [16, 42]. Recommendations emerged from observational cohort studies showing links between greater family meal frequency and healthier child dietary intake [43, 44]. However, the literature linking family meal frequency and child obesity is relatively inconsistent, with studies showing positive [45], inverse [46, 47], and null [43] associations. These associations may also be moderated by race/ethnicity, socioeconomic status, and child sex [46]. These inconsistent associations may be due to demographic factors acting as moderators but may also be due to structural and relationship-based characteristics of family meals that have received less attention in work to date. Emotionally positive, harmonious family mealtime interactions have been associated with a lower prevalence of child obesity in most studies [42, 48]. In contrast, greater parental oversight and management have been associated with a lower prevalence of child obesity in some studies [49] but not in other studies [42, 48]. Studies examining the quality of mealtime routines, defined as structural and interpersonal characteristics of the family meal (i.e., the length of the meal, types of food served, communication, affect of family members present, etc.), have also found inconsistent associations with child weight [48, 50]. In summary, although family mealtimes are frequently recommended as a child obesity prevention target, much additional work is needed to confirm a causal association in randomized controlled trial designs, to examine moderators of the association, and to identify features of the family meal that confer protection.

Timing of Eating: Structured Meals and Snacking

Snacking among young children has increased in the last 20 years [51], and frequent snacking has been theorized to contribute to obesity. Opportunities to eat have become increasingly common as food is now ubiquitous in the environment. Very few studies have examined snacking behavior and child obesity risk. It is possible that allowing children to snack when hungry could appropriately reinforce physiologic hunger cues. On the other hand, snacking could have unintended consequences on physiology that lead

to changes in metabolism that are obesity promoting. The effect of snacking on obesity risk also needs to consider the frequency, timing, and composition of snacks consumed. There have been very few studies of snacking, likely because snacking behavior is difficult to measure accurately. Most snacking studies use parent-report questionnaires, which may have substantial error. The few available studies suggest that having more structured eating times is associated with a lower risk of child obesity [52]. Much additional work is needed to understand the ideal eating patterns for obesity prevention in young children.

Dietary Composition

Practice guidelines recommend that parents encourage the consumption of fruits and vegetables [16, 53] and fiber-containing foods [16, 53]. Parents are also advised to encourage dietary variety [54] by providing "opportunities for children to enjoy a variety of nutritious foods by regularly exposing them to, and encouraging them to taste, these foods" [55]. Despite these practice guidelines, there are little to no data supporting an association between a specific dietary composition and obesity prevention in children [54, 56]. There are relatively robust data to support limiting children's intake of sugar-sweetened beverages as an obesity prevention strategy [57], but evidence for other foods or dietary patterns is equivocal. In summary, it is unclear how much effort parents should place on promoting or discouraging the intake of certain foods in the service of obesity prevention given the lack of evidence for a causal effect.

Parenting Reponses to Child Eating Behaviors

Children are not blank slates; they come to the parent-child feeding relationship with predispositions to certain types of eating behaviors, and parents are faced with the task of responding to these behaviors in adaptive ways. A growing body of research in the last 20 years has informed our understanding of the complexities and determinants of eating behaviors. We will discuss here some of the eating behaviors that have received particular attention in children and how they may contribute to parent feeding behaviors.

Food Preferences

Food preferences are the primary predictor of children's intake [58] and dietary preferences established in childhood persist [59]. Food preferences seem to have an innate component (preference for sweet and dislike for bitter is observable within hours of birth [60]) but are also malleable (greater exposure, even prenatal exposure via transmission of the mother's diet in the amniotic fluid, leads to greater liking [61]). For example, in experimental designs, consumption of carrots during pregnancy was associated with greater infant liking for carrots when solid foods were introduced. In addition, infants who consume elemental formulas in infancy (which have a sour taste) have greater liking for sour flavors at the preschool age range. There is a relatively large body of research examining the ontogeny of flavor preferences in infancy and early childhood [61, 62]. It is unknown, however, how these flavor preferences and their development in early childhood are linked to obesity risk. This may be a valuable focus for obesity prevention research.

Eating in the Absence of Hunger

The continued consumption of foods past satiety, referred to as eating in the absence of hunger (EAH), is correlated with greater food responsiveness and enjoyment and less satiety responsiveness, as well as greater risk of obesity [63]. Interventions that reduce responsiveness to food cues [64, 65] have been shown to reduce EAH, but interventions that increase children's awareness of hunger and satiety cues had no effect [64]. Thus, EAH may primarily reflect food enjoyment and responsiveness as opposed to sensitivity to hunger and satiety cues. EAH has been linked to certain genetic risk alleles [66]. Thus, a parent

faced with child with high eating in the absence of hunger must find strategies for responding to a child who enjoys food and will eat food when given the opportunity, even when already satiated, because of the pleasure it provides. Encouraging parents to teach children to attend to hunger and satiety cues is unlikely to be effective for these children. Parents need new, evidence-based strategies to prevent excessive intake of palatable foods among children who are genetically predisposed to eat in the absence of hunger.

Responsiveness to Hunger and Satiety

On average, infants downregulate volume of milk intake in response to more calorically dense feedings [67] or the provision of additional calories in the form of solid foods [68, 69]. Thus, infants have the capability of adjusting caloric intake in response to caloric loads. Compensation is not perfect, however, a lesser ability to do so has been identified in infants with poor growth [70]. There is a notable lack of research regarding individual differences in satiety responsiveness. For example, it is generally assumed that all young children will effectively downregulate intake in response to a larger caloric preload or greater caloric destiny. However, there is likely substantial variability within the population with a lesser ability to accurately downregulate possibly linked to a higher risk of obesity. Children who are less able to downregulate intake accurately in response to internal satiety cues may require more parental monitoring and the provision of more external cues (i.e., predetermined portion sizes) to prevent excess caloric intake and obesity. Much additional work is needed in this area, particularly with regard to adaptive strategies parents might undertake to support their children in maintaining a healthy weight.

Emotional or Stress Eating

Psychosocial stressors are associated with an increased risk of childhood obesity. In general, it is theorized that stress interferes with the ability to exercise self-restraint or self-control in relation to tempting foods. One potential mechanism is thought to be that stress increases cortisol, which increases appetite [71]. Ongoing work seeks to understand if stress causes increases in eating in the absence of hunger, reduces the ability to delay gratification for food, or increases responsiveness to food cues. Interventions to reduce eating in response to stress or emotion in young children could focus on reducing stress, improving the ability to cope with stressors, or reducing the stress eating that occurs in response to those stressors. Indeed, at least two interventions to date that have focused on improving children's emotional and behavioral regulation have shown beneficial effects on obesity risk [72, 73]. Importantly, however, parents of children from low-income populations, who are at the highest risk of psychosocial stressors and obesity, generally do not believe that their children experience enough stress to cause stress eating and view stress eating as occurring only in the context of severe life stressors such as abuse, neglect, or a death in the family [74]. Interventions might consider providing education about the potential role of psychosocial stress in conferring obesity risk and shaping children's eating behavior and providing parents tools for how to improve children's ability to cope with stressors or prevent eating in response to a stressor.

Difficult Temperament

Temperament is a modifiable but relatively enduring child characteristic that includes constitutional differences in reactivity and self-regulation. Temperamental traits such as lower inhibitory control, higher surgency, and negative affectivity are thought to lead to more emotional and disinhibited eating, which are in turn linked with a higher risk of obesity [75]. Children with lower *inhibitory control* may not be able to restrain themselves when faced with tempting food. Children with this temperamental profile may impulsively eat and require significant external controls from their parents to prevent overeating. *Surgency* is characterized by impulsivity and intense pleasure. These children tend to eat more in the absence of hunger

and are less picky in their eating, both of which confer greater obesity risk. *Negative affectivity* is characterized by mood instability and over-reactivity, including dysregulated negative emotions. Children with more negative affectivity may self-soothe with food to cope with emotional stress. Parents of children with these temperamental traits likely will need to use different parenting strategies tailored to their child's particular temperamental profile and the manner in which that temperamental profile confers increased obesity risk. Ultimately, there is unlikely to be a "one size fits all" approach to parenting to prevent childhood obesity, but approaches will need to be tailored to the individual child's risk factors.

Summary

Early childhood may be a critical period for preventing obesity and establishing lifelong habits linked with obesity risk. Thus, parenting in early childhood is theorized to play a critical role in preventing obesity throughout the lifespan. Parents are generally eager for strategies they can employ to effectively prevent obesity in their children, but the evidence linking particular parenting approaches to child obesity risk is equivocal and does not provide support for clear guidelines. More randomized controlled trials are needed to determine causation and to characterize individual behavioral phenotypes that require specific parental management approaches. Given the lack of evidence that child obesity is due to inadequate or inappropriate approaches to child feeding, caution should be exercised in attributing a child's obesity to parenting. The current evidence suggests that the role of parenting in causing a child's obesity is modest, at best. Just as individuals with obesity experience substantial stigma, parents of children with obesity experience stigma, as they are often perceived as neglectful or inept. It is essential to invoke a more complex view of childhood obesity and reduce the blame placed on parents as the sole agents responsible for a child's obesity. Although early feeding practices are contributors to obesity risk, as with all obesity risk factors, their individual effect size is modest.

Editor's Comments and Questions

1. Having long worked with parents frustrated by the apparent resistance of their children to standard dietary recommendations, I am sympathetic to your idea that the associations between parental behavior and child feeding are "in all likelihood bidirectional and transactional" and shaped by innate or acquired differences in child temperament and sensitivity to the hedonic properties of food. I also agree wholeheartedly with your recommendation that parenting approaches "be tailored to the behavioral phenotype of the individual child."

But given the lack of a strong base of evidence in support of specific feeding practices, what general guidelines would you recommend for preventing obesity in young children? How might your approach be altered if one or both parents are obese?

2. You argue that "food preferences are the primary predictor of children's intake and that dietary preferences established in childhood persist." Yet population increases in the prevalence of childhood (or adult) obesity cannot be readily explained by recent changes in *innate* food preferences; presumably the rise in obesity reflects increasing access to, and intake of, palatable, high-calorie foods and changes in daily energy expenditure.

When I spent the first of two sabbaticals in Paris in 1993, I was struck by the general expectation that young children should (and would) eat the same food as their parents. There were at the time no "happy meals" or "children's meals"; a typical school lunch for my 6-year-old son might consist of baked fish, broccoli, milk, and French cheese. There was also little or no snacking between meals. Presumably this had a powerful influence on food preference and might

(among other things) have contributed to the very low rates of childhood obesity in France. Things of course have changed, even in France, with increasing penetration of fast-food restaurants, but in many follow-up visits, I continue to be impressed with the relative tolerance of French children for foods that are considered intolerable by many American children (and adults). It may be relevant that governments in the European Union and parts of Canada have for many years actively limited the marketing of junk food to young children on television and in schools.[a,b] Unfortunately, online advertising to children has risen in parallel.[b]

Authors' Responses

1. The most common guidelines that exist around feeding (i.e., MyPlate, American Heart Association, and American Academy of Pediatrics) are good places to start as they recommend the promotion of a balanced diet and active lifestyle. However, these guidelines may be difficult for families to adhere to, especially those with two working parents, with limited resources, or with children with more challenging eating temperaments. Even when parents try to do their best with regard to obesity prevention, they may not be able to completely overcome the strong environmental and genetic influences at play. We encourage families to try to find a middle ground when it comes to lifestyle—eating healthy yet affordable and palatable foods in moderate portions, incorporating exercise when possible, but also recognizing the external and internal influences on a child's obesity risk. Focusing on being healthy as a family, and instilling body acceptance and positive self-image in children, may be more important for parents than concentrating on the numbers on the scale.
2. The editor raises many excellent points. The global food environment has certainly become more obesogenic over the last several decades and plays a role in children's obesity risk. However, it is important to consider the interaction between an individual's genetic and behavioral risk of obesity and the food environment. An individual's innate preference for sweet or fatty foods, combined with a genetic propensity toward weight gain in a more obesogenic food environment, are all factors which likely interact to increase obesity risk.

Repeated exposure to different foods increases liking and acceptance of those foods by children.[c] That exposure can begin in utero, with the foods their mothers consumed during pregnancy.[d] The fact that French children are expected to try and eat the same foods that their parents do is likely a result of both of these factors. While developing a preference and acceptance for healthy foods (such as vegetables and baked fish) likely has some health benefits, recent work has shown that greater dietary variety and diversity are actually associated with higher body mass index z-scores in American children.[e] These findings call into question whether targeting dietary variety through increased food acceptance should be part of obesity prevention strategies in the USA.

Perhaps the biggest differences between French and American children when it comes to eating, diet, and obesity risk are the societal norms and policies that support healthy lifestyles in each country. In France, factors such as government subsidies for healthy foods and quality childcare, parental leave, a 35-hour workweek, and stricter food marketing regulations all likely contribute to helping families make healthy choices in child feeding. Without

these supports and cultural traditions, American families arguably have more obstacles to overcome in child feeding and obesity prevention.

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16 Dietary Interventions in the Treatment of Paediatric Obesity

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Introduction

Paediatric obesity is a major worldwide health issue. Prevention of obesity in childhood and adolescence is important. However, effective treatments for those already affected are needed to reduce the impacts of obesity on their physical, psychological and social development. Obesity management requires a coordinated model of care to deliver a sustained result. Table 16.1 outlines the key principles of obesity management in children and adolescents. The underlying principle of obesity treatment is to focus on changes in behaviours, including diet and physical activity, which influence body weight and adiposity. In this chapter, we will focus on the role of dietary intervention in the treatment of paediatric obesity.

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Efficacy of Dietary Interventions

The aim of dietary intervention in weight management is to contribute to an energy deficit. Numerous randomised controlled trials (RCTs) and meta-analyses have demonstrated that interventions that included a dietary component were efficacious in weight loss at least in the short to medium term in children and adolescents [1–3]. The latest systematic review and meta-analyses by Ho and colleagues [1], which included 38 studies, estimated that the effect size for lifestyle interventions with a dietary component was a decrease in body mass index (BMI) of 1.30 kg/m^2 [95% CI, 1.03–1.58] and a decrease in total body fat of 3.2% [95% CI, 1.39–5.01] at the end of active intervention (range 3–12 months) compared to usual care or minimal intervention. This review also demonstrated that the weight loss effect was sustained after programme completion and that studies with an intervention period

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Table 16.1 Principles of obesity management in children and adolescents

• Management of obesity-associated co-morbidities
• Family involvement
• A developmentally appropriate approach
• Long-term behaviour modification
• Dietary change
• Increased physical activity
• Decreased sedentary behaviours
• Consideration of the use of pharmacotherapy and other forms of nonconventional therapy

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longer than 6 months had a greater weight loss than shorter-term interventions [1]. Inclusion of an exercise programme did not improve weight loss, but those who received an exercise intervention in addition to a dietary component had a greater increase in lean body mass and a greater reduction in total fat compared to those who received a dietary component alone [4].

Structured lifestyle intervention programmes incorporating a dietary component have also been associated with improved cardio-metabolic outcomes. A meta-analysis of five RCTs including 440 participants aged between 8 and 16 years showed that structured lifestyle interventions incorporating a dietary component resulted in significant improvements in total cholesterol [weighed mean difference 0.28 mmol/L (10.81 mg/dL); 95% CI, 0.23–0.34] and triglycerides [0.15 mmol/L (13.29 mg/dL); 95% CI, 0.01–0.24] up to 2 years from baseline, as well as improvements in fasting insulin [55.1ρmol/L (7.93 uU/mL); 95% CI, 39.1–71.2] and homeostatic model assessment of insulin resistance (HOMA-IR, 2.32; 95% CI, 1.39–3.25) up to 1 year from baseline [4]. However, the impact of lifestyle interventions on blood pressure is less certain, and long-term data are limited. Importantly, evidence suggests that lifestyle interventions that included a dietary component lead to improvement in cardio-metabolic outcomes in children and adolescents with obesity even in the absence of weight loss or body composition change [1, 2]. Including an exercise component to the intervention can lead to greater improvements in high-density lipoprotein, fasting glucose and fasting insulin levels, but not total cholesterol or triglycerides (Table 16.2) [4]. Nevertheless, partial weight regain and subsequent regression in cardio-metabolic profiles to baseline levels are common in lifestyle intervention programmes at follow-up [4]. Longer-term studies are warranted to examine if the improvements in cardio-metabolic profile that resulted from obesity treatment in childhood will prevent the development of obesity-associated cardiovascular co-morbidities in adulthood.

Dietary Interventions

For many children and adolescents who are overweight, dietary interventions are frequently aimed at weight maintenance that is to slow or prevent weight gain rather than weight loss. However, given the high prevalence of obesity, the increasing prevalence of severe obesity and co-morbidities and the high number of youth who are heavier than their ideal adult body weight, dietary interventions for weight loss are frequently indicated. While the appropriateness of weight loss can be contentious due to proposed physiological and psychological impacts, there is no evidence to suggest that adiposity loss in children and adolescents with obesity causes harm.

The optimal diet for achieving an energy deficit in children and adolescents with obesity is unknown. Intervention trials have examined a number of different dietary strategies with the general agreement that adherence to energy restriction remains the most effective for weight loss [5]. However, achieving long-term adherence to energy restriction is challenging, and it is unlikely that one dietary strategy will fit all. In addition, there is potential for the specific application of certain dietary strategies to lead to greater short-term weight loss and target particular cardio-metabolic risk factors [5]. It is also essential that treatment options are acceptable to both the child/adolescent and their parents/caregivers. Below we explore some conventional and novel dietary approaches.

Table 16.2 Effects of dietary and exercise interventions on anthropometric and cardio-metabolic outcomes

Study	Study arms (follow-up time point)	Sample size at follow-up	BMI change, kg/m^2	Body fat change, %	TC change, mmol/L	HDL-C change, mmol/L	LDL-C change, mmol/L	TG change, mmol/L	Fasting glucose change, mmol/L	Fasting insulin change, pmol/L	HOMA-IR change
Diet-only (D) compared with diet-plus-exercise (D + E) interventions											
Becque 1988 [50]	D (20 wk)	11	N/A	−3.5	−0.24	0.10	N/A	−0.20	N/A	N/A	N/A
	D + E (20 wk)	11		−3.0	−0.55	0.21*#		−0.50			
Rocchini 1988 [51, 52]	D (20 wk)	15	N/A	−6.0*	N/A	N/A	N/A	N/A	−0.11	−34.7*	N/A
	D + E (20 wk)	18		−4.0*#					−0.11	−48.6*	
Sung 2002 [53]	D (6 wk)	41	−0.5	−0.2	−0.3*	−0.1*	−0.2	0.1	N/A	N/A	N/A
	D + E (6 wk)	41	−0.2	−0.7*	−0.3*	−0.1	−0.4*	0.3			
Woo 2004, Yu 2004, Yu 2005 [54–56]	D (6 wk)	41	−0.6*	−0.2	−0.3*	−0.1*	−0.2	0.0	N/A	N/A	N/A
	D + E (6 wk)	41	−0.2	−0.7*	−0.3*	−0.1	−0.3*	0.3			
	D (1 y)	41	−0.2	−1.3	−0.2*	0.2	−0.4*	0.2			
	D + E (1 y)	22	0.1	−4.9*	0.0	0.2*	−0.3*	0.1			
Ribeiro 2005 [57]	D (4 mo)	18	−3.0*	N/A	−0.18*	0.00	−0.03	−0.32*	−0.28*	−83.34*	−2.0*
	D + E (4 mo)	21	−3.0*		−0.39*	0.13*#	−0.36	−0.08*#†	−0.28*	−34.73*#†	−1.4*†
Davis 2009 [58]	D (16 wk)	10	0.3	N/A	N/A	N/A	N/A	N/A	0.14	31.25	N/A
	D + E (ST,16 wk)	9	1.1						−0.20	−5.56	
	D + E (CAST,16 wk)	15	−0.5						−0.24	−3.47	
Shalitin 2009 [59]	D (12 wk)	55	−2.06*	−4.48*	−0.31*	−0.07*	−0.11	−0.28*	0.02	4.44	0.17
	D + E (12 wk)	55	−2.02*	−3.48*	−0.28*	−0.02	−0.19*#	−0.16*	−0.08	−12.92	−0.42
	D (1 y)	55	0.36	−3.63	−0.42*	−0.02	−0.29*	−0.22*	0.06	23.13	0.74
	D + E (1 y)	55	−0.06	−4.56*	−0.18	0.004	−0.15	−0.08	0.12	28.68*	0.93*

(continued)

Table 16.2 (continued)

Study	Study arms (follow-up time point)	Sample size at follow-up	BMI change, kg/m^2	Body fat change, %	TC change, mmol/L	HDL-C change, mmol/L	LDL-C change, mmol/L	TG change, mmol/L	Fasting glucose change, mmol/L	Fasting insulin change, pmol/L	HOMA-IR change
Okely 2010, Burrows 2008, Burrows 2010 [60–62]	D (6 mo)	42	−0.8	N/A							N/A
	D + E (6 mo)	60	−0.9								
	D (1 y)	42	−0.5								
	D + E (1 y)	60	−0.2								
					−0.07	0.04	−0.09	−0.03	0.07	0.69	
					0.07	0.03	0.03	0.00	−0.11	−20.14	
					−0.03	−0.01	−0.01	−0.02	0.11	−31.25	
					0.17	0.06	0.06	0.00	−0.03	−23.61	
Diet-only (D) compared with exercise-only (E) interventions											
Kelishadi 2008 [63]	D (6 mo)	47	−1.1*	N/A	−0.24*	0.03	−0.13	−0.17*	−0.17	−8.1	−0.9
	E (6 mo)	45	−1.04*		−0.2*	0.04	−0.19	−0.14	−0.16	−7.4	−0.7
	D (1 y)	45	0.7		−0.03	0.02	−0.04	0.05	−0.06	2.7	0.3
	E (1 y)	42	0.5		0.06	0.02	0.03	0.04	0.04	2.5	0.4
Shalitin 2009 [59]	D (12 wk)	55	−2.06*	−4.48*	−0.31*	−0.07*	−0.11	−0.28*	0.02	4.44	0.17
	E (12 wk)	52	−1.01*#	−1.33*	−0.03	−0.06	0.10#	−0.15*	−0.11	−10.83	−0.39
	D (1 y)	55	0.36	−3.63	−0.42*	−0.02	−0.29*	−0.22*	0.06	23.13	0.74
	E (1 y)	52	0.42	−1.16	−0.16	−0.04	−0.16	0.06	−0.09	12.92	0.36
Okely 2010, Burrows 2008, Burrows 2010 [60–62]	D (12 wk)	42	−0.8	N/A	−0.07	0.04	−0.09	−0.03	0.07	0.69	N/A
	E (12 wk)	63	−0.3		0.07	0.06	0.10	0.13	−0.08	−14.58	
	D (1 y)	42	−0.5		−0.03	−0.01	−0.01	−0.02	0.11	−31.25	
	E (1 y)	63	0.4		0.18	−0.02	0.20	0.28	0.04	−16.67	

BMI, body mass index; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *TGs*, triglycerides; *HOMA-IR*, homeostasis model assessment of insulin resistance; *D*, dietary intervention; *E*, exercise intervention; *wk*, week(s); *y*, year; *mo*, month(s); *N/A*, not applicable; *ST*, strengthen training; CAST, combined aerobic and strengthen training; *, post-treatment significantly different from baseline ($p < 0.05$); #, post-treatment significantly different

Conventional Approaches

Currently, the most frequently reported dietary interventions for weight management in dietary intervention trials are healthy eating advice, which is low in fat, based on dietary guidelines or the Traffic Light/Stop Light diet [1, 4, 6].

Healthy Eating Advice Based on Dietary Guidelines

Food-based dietary guidelines provide advice on foods and food groups to provide the required nutrients to promote overall health and prevent chronic diseases. In many countries, including Australia, the USA and the UK, current guidelines recommend a diet that is high in carbohydrate (45–65% of daily energy) and low in fat (less than 35% of daily energy), with protein contributing approximately 15% of daily energy. This diet is often supported by food guides, in the form of food pyramids and food plates (e.g. Fig. 16.1), which are used for consumer education. It is recommended that these guidelines be adopted at a population level [7, 8], including for the treatment of child and adolescent obesity.

A diet based on the dietary guidelines may also be energy restricted. Determining the appropriate energy targets for weight loss can be challenging, needs to be assessed on an individual basis and will depend on a number of factors including age, sex, physical activity levels, co-morbidities and the speed of weight loss required. Dietary intervention trials involving an energy-restricted diet are often based on either a standardised daily kilocalorie (kcal) deficit of 300–500 kcal, 30% less than the reported energy intake or 15% less than the estimated energy requirement [1]. Some studies impose energy restrictions on snacks and beverages only. However, if energy restriction is indicated, a diet based on dietary guidelines can present challenges in achieving micronutrient adequacy, particularly essential fatty acids, and careful selection of foods is required [9]. This diet is generally successful in achieving weight loss in the short term in children and adolescents [1]. In adults, a 2015 systematic review and meta-analysis suggested that these diets are equally as effective as other dietary interventions, including low carbohydrate and higher fat, of similar intensity in the long term [10].

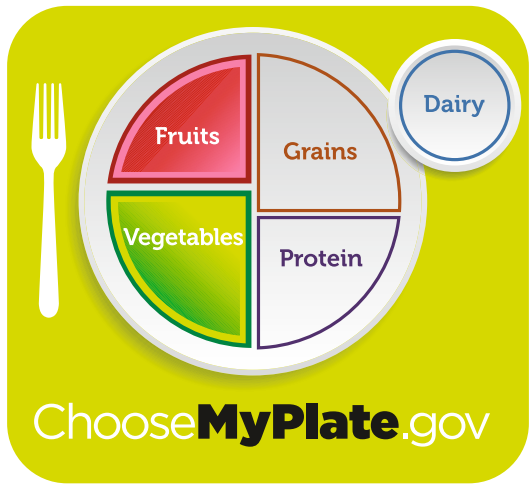

Fig. 16.1 Choose MyPlate. MyPlate was developed by the United States Department of Agriculture to assist individuals create healthier eating styles (Source: https://www.choosemyplate.gov. US Department of Agriculture. Public Domain)

Traffic Light/Stop Light

The Traffic Light/Stop Light diet is an energy-controlled approach. Foods in each category are colour coded according to their caloric densities per average serving: green for low-calorie foods that can be eaten freely, yellow for moderate-calorie foods that can be eaten occasionally and red for high-calorie foods that should be eaten rarely. This diet was one of the original diets to treat childhood obesity as well as used in intervention trials [6]. Similar to a diet based on dietary guidelines, this diet is successful in achieving modest weight loss in the short term in children and adolescents [1].

Novel Approaches

While there is evidence to support conventional dietary interventions short term, their effectiveness in sustaining long-term changes remains uncertain. Hence, there has been recent interest in exploring different dietary strategies that optimise weight loss as well as improve cardio-metabolic outcomes. These strategies include modifying the macronutrient content and/or the quality of carbohydrate, as well as novel dietary approaches to restrict energy intake.

Increased-Protein Diet

An increased-protein diet typically aims for approximately 26–44% of daily energy as carbohydrate, <35% as fat and 20–40% as protein [11]. These diets are hypothesised to lead to greater weight loss by evoking (a) sustained satiety despite reduced energy intake, (b) sustained energy expenditure despite loss in body mass by sparing loss of fat-free mass and (c) increased dietary-induced thermogenesis, because the thermal effect of protein is greater than that of carbohydrate or fat [12]. In children and adolescents, there have been seven studies, ranging in duration from 1 to 12 months, comparing isocaloric increased-protein (mean 24.4 ± 3.9% of energy) and standard-protein (mean 16.3 ± 2.1% of energy) diets [5, 13]. The studies included boys and girls, aged 7–18 years, with a mean sample size of 110 participants [5]. All studies found improved weight, fasting glucose, fasting insulin, insulin sensitivity, blood lipids and blood pressure irrespective of diet group and irrespective of whether participants were free-living or in highly controlled environments (boarding school or camp). Figure 16.2d shows the 12-month change in glycaemic status and body composition measures from one of the included RCTs undertaken by Garnett and colleagues [14]. This study specifically targeted adolescents with insulin resistance and/or prediabetes and randomised 111 participants to a hypocaloric diet, which was either increased protein (25–30% of energy) or standard protein (15% protein). The authors reported no significant differences between diet groups at any time point. The authors concluded, as did the systematic review and a later similar study by Truby et al. [13], that the protein content of the diet appears to have little effect when given isocalorically. The results emphasise the importance of total energy intake for improved weight status in children and adolescents with obesity.

In adults, results from several trials have indicated that increased-protein diets increased fat loss, attenuated reductions in fat-free mass and improved an array of cardio-metabolic factors, including glucose homeostasis and the blood lipid profile compared to standard-protein diets [15]. However, the effects are not consistently reported. A recent systematic review that compared energy-restricted, isocaloric, high-protein (mean 30.5 ± 2.4% of energy) with a standard-protein (mean 17.5 ± 1.5% of energy) diet concluded that the high-protein diet provided modest benefits for reductions in body weight (0.79 kg; 95% CI, 1.50-0.08 kg), fat mass (0.87 kg; 95% CI, 1.26-0.48 kg) and triglycerides [0.23 mmol/L (8.9 mg/dL); 95% CI, 0.33-0.12 mmol/L], with better preservation of lean body mass. Changes in fasting plasma glucose, fasting insulin, blood pressure, total cholesterol and low- and high-density cholesterol were similar across dietary treatments [15].

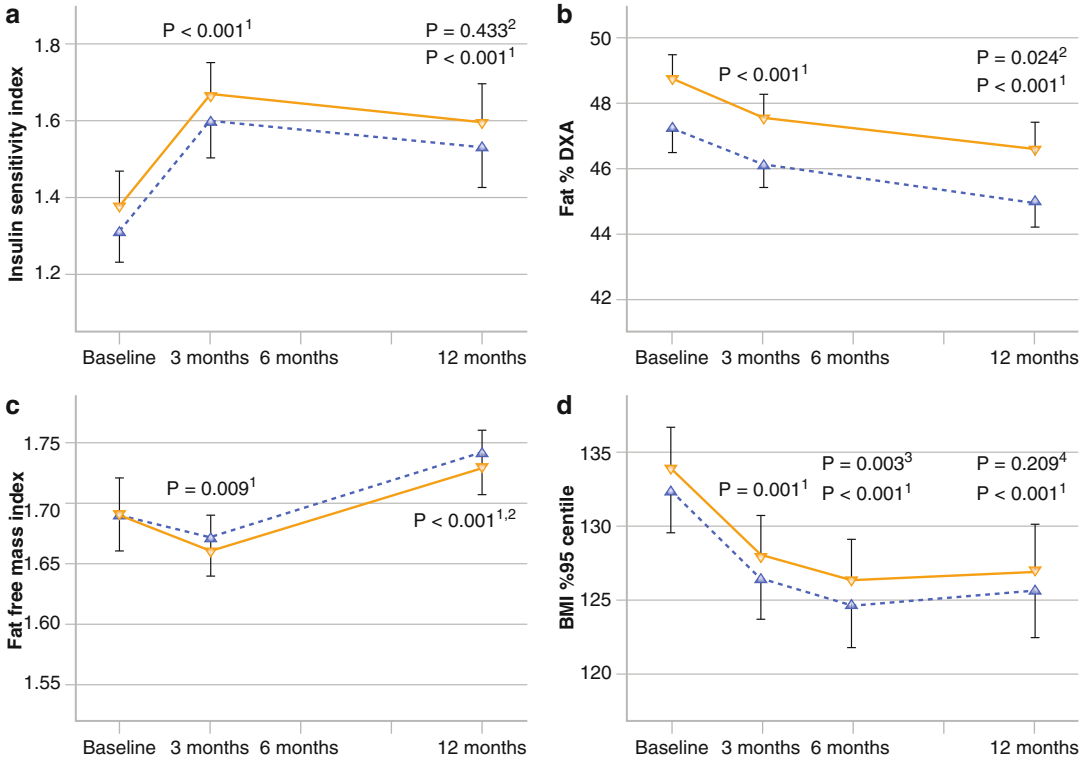

Fig. 16.2 (**a**–**d**) Glycaemic status and body composition measures by dietary group over the 12-month intervention. Estimated marginal means (SE) are presented from linear mixed models for the increased-protein diet group (*downward triangle*) and the high-carbohydrate diet group (*upward triangle*). Differences between diet groups were not significant at any time period. (**a**) Insulin sensitivity index. [1]Significance between baseline and 3 months and 12 months as indicated. [2]Significance between 3 and 12 months. (**b**) Total body fat percent (Fat % DXA). [1]Significance between baseline and 3 months and 12 months as indicated. [2]Significance between 3 and 12 months. (**c**) Fat-free mass index. [1]Significance between baseline and 3 months and 12 months as indicated. [2]Significance between 3 and 12 months. (**d**) BMI%95th centile. [1]Significance between baseline and 3 months, 6 months and 12 months as indicated. [3]Significance between 3 and 6 months.[4]Significance between 6 and 12 months (Source: Garnett SP, Gow ML, Ho M, Baur LA, Noakes M, Woodhead HJ, Broderick CR, Chisholm K, Briody J, De S, et al. Improved insulin sensitivity and body composition, irrespective of macronutrient intake, after a 12 month intervention in adolescents with pre-diabetes; RESIST a randomised control trial. BMC Pediatrics. 2014;14:289)

It is not clear why the protein effect is not seen in children and adolescents. Achieving dietary protein targets in studies of free-living children and adolescents is difficult, and in part the lack of difference may be due to the reported lower protein intake in youth [5, 16]. In addition, some will contend that RCTs are not the ideal study design to determine the effect of dietary intervention. The isocaloric nature of experimental diets may blunt the satiating effect of protein thought to contribute to a lower ad libitum total energy intake and consequent improved weight loss as reported in some adult studies [12, 17].

Very Low-Carbohydrate Diet

A popular alternative to the low-fat diet is a very low-carbohydrate diet, typically aiming for <50 g carbohydrate per day with high or ad libitum fat and/or protein intake (e.g. the Atkins diet) (Table 16.3). A recent systematic review

Table 16.3 Classification of diets based on carbohydrate content

Carbohydrate diet classification	Amount of carbohydrate	Example of dietary pattern
Typical/high-carbohydrate diets	45- > 65% of total calories	Low-fat diet, Traffic Light/Stop Light diet, standard-protein diet, lower-GI diet
Moderately restricted carbohydrate diets	26–44% of total calories	Intermittent fasting diet, increased-protein diet
Low-carbohydrate diets	51–130 g/day (or approximately 16–26% of calories of a 2000 calorie diet)	Low-carbohydrate diet
Very low-carbohydrate diets	Typically 20–50 g/day or 5–15% of total calories	Very low-carbohydrate diet, very low-energy diet

Source: Gow ML, Garnett SP, Baur LA, and Lister NB. The Effectiveness of Different Diet Strategies to Reduce Type 2 Diabetes Risk in Youth. Nutrients. 2016;8(8):486

suggested that a very low-carbohydrate diet may result in greater weight loss (a mean decrease in BMI of 1.46; 95% CI, 0.44–2.48 and a mean decrease in BMI z-score 0.25; 95% CI, 0.06–0.44) immediately following active treatment (10–26 weeks) compared with a low-fat diet [5]. However, the difference between diet groups was not maintained at the 2-year follow-up, nor was the difference observed in the larger, higher methodological quality studies [18, 19]. The current evidence suggests that a very low-carbohydrate diet may lead to greater short-term weight loss and may be useful when indicated, for example, in severe obesity prior to surgery.

In terms of cardio-metabolic outcomes, very low-carbohydrate diets reportedly improve insulin levels and/or insulin resistance compared with a low-fat diet immediately following active treatment [18, 20] and at follow-up [5]. These findings suggest that a very low-carbohydrate diet as part of obesity treatment may facilitate improvements in hyperinsulinemia compared with a traditional low-fat approach in children and adolescents. Furthermore, a very low-carbohydrate diet may also facilitate improved body composition [21] and/or triglycerides but may increase LDL cholesterol levels [18, 22]. In adults with type 2 diabetes, a very low-carbohydrate diet may improve glucose status and lipid profile when compared to a high-carbohydrate diet (>200 g/day). To date, there is insufficient evidence for use of very low-carbohydrate diets in children and adolescents with diabetes [23].

There have been no reported adverse effects on cardio-metabolic profile in association with following a very low-carbohydrate diet in children and adolescents, suggesting the short-term safety of the diet. The long-term safety of very low-carbohydrate diets in children and adolescents is unknown. One concern is that restricting carbohydrate in the diet, without a sufficient increase in vegetable consumption, reduces the intake of nutrients obtained from high-quality carbohydrates, particularly fibre and phytochemicals [24]. An increased feeling of fatigue has also been a reported side effect of following a very low-carbohydrate diet in adults [25]. This could result in a reduced desire to complete physical activity in youth with overweight or obesity and should be considered in an individual who is, or plans to be, very active as part of their weight loss regimen.

Low Glycaemic Index/Glycaemic Load

A diet that has a lower glycaemic index (GI) generally refers to a balanced diet that incorporates carbohydrate foods that have reduced glycaemic load (GL), i.e. foods/meals that produce a slower rise in blood glucose levels and have lower overall carbohydrate content [26]. However, consumption of lower-GI foods does not necessarily translate to a "healthy" diet,

with some discretionary foods such as ice cream, cakes and potato crisps having a low GI. In children and adolescents, a 2015 systematic review that included nine RCTs with a duration between 10 and 96 weeks and a total of 1065 children and adolescents found that lower-GI/GL diets produced greater improvements in insulin resistance (HOMA-IR mean difference 0.70; 95% CI, 0.04–1.37) and triglyceride levels (mean difference 0.17 mmol/L; 95% CI, 0.05–0.30) compared to higher-GI/GL diets [27]. However, there was no beneficial effect for weight loss or cholesterol levels (total, HDL or LDL). Similar findings have been reported in young adults with obesity [28].

The DiOGenes study is the largest study conducted to date which examined the effect of varying the GI and protein content of the diet on weight and cardio-metabolic outcomes in children, recruiting families from eight European countries. Eligible parents were randomised as a family unit to one of five ad libitum diets: low-protein and low-GI, low-protein and high-GI, high-protein and low-GI, high-protein and high-GI and control diet (national dietary guidelines, medium protein content and no instructions on GI) [29]. A difference of 15 GI units between the higher-GI and lower-GI diets was targeted. The results of this study showed that neither GI nor protein had an isolated effect on body composition among children following an ad libitum diet. However, the low-protein, high-GI combination increased body fat, whereas the high-protein, low-GI combination was protective against obesity [30]. It is important to recognise that the children in the DiOGenes study were not necessarily overweight; they were the children of parents who were overweight or obese. The children were not given advice on weight loss but were educated on the diet's ability to regulate appetite [30].

Very Low-Energy Diet

A very low-energy diet (VLED) is a dietary approach that has gained popularity due to its association with rapid weight loss. It is a very strict diet aiming for <800 kcal/day. VLEDs are largely protein based and contain essential fatty acids, vitamins and minerals but very little carbohydrates (typically <50 g) and are aimed at inducing ketosis [31]. They reduce portion size and, consequently, energy intake. Because a VLED is difficult to follow, it is usually implemented short term, aiming for rapid weight loss, and comprised of meal replacement products (e.g. shakes, bars, soups, desserts) to achieve nutritional adequacy.

Studies in adolescents with obesity have demonstrated that a VLED can safely induce rapid weight loss in the short term (4–15 kg over 3–12 weeks) while preserving lean body mass [21, 32–34]. Studies have also demonstrated improvements in blood pressure, total cholesterol, LDL and HDL cholesterol, triglycerides, fasting glucose, fasting insulin, HbA1c and insulin sensitivity [21, 32, 33]. One of these studies found that a short-term (10 weeks) daily VLED (600–800 kcal/day) compared with a hypocaloric low-fat diet produced significantly greater reductions in percentage body fat while maintaining lean body mass [21]. In another study comparing a VLED with a hypocaloric low-fat diet, weight loss was greater in the VLED group at 4 months, but this was not sustained at 12 months [32]. A recent pilot study investigated the effects of an 8-week VLED in adolescents with type 2 diabetes [34]. Rapid weight loss was achieved, and 6 months after the VLED intervention, four of the five participants who adhered to the diet had reversal of type 2 diabetes. These results highlight the potential benefit of following a VLED beyond weight loss [34].

Overall VLEDs are tolerated by adolescents and result in rapid weight loss, improvements in body composition and improved metabolic risk profile short term, but long-term outcomes are not clear. In adults the metabolic benefits of bariatric surgery have been reproduced by VLED [35]. The diet, although strict, may be an alternative to pharmacological therapies or surgical

interventions to treat adolescents with severe obesity. VLEDs require intensive monitoring by a team of health professionals.

Intermittent Fasting

Intermittent fasting is also known as "intermittent energy restriction" and "alternative day fasting". This diet has been popularised as the 5:2 diet and has gained much media interest and celebrity endorsement. Intermittent fasting includes 1–4 "fasting" (or VLED) days per week, where energy intake is drastically limited (typically less than 600 kcal), and 3–6 "feeding" days per week, where food is either consumed ad libitum or a diet based on healthy eating guidelines. It is speculated that intermittent fasting comprising of shorter periods of energy restriction coupled with longer periods of habitual energy intake may be more sustainable and promote better adherence than continuous daily energy restriction [36]. To date, studies examining the effectiveness of intermittent fasting have not been conducted in children or adolescents.

In 2016 there were two systematic reviews of adult trials comparing intermittent fasting with daily energy restrictions [37, 38]. While there were conflicting results from individual studies on which group achieved the greatest weight loss, overall both reviews indicated that intermittent fasting is as equally effective as daily energy restriction in the short term (5 weeks to 6 months) and long term (12–18 months) to help individuals with obesity decrease weight (4–8%) and body fat and reduce cardio-metabolic risk [37, 38]. Measures of compliance were limited, but one study indicated that short-term compliance for the intermittent fasting group was effective but not in the long term [39]. A greater number of adverse effects were also experienced in the intermittent fasting group which included headache, lack of energy and difficulty fitting the diet into their daily routine. Trials are ongoing in children and adolescents.

Potential Risks of Dietary Interventions

Disordered Eating and/or Eating Disorders

A concern about using dietary energy restrictions in obesity treatment is the potential risk of developing or exacerbating disordered eating and/or eating disorders. Overweight children are more likely to have dysfunctional eating behaviours, including emotional eating and restrained eating, compared to normal-weight children [40, 41], and overweight adolescents are more likely to engage in disordered eating, such as binge eating [42]. The RESIST study examined the impact of using a prescriptive hypocaloric meal plan (500 kcal less than the recommended daily energy intake) on the psychological dimensions of eating behaviours in over 100 adolescents with obesity [43]. The results of the RESIST study showed that a prescriptive dietary approach led to significant reductions in dysfunctional eating behaviours, particularly external and emotional eating, and the intervention did not elicit any adverse effects on dietary restraint in adolescents with obesity. Evidence from an earlier systematic review also supports the view that professionally administered paediatric weight loss interventions do not increase the risk of eating disorders and may, indeed, improve psychological wellbeing in adolescents with obesity [44]. Furthermore, there is evidence that adolescents seeking weight management have a preference for prescriptive dietary advice, as opposed to unstructured advice [43, 45]. In adults, a recent systematic review of the safety of severe dietary energy restriction (430 to 1200 kcal/day) in overweight and obese adults reported that clinically supervised programmes do not necessarily trigger binge eating in overweight individuals without pre-existing binge eating disorder [46]. On the contrary, severe dietary energy restriction does not exacerbate and may even reduce binge eating in overweight individuals with

pre-existing subclinical binge eating or binge eating disorder. These findings indicate that dietary interventions are generally safe when they are run by professional teams. In view of the association between obesity and disordered eating, it is recommended that eating behaviour should be monitored during, and preferably also after, obesity treatment.

Nutritional Adequacy of Reduced Energy Diets

Children and adolescents have unique and differing nutrition requirements, including calcium, iron and zinc, and energy-restricted diets reduce the opportunity to meet micronutrient requirements by limiting overall food intake. There is a paucity of data on the effect of energy restriction on nutritional adequacy. There is one recent paper which has examined the nutritional adequacy of three energy-restricted diets which are utilised in clinical practice for adolescents with obesity: a diet based on dietary guidelines, a modified-carbohydrate diet and an intermittent fasting diet [9]. In this paper the authors undertook dietary modelling and demonstrated that these eating patterns can be adapted to achieve nutritional adequacy and energy restriction; however, they did need careful consideration to meet nutritional requirements of adolescents.

Reduced Resting Metabolic Rate and Lean Body Mass

Concerns have been expressed that dietary restrictions used in obesity treatment in children and adolescents may adversely decrease resting metabolic rate and lean body mass [47]. Results from a systematic review which included five RCTs comparing diet-only interventions with a diet-plus-exercise interventions reported that an energy-restricted diet (900 to 1400 kcal/day) along with a moderate protein content (20–30%) did not result in a loss of lean body mass in 6- to 18-year-olds over 4 months [4]. Loss of lean body mass was reported in one small study (n = 38) in which children with obesity (8–12 years old) were prescribed an 1800 kcal high-carbohydrate low-fat diet (65% total energy from carbohydrate,15% from protein and 20% from fat) and participated in supervised exercise training three times/week (60 min/session) [48]. Participants lost 1.3 kg [95% CI, -2.01–0.59] in lean body mass over 4 months. Overall these findings suggest that for lifestyle interventions with an exercise component, diets with an increased protein content may protect against the loss of lean body mass.

Conclusion

The current evidence indicates that an improvement in weight status can be achieved in children and adolescents with obesity, irrespective of the dietary macronutrient profile or dietary pattern, provided the diet is energy reduced. This suggests that the primary objective of dietary interventions should be to reduce total energy intake. However, there is some inconsistent evidence from child and adolescent obesity treatment intervention studies to suggest that very low-carbohydrate diets, VLEDs and lower-GI diets may achieve greater weight loss compared with a more traditional low-fat diet, at least in the short term. These diets also appear to have advantages over a low-fat diet for improving cardiometabolic risk profile. A common feature of these diets is that they ultimately reduce glycaemic load by modifying diet carbohydrate quality or quantity compared with the traditional low-fat approach. These dietary options give clinicians multiple diet strategies to offer children and adolescents, which may assist in achieving greater weight loss compared with a low-fat approach. Hence, diets may be personalised depending on patient preference and suitability.

Editor's Comments and Question

Social media and mainline newspapers are awash with testimonials "demonstrating" that obesity and its complications are caused by discrete macronutrients such as sugar, fructose or saturated fat. However, as discussed in Chap. 1, it is the *patterns* of dietary intake, rather than the intake of single macronutrients, that are the principal determinants of childhood weight gain. Diets that are high in energy density, fat and sugar and low in fibre, fruits and vegetables are associated with higher percent body fat and excess adiposity in childhood and adolescence. Total caloric intake, as you note, is critically important.

It is not surprising, then, that reductions in any *single* macronutrient have had little or no effect on body mass index in obese children[a,b,c] and that long-term weight loss in obese adults is determined by total energy intake, rather than the specific macronutrient content of the diet[d,e,f]. Moreover, the effect of any *single* macronutrient on metabolic risk (e.g. type 2 diabetes mellitus) pales in comparison to the effect of obesity itself[g].

Common-sense approaches to diet can reduce weight in obese children and prevent weight gain in children at risk: in my experience, nearly anyone can lose weight by eliminating sugar drinks and reducing intake of fried and fast foods and high-density starches. The trick is actually doing it.

Where do you place your focus in promoting weight loss in obese children?

Authors' Response

The focus of our approach to weight loss in children is dependent upon a number of factors including the age of the child, the amount of weight loss required and the presence or absence of co-morbidities.

For the younger child, the focus of treatment is the family, and generally we aim at simple changes as you have indicated above. We encourage drinking water and limit the intake of fruit juice, cordial and soft drink. We encourage the use of low-fat dairy food types for children over the age of 2 years instead of full cream and encourage the consumption of fruits and vegetables. We also consider it important to eat breakfast and to sit down and enjoy meals together as a family with the television switched off.

In our adolescent clinic, where many of the adolescents present greater than their ideal adult weight with several co-morbidities, we aim for weight loss. We offer a number of the weight loss strategies as discussed in this chapter. Diets are personalised depending on patient preference and suitability. Adolescents are allowed to change strategy; *we are acutely aware that if there is no weight loss in the first 3 months of treatment, a different strategy is indicated*[h].

Our primary focus for adolescents with obesity and type 2 diabetes is rapid weight loss. We recognise the severity of the condition including increased morbidity and mortality. The traditional approach has been the management of blood sugar levels, but results from our recent study have indicated that it is possible to reverse the pathology of type 2 diabetes with a very low-energy diet in adolescents as seen in adult studies[i]. We see this as a first-line treatment option in newly diagnosed youth.

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Vegetarian Diets and Pediatric Obesity

17

Gina Segovia-Siapco, Sarah Jung, and Joan Sabaté

Introduction

For the past decade, dietary guidelines [1] and research, policy, and public health efforts [2] toward curtailing the obesity epidemic have focused on improving the health of children, particularly maintenance of healthy weight. The growing childhood obesity epidemic is a major health concern due to the significant threat it poses to the present and future health of children and the wide range of its physical and psychological consequences. Overweight or obesity during childhood increases the likelihood for the same condition during adulthood [1, 2] and its comorbidities not only later in life but while these young individuals are still growing and developing into adults [3]. It is projected that, in the absence of an effective intervention, the potential global incidence of children with obesity-linked complications will by the year 2025 include 12.7 M with impaired glucose tolerance, ~4 million with type 2 diabetes, ~28 million with hypertension, and ~38 million with nonalcoholic fatty liver disease (hepatic steatosis) [4]. Expert committees agree that due to difficulties associated with managing adult obesity, preventing excess weight gain over the life course is perhaps the only feasible solution to controlling the obesity epidemic [5]. Thus, addressing pediatric obesity through realistic interventions that have long-term sustainability would be a judicious approach to addressing the obesity epidemic.

Several factors contribute to the development of obesity, but food choices/dietary habits play a significant role. Food choices and dietary behavior can be shaped early in life [6, 7]. Epidemiological studies have shown that high intake of high-energy density diets and high energy-dense foods and low consumption of fruits and vegetables are two of the many risk factors associated with pediatric obesity [7], but "diet as a whole" is considered a more important determinant of pediatric obesity than any single food or nutrient [8]. The change from plant-based traditional diets to Western-type diets characterized by highly processed foods and high-fat animal-based products has been implicated in the increasing global prevalence of obesity [9] including among children [10] and cardiovascular disease (CVD) [11]. Vegetarian diets are characteristically high in whole grains, fruits, vegetables, legumes and soy proteins, and nuts—each of which may have beneficial health effects [12]—and are more environmentally sustainable due to less use of natural resources [13]. In this chapter, the vegetarian dietary pattern is presented as a judicious sustainable option in addressing pediatric obesity.

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Adequacy of the Vegetarian Diet

The Academy of Nutrition and Dietetics position paper on vegetarian diets states that *when* "*appropriately planned,* vegetarian, including vegan, diets are healthful, nutritionally adequate, and may provide health benefits for the prevention and treatment of certain diseases" [13]. It further posits the appropriateness of vegetarian diets for all life cycle stages—pregnancy, lactation, infancy, childhood, adolescence, and older adulthood—and athletes [13]. For young children, the provision of a balanced nutrient-rich plant-based diet is particularly crucial for their growth and development; thus, planning is important. Due to the nature of plant foods—that is, absence of vitamin B_{12} that is only found in foods of animal origin and presence of phytates and other phytochemicals that may hinder absorption of certain minerals—specific nutrients need attention in planning nutritionally adequate diets for young vegetarians. These include iron, zinc, vitamin B_{12}, calcium, and vitamin D. Contrary to what most parents fear, vegetarian diets are sufficient or even exceed recommendations for protein; nevertheless, vegan children may need slightly higher amounts of protein than their non-vegan counterparts because of the protein digestibility and amino acid composition of their foods [14].

The rise in number of fortified food products and available supplements and extensive dissemination of nutrition and scientific information through media have pacified concerns about the adequacy of vegetarian and even vegan diets. However, instead of focusing only on strict vegetarian diets as an intervention to mitigate the obesity epidemic, the health-promoting components of vegetarian diets, i.e., foods of plant origin or being plant based, warrant equally important consideration.

When a vegetarian diet is appropriately planned, it can be nutritionally adequate for adults and children and can promote health and lower the risk of major chronic diseases. The nutrients of concern in the vegetarian diet include vitamin B_{12}, vitamin D, omega-3 fatty acids, calcium, iron, and zinc. Vegans in particular require reliable sources of vitamin B_{12} from fortified food or supplements [13]. Although a vegetarian diet can meet current recommendations for all of these nutrients, the use of supplements and fortified foods provides a useful shield against deficiency [15]. The American Dietetic Association, now the Academy of Nutrition and Dietetics, and the American Academy of Pediatrics agree that well-planned vegan and vegetarian diets can satisfy the nutritional needs and promote normal growth of infants and young children [16]. A vegetarian style of eating follows the dietary guidelines and meets requirements of the Recommended Dietary Allowances for nutrients [16].

People choose to adopt vegetarian diets for varied reasons including, but not limited to, health concerns, religious or ethical beliefs, and metaphysical, ecological, socioeconomic, and political reasons. Foods of animal origin are associated with environmental damage, but plant-based diets require less natural resources and, thus, are more environmentally sustainable [13]. In the United States, the prevalence of vegetarianism among children is estimated at 2–4% based on a nationally representative sample of youths aged 8–18 years in 2010 [17]. In the next section, the different dietary patterns adopted by vegetarians are discussed.

The Vegetarian Dietary Patterns

Vegetarianism has a long-standing history in human culture and often associated with beliefs, lifestyles, and health attitudes and is widely practiced among many religious doctrines. Hinduism confers spiritual value on abstinence from meat and encourages practice of vegetarianism to avoid inflicting pain on an animal. Buddhism prohibits the taking of life so its followers may consume a vegetarian diet that includes dairy products and eggs but not meat. Among Christians, Seventh-Day Adventists typically follow vegetarian diets for health reasons, while those who are nonvegetarians only consume meats considered as clean according to health laws found in the Bible.

The vegetarian dietary pattern is mainly plant based, but since there is no single vegetarian eating pattern, vegetarian diets vary only according to the extent of avoidance of animal products. Vegetarian diets can be totally plant based

(i.e., plant only), such as in strict vegetarian or vegan diets, or plant based with limited types and/or amounts of foods of animal origin. Lacto-ovo vegetarianism, which includes milk, dairy products, and eggs, is the most widely practiced form of vegetarianism. Semi-vegetarianism—which can include pescovegetarian (includes fish), pollovegetarianism (includes chicken), and flexitarianism (occasionally includes small amounts of meat in a plant-rich diet)—is a relatively new term associated with vegetarianism that may broaden the accessibility of vegetarian diets to the general public. Table 17.1 lists the various vegetarian dietary patterns and the definitions usually attributed to them.

Table 17.1 Definition of vegetarian dietary patterns

Dietary pattern	Definition
Vegetarian	Considered a general term, refers to a plant-based diet which is completely devoid of or includes egg and/or dairy or limited amounts of animal flesh foods such as poultry, red meat, and fish
Vegan	Completely or strictly plant-based diet, with no animal-derived food (flesh and animal products), such as dairy products, eggs, and sometimes honey
Lacto-ovo vegetarian	A plant-based diet with dairy products and eggs
Lacto-vegetarian	A plant-based diet with dairy products
Ovo vegetarian	A plant-based diet with eggs and/or egg products
Pescovegetarian	A predominantly plant-rich diet which includes fish but excludes meat and meat products; may also include eggs and dairy products
Pollovegetarian	A plant-rich diet which includes chicken/poultry but excludes red meats; may also include eggs, dairy products, and/or fish
Flexitarian	A plant-rich diet with occasional meat or fish
Semi-vegetarian	A pescovegetarian, pollovegetarian, or flexitarian diet

Discourse on benefits, nutritional adequacy, and health effects of different dietary patterns are often based on the amount of plant foods in the diet. Efforts directed toward ensuring the nutritional adequacy and health benefits of vegetarian diets, as suggested by Haddad, Sabate, and Whitten who designed the Vegetarian Food Guide Pyramid [18], involved inclusion of vegetarian dietary pattern adaptations and recommendations to meet dietary guidelines in both the 2010 and 2015 Dietary Guidelines for Americans.

Health Benefits Associated with Vegetarian Diets and Their Components

Pediatric obesity increases the risk for several cardiometabolic problems. A low-saturated fat diet that emphasizes plant foods, such as a vegetarian diet, may lower one's risk. The nutritional advantages to vegetarian diets have been confirmed by clinical research; likewise, prospective studies have determined that adoption of a vegetarian diet at a young age can establish lifelong healthy eating habits associated with lowered risk for chronic diseases [12, 19]. Due to the absence of or minimal inclusion of meat and meat products, vegetarian diets could be potentially low energy but nutrient dense. Compared to their nonvegetarian counterparts, vegetarian children and adolescents have a lower intake of total fat, saturated fat, and cholesterol and a higher intake of fruits, vegetables, and fiber [20]. They are also leaner than nonvegetarian children [20, 21].

The benefits associated with vegetarian diets are largely dependent on foods consumed. Vegetarian diets that include unrefined and unprocessed plant foods provide minerals (K, Mg), antioxidant vitamins (C and E), dietary fiber, and a host of phytochemicals that synergistically work with nutrients to prevent systemic inflammation, insulin resistance, oxidative stress, and dyslipidemias. Emphasis on whole foods results in dietary patterns that are nutrient dense and low energy as well as rich in B vitamins that serve as coenzymes in energy metabolism and, thus, efficiently produce energy from consumed foods.

Protection Against Type 2 Diabetes

Fruits and vegetables are low-calorie nutrient-dense foods that also contain a host of phytochemicals that have antioxidant and other health-beneficial properties. The substantial dietary fiber content of these foods may also confer protective effects against T2D. High combined intake of fruits and vegetables, particularly cruciferous vegetables, confers slight protection against T2D [15, 16]; but, intake of root vegetables and green leafy vegetables is specifically found to provide a more pronounced reduction of T2D risk. Thus, including such foods in the diet may be beneficial for persons at risk for T2D [22].

Reduction of Cardiometabolic Risk Factors

Risk-reducing effects of plant-based foods for cardiovascular problems are well established in adults. In the Dietary Approaches to Stop Hypertension (DASH) trial, blood pressure levels decreased when adult subjects who were in the control diet were randomly assigned to either a diet rich in fruits and vegetables or a diet rich in fruits, vegetables, low-fat dairy products, and reduced dietary fat and cholesterol [23].

Research also confirms the benefits of increasing plant-based foods in children's diets. The Special Turku Coronary Risk Factor Intervention Project (STRIP), a prospective intervention study done among Finnish children, focused on personalized dietary counseling that aimed to limit saturated fatty acid (SFA) intake and increase unsaturated fat, vegetable, and fruit intake from infancy until age 15–20 years. Findings showed reduced risk of metabolic syndrome by 41%, decreased risk of hypertension in both genders by 17%, and reduced risk of hypertriglyceridemia in males by 29% when compared to those who did not receive the intervention [24]. In a similar vein, the Dietary Intervention Study for Children (DISC), a randomized controlled clinical trial started in 1987 among preadolescent children (aged 8–10 years) with elevated low-density lipoprotein cholesterol (LDL-C), tested the efficacy of a dietary intervention compared to usual care in lowering LDL-C and reducing chronic disease development over time. The dietary intervention focused on lowering total fat, SFA, and cholesterol and increasing dietary fiber from fruits, vegetables, and other plant-based foods. Greater decreases in LDL-C were seen for the intervention group compared to the control (usual care) group during the follow-up years until adolescence [25, 26]. In a follow-up study of the original female participants when they turned 25–29 years old, none of the participants had metabolic syndrome or elevated cardiometabolic risk factors, but those who were in the dietary intervention group were found to have significantly lower fasting plasma glucose and systolic blood pressure compared to their counterparts [27]. In another short-term (4-week) trial among obese hypercholesterolemic children aged 9–18 years who were randomly assigned to a plant-based, no-fat diet, there were significant reductions in systolic blood pressure, total cholesterol, LDL cholesterol, high-sensitivity C-reactive protein, serum insulin, and myeloperoxidase values from baseline values [28]. All these studies, both long term and short term, show that improving the quality of food choices and intake during childhood—as simple as replacing SFA with unsaturated fatty acid-rich foods and eating whole grains and more fruits and vegetables—has long-term beneficial health effects that may reduce cardiometabolic risk.

Adolescents consuming mainly vegetarian foods showed significantly better scores on markers of cardiovascular health, including BMI, waist circumference, total cholesterol/HDL cholesterol (TC:HDL-C) ratio, and LDL cholesterol [29]. Those who consume nuts more than once per week also showed lower scores for BMI and serum glucose irrespective of their vegetarian status [29]. Surprisingly, exercise on its own was not statistically associated with any of the risk factors tested, suggesting that diet may be the most significant factor in promoting health during adolescence [29].

Maintenance of Healthy Body Mass Index

Evidence shows that plant protein not only improves body composition but also results in lower body weight compared to animal protein [30, 31]. An observational study among European children found that plant protein intake may play a role in preventing obesity, as shown by the inverse associations between plant protein and BMI z-score and body fat percentage [32]. In a similar vein, regular intake of specific plant foods may prevent overweight among children and adolescents; this was demonstrated by a study of 1764 healthy children and adolescents (aged 6–19 years) who were attending 16 Seventh-Day Adventist (SDA) schools and 13 public schools [33] and another study of 215 adolescents attending five SDA secondary schools which found that vegetarians had lower BMI and waist circumference compared to their nonvegetarian counterparts [29].

The consistency in the association between plant-based consumption and lower BMI exists across time and continents, suggesting that these findings can be applied to the general population in the current food environment. However, a healthy BMI may not be due only to the protective effect of a vegetarian diet but to the lifestyle factors commonly associated with vegetarians as well. For instance, vegetarian or healthy eating pattern among Greek adolescents was associated with more sports activities outside school and less TV watching [34].

Improved Overall Nutrient Intake Profile

A 2002 article reported that vegetarians in a multiethnic adolescent population were more likely to meet the objectives of Healthy People 2010, with less proportion of vegetarians eating less total fat and saturated fat and a greater proportion eating more vegetables and five servings of fruits [35]. Compared to their omnivore counterparts, the diet of Hong Kong Buddhist Chinese vegetarian children is lower in fat (20–23%) and has more fiber (5.8–8.7 g/day) and better polyunsaturated to saturated fatty acid ratio (1.0–1.1), which is closer to the nutritional recommendations for a healthy diet [36]. The growth and bone mineral density of these Chinese vegetarian children were found to be comparable to the general omnivore population, and their prevalence of iron-deficiency anemia and other nutrient deficiencies is low; growth retardation is nil. These findings suggest that a Chinese vegetarian diet can be suitable for fast-growing children [36].

In a poor-resource population where diet is predominantly plant based and mainly composed of grain, roots/tubers, pulses, and legumes or nuts, iron-deficiency anemia prevalence among preschool children is low [37]. This indicates that animal-source foods are not essential for iron status. Young Swedish vegans ate mostly legumes, vegetables, fruits, and berries and took dietary supplements for their vitamins B_{12} and D and calcium and selenium. Their vegetable intake is significantly higher, and the variety of their fruit intake is wider than that of their omnivore counterparts [38]. An assessment of the short-term (6-month) impact of a nutritional intervention aimed at reducing childhood overweight in healthy German preschool children aged 3–6 years revealed significantly increased intake of fruits and vegetables [39]. Although no significant effects were seen on anthropometric parameters, the authors predict that this change in fruit and vegetable intake may eventually lead to favorable anthropometric changes if sustained over a longer time period.

Prevention of Pediatric Obesity with a Vegetarian Diet

Vegetarians are more likely to eat plant foods—e.g., fruits and vegetables—than their counterparts, and in so doing, they consume more low-energy density meals. Thus, they tend to be leaner than nonvegetarians. However, unplanned diets may potentially place vegetarians or vegans at risk for certain nutrient deficiencies [13, 40]. Developmental changes during the transition from adolescence to adulthood may affect how

adolescents eat relative to how they perceive their appearance, express their individuality and uniqueness, or explore new lifestyles or establish their identities. For this reason, adolescents and young adults may be more vulnerable to disordered eating behaviors when focus is on losing weight to conform to what they perceive to be desirable or appealing. Disordered eating is found to be more frequent among adolescents and young adults who report that they are "vegetarians" [41–43]. As these disordered eating patterns generally precede the adoption of a vegetarian diet, it is doubtful that vegetarianism leads to disordered eating.

Habits that protect against childhood obesity include eating more vegetables and fruits, eating meals with family, and being physically active. Because children's eating behaviors are influenced by family, caregivers, friends, schools, marketing, and the media, successful interventions for preventing childhood obesity must incorporate counseling and nutrition education into family- and school-based programs, to encourage physical activity and dietary change [44]. Nutrition intervention programs that are family based have been found to be successful in promoting healthful eating, limiting screen time, and preventing obesity among children and preadolescent youth [45]. A plant-based diet is associated with a greater intake and/or variety of plant foods, which may have a significant influence on the primary prevention of overweight and obesity for weight loss and weight maintenance in children and during adulthood [46].

Although there have been concerns that a diet too high in dietary fiber may lead to growth retardation and malabsorption of minerals, the larger problem is that stripping refined foods of fiber increases the risk for obesity in children. A fiber-rich diet could reduce energy intake due to increased satiety and may be of great benefit in terms of weight maintenance. Although a high-fiber diet has been established to have negligible impact on mineral balance in adults, there is little available research among children. With the rapid growth of infants, it is theorized that dietary fiber would have a major effect on growth by reducing energy intake. However, this potential effect has yet to be established.

Height and weight data obtained from a 2-year longitudinal survey were analyzed for 2272 children aged 6 through 18 years who were attending public schools or Adventist schools in southern California. Adventists avoid use of alcohol or tobacco, and many adhere to a lacto-ovo vegetarian diet [20]. Age-adjusted regression analysis showed that SDA schoolboys were 1.6 cm taller than public schoolboys, while no significant differences were observed in height for girls. After controlling for height, boys and girls in the SDA schools were found to be leaner than their public school peers, by 1.27 and 1.16 kg, respectively. When compared with their meat-consuming peers, Adventist vegetarian children were taller by 1.8 cm in boys and by 1.9 cm in girls after controlling for age, mother's and father's heights, and father's occupation, which was used as an indicator of socioeconomic status [47]. These results suggest that a health-oriented lifestyle in childhood and adolescence, such as the one followed by Adventists, is compatible with adequate growth and may protect against overweight and obesity [20].

Adult vegetarians, including those who continue to consume dairy products, have been shown to have a lower BMI than their meat-eating counterparts, and although the association is less clear in young children, by adolescence, vegetarians generally have a lower BMI than nonvegetarians [47]. A meta-analytic review found that weight gain prevention programs with greater beneficial effects are those that target children and adolescents, possibly because of parental involvement in children's obesity prevention programs and, for adolescents, due to their ability to grasp intervention material and exercise control over their food intake [48]. A 4-week prospective trial involving obese hypercholesterolemic children aged 9–18 years and their parents randomly assigned these child-parent pairs to either a plant-based (PB) no-fat diet or the American Heart Association (AHA) diet. Both diet groups had significant reductions in cardiovascular disease

(CVD) risk factors, which included anthropometric (BMI z-score, weight, waist circumference, mid-arm circumference), clinical (systolic and diastolic blood pressure), and biochemical (lipid profile, blood glucose, HbA1c, insulin, and others) parameters. Anthropometric-related measures that significantly decreased in children of both diet groups were weight and mid-upper arm circumference; additionally, BMI z-scores decreased for the PB diet group, and waist circumference decreased for the AHA diet group. Six other CVD risk factors decreased for the PB group and one other factor for the AHA [29]; similar findings were noted among the parents. The decrease in obesity/overweight and CVD risk among the children who followed a healthy plant-based diet indicates that there could be a lifetime health benefit in starting children on such diets early in life.

Mechanisms that Explain the Health Benefits of Vegetarian Diets

A diet rich in whole grains and cereals, fruits, vegetables, legumes, and nuts provides antioxidant vitamins/provitamins (C, E, beta-carotene), minerals (selenium), folic acid and other B vitamins, dietary fiber/resistant starches, and bioactive nonnutritive phytochemicals (flavonoids, phytosterols, polyphenols, and others). Absence of meat in the diet translates to low intake of saturated fatty acids and cholesterol. As plant foods are mostly comprised of water, which is noncaloric, high intake of plant foods and lesser intake of saturated fats may contribute to the overall low-energy density of the vegetarian diet [46]. The high amount of dietary fiber can also increase satiety, reduce blood sugar levels, and prevent overeating.

The gut microflora of the infant develops slowly and in response to diet. It is necessary to understand the implications for the microflora of increasing fermentable components in the diet of the young and any long-term effects. Plant-based dietary patterns may promote a more favorable gut microbial profile because they are rich in dietary fiber and fermentable substrates—nondigestible carbohydrates—which are metabolized to short-chain fatty acids by the gut microbiota. Studies have shown significant differences between the gut microbiota composition of vegetarian and nonvegetarian [49–52] and obese and nonobese [53, 54] children. For instance, *Bacteroides* is significantly lower in vegetarians and vegans compared to omnivores, and obese children have a lower amount of *Bifidobacteria* and a higher amount of *Escherichia coli* compared to nonobese counterparts [49, 51]. The presence of *B. fragilis* in early infancy tended to be associated with higher BMI later in childhood but only if dietary fiber intake is low [52]. Exploring further the role of the gut microbiota in the development of childhood obesity and how they are associated with dietary intake may potentially reveal new strategies for obesity prevention during the early years. Studies indicate that the more protective gut bacterial species found in vegans may explain the lower inflammation in vegans compared to omnivores [55].

Methods to Initiate and Increase Fruit and Vegetable Intake in Young Children

Intake of a variety of fruits and vegetables is part of a healthy vegetarian diet. Preference for fruits and vegetables early in life predicts increased intake later in life [56], and this could have beneficial long-term effects. Genes and the shared environment influence food preferences, and studies on twins indicate greater genetic influence on preference for vegetables and fruits and more shared environment influence on snacks and desserts [57–59]. Vegetables appear to be the most disliked food among young children [60], and fruits are preferred over vegetables [61]. Focusing interventions on increasing taste preference may result in increased fruit and vegetable intake [62]. Four strategies that could increase fruit and vegetable intake are discussed below.

Repetition

Studies have shown that repeated exposure increases children's preference for food or flavor. In addition, making the foods available is more likely to increase consumption [63]. To compare the effectiveness of different learning strategies in promoting the intake of a new vegetable, UK children aged 9–38 months were randomly assigned to one of the three conditions: repeated exposure, flavor-flavor learning, and flavor-nutrient learning. Each child was offered ten exposures to their respective version of a new vegetable (artichoke). Repeated exposure to three variants of the new vegetable was sufficient to increase its intake regardless of the addition of a familiar taste or energy content [64]. The study found that five repetitions seem enough to increase intake of the new vegetable compared to the initial exposure. The Academy of Nutrition and Dietetics maintains that a minimum of eight to ten exposures to a new food can encourage children to overcome their neophobic response and choose to eat the food [16]. In light of the present childhood obesity epidemic, *repeated exposure* is a simple and effective technique that does not require the addition of significant amounts of energy, an elaborate preparation method, or a reward. More importantly, *repeated exposure* can be used both at home and day-care settings to improve acceptance of new vegetables [64]. Repetition methods to increase fruit and vegetable intake are most effective when paired with the modeling of healthy eating behaviors by adult caregivers [16].

Sequence

In a single-school randomized crossover trial, preschoolers were found to significantly increase their intake of fruit, but not vegetable, when fruits and vegetables were served to them first before other meal items compared to when fruits and vegetables were served in tandem with other menu items in a traditional family-style meal service which allows a child to self-serve [65]. When served provider-portioned meals where specific food quantities were on each child's plate, fruit and vegetable intake was significantly lower and energy intake significantly higher compared to the traditional family-style meal service [65]. This indicates that serving fruits in advance of other meal items and in the context of currently recommended traditional family-style meal service [16] where children can self-serve could increase fruit intake in young children. Since vegetables vary greatly in taste, texture, and form, efforts on vegetable preparation and presentation may be needed to increase vegetable intake.

Portion Size

The amount of food served to a child, specifically entrée foods, influences total energy intake of children [66, 67]. To determine if serving varying portions of an entrée has an effect on intake of other foods in an ad libitum diet, a within-subject study design was used in a group of children aged 3–6 years [68]. Six macaroni and cheese portions (100–400 g in 60 g increments) were served at separate meals together with fixed portions of unsweetened applesauce, green beans, whole-wheat roll, and milk or soy milk. Increasing portion size significantly increased children's entrée intake and decreased intake of other foods served with the entrée, especially fruits and vegetables. As a result, children consumed a significantly more energy-dense lunch as portion size increased and had more food wastage [68]. BMI percentile moderated the positive association between portion size and entrée intake—overweight children showed greater increases in entrée intake with increasing portion size [68]. Serving smaller age-appropriate entrée portions may be one strategy to decrease intake of energy-dense foods and promote intake of fruits and vegetables served with the entrée.

Presentation

One study among elementary schoolchildren showed that giving healthy foods, specifically vegetables, attractive names increased the intake

of those foods [69]. The students were 16% more likely to significantly persistently choose more hot vegetable dishes when they were given fun or attractive names [69].

Planning Vegetarian Diets for Children: How to Ensure Adequate Nutrition

A well-balanced lacto-ovo vegetarian diet, including dairy products, can satisfy all nutritional needs of the growing child. In contrast, a vegan diet, which excludes all animal food sources, should be supplemented with vitamin B_{12} and should also ensure adequate intakes of calcium and zinc and energy-dense foods containing enough high-quality protein for the development of young children. Due to the nature of most plant foods, certain nutrients could be at stake in inappropriately planned vegetarian diets. The guidelines for a nutritionally adequate vegetarian diet are illustrated in a Vegetarian Diet Pyramid shown in Fig. 17.1 [18, 70, 71]. Table 17.2 lists pointers that clinicians may use when counseling vegetarian clients. Additionally,

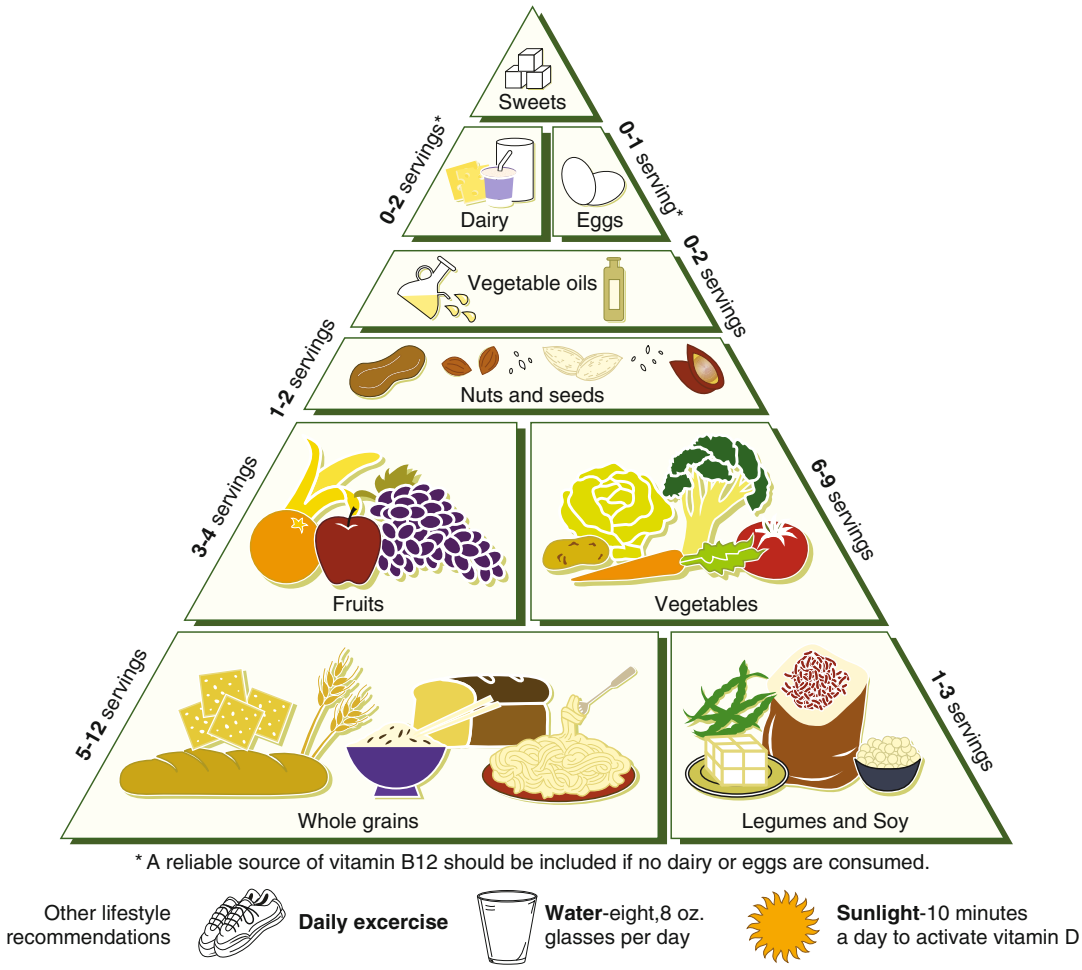

Fig. 17.1 The Vegetarian Food Guide Pyramid. Guidelines for healthful vegetarian diets include variety of plant foods in abundance, emphasis on unrefined foods, a healthy range of fat intake, adequate water and other fluids, regular physical activity, and moderate sunlight exposure (Developed and Copyrighted by the School of Public Health at Loma Linda University, California, USA. Reproduced with permission)

Table 17.2 Raising a vegetarian child: counseling points for health providers

Life stage	Counseling points
Infancy	*If the infant is breastfed:* • Supplement with vitamin B_{12} if the vegetarian mother is not supplementing or consuming adequate food sources. If the mother is lacto-vegetarian, check vitamin B_{12} serum level/urinary methylmalonic acid. If the mother is vegan, both the mother and child should supplement with vitamin B_{12} • Supplement a *full-term* infant with liquid iron beginning at 4 months *if at least 50% breastfed*; supplement a *preterm* infant with liquid iron starting at 1 month until 1 year of age • Assess sunlight exposure; supplement with 400 IU of vitamin D if the infant is exclusively or partially breastfed *If the infant is bottle-fed:* • Advise against use of rice drinks, non-adopted soy drinks, and almond drinks which are not suitable milk substitutes even if calcium fortified • Ensure use of iron-fortified infant formula or soy formula until 12 months; additional iron supplementation is not necessary • Ensure 400 IU of vitamin D from formula is taken daily *During weaning:* • Consider an iron supplement in breastfed infants from 6 months onward • Ensure source of calcium and protein by ascertaining continued breastfeeding or feeding a minimum of 400 ml of infant formula • Ensure 400 IU of vitamin D from food sources or infant formula. • Review introduction of solids with protein-rich foods (e.g., pureed tofu, pureed legumes, soy yogurt) starting at 6 months or when infant shows readiness for solid foods. – Ensure sufficient caloric density of meals by adding oil rich in alpha-linolenic acid (flaxseed, canola, rapeseed, or walnut oil). – Assess parents' knowledge on food preparation and their access to a variety of nutrient-rich foods. – Request that parents keep a 7-day food diary and refer to a dietitian for evaluation.
Toddler/preschool	• Evaluate calcium and vitamin D sources (fortified dairy products, etc.) and sunlight exposure • Ensure sources of vitamin B_{12} and iron and foods that increase iron absorption (e.g., vitamin C-rich foods) • Ensure sufficient caloric intake; advise healthy snacking on a variety of nutritious foods and inclusion of energy-dense foods such as refined grains • Review choking hazard with certain foods; recommend grinding nuts and cutting vegetables into bite size pieces • Limit raw unprocessed foods which have lower digestibility compared to cooked/fermented products and more difficult to ingest due to inadequate mastication skills at this age • Assess vegan/vegetarian food availability at day care • Request that parents keep a 7-day food diary and refer to a dietitian for evaluation
School age	• Evaluate calcium intake; supplement if intake from calcium-fortified foods is inadequate • Assess nutrition knowledge of the child and educate accordingly • Assess availability of vegetarian options in school lunch; advise parents to discuss food choices and alternatives with the child's friends • Counsel parents and the child that this may be the first time the child learns the diet is considered "alternative"; nutrition education at school may be different from the typical home diet
Adolescent	• Determine the rationale for adopting a vegetarian diet • Assess nutrition knowledge and provide vegetarian nutrition information sources; teach how to read food labels • Ensure sources of vitamin B_{12} and calcium. Fortified foods are alternative sources. When necessary, recommend supplements • Evaluate weight and body image concerns and frequency of dieting and exercise patterns to lose weight. Check the growth curve. Consider that the adolescent may attempt to camouflage an eating disorder with a "vegetarian" diet • Encourage parental support and assistance with menu planning • Encourage vegetarian/vegan teens in omnivore households to plan a vegetarian/vegan meal for the family • Assess availability of vegetarian options in school lunch

Data from: Dunham L, Kollar LM. Vegetarian eating for children and adolescents. J Pediatr Health Care. 2006;20(1):27-34; and Van Winckel M, et al., Clinical practice: Vegetarian infant and child nutrition. European Journal of Pediatrics. 2011;170(12):1489–94

Table 17.3 Vegetarian resource websites

Group	Website
Vegetarian Resource Group	https://www.nutritionsociety.org
MedlinePlus	https://medlineplus.gov/vegetariandiet.html
USDA NAL Vegetarian Nutrition	https://www.nal.usda.gov/fnic/vegetarian-nutrition
Physicians Committee for Responsible Medicine	http://www.pcrm.org

a list of vegetarian websites that provide clinical guidance for children and adolescents is provided in Table 17.3.

Below are a few pointers when planning vegetarian diets for children.

Iron

Absorption of nonheme iron, which is an iron coming naturally from plant products, can be enhanced if consumed in combination with vitamin C-rich foods. For example, adding a tomato or lemon juice to raw vegetable salad or eating fruits with plant-based foods will improve the absorption of the nonheme iron. Compounds called phytates, along with some additional factors naturally found in legumes, nuts, and whole grains, can inhibit iron absorption, so it is important to consume a variety of iron-rich foods daily [14, 72, 73]. Vegetarian and vegan children are also at greater risk of iron-deficiency anemia, although adequate iron status is achievable with well-planned vegetarian diets [72]; this is evidenced by a study among British toddlers aged 1.5–4.5 years that found iron status was not associated either with iron intake or with consumption of a vegetarian diet [74, 75]. On the other hand, despite having similar total iron intake, low heme iron in the diet of vegetarian adolescent girls aged 11–18 years accounted for the higher prevalence of poor iron status (low hemoglobin, serum ferritin, and transferrin saturation) in this group compared to their meat-eating counterparts [75].

Zinc

Zinc absorption is affected by the phytates that naturally occur in whole grains and legumes. Some vegetarians may require a higher intake of zinc than the dietary reference intake. Methods such as soaking dried beans, and then discarding the soaking water before cooking, will remove most of the phytates and help enhance zinc absorption [14, 72, 73].

Calcium

To achieve adequate calcium intake, vegetarians can consume calcium-fortified soy formulas, soy and other milk or dairy alternatives (e.g., soy cheese, soy yogurt), and various other calcium-fortified foods. Eating these foods in the age-appropriate amounts will ensure adequate calcium intake [73]. For infants, it is important to note that commercial soy milk should not be introduced before the end of the first year because of the low bioavailability of iron and zinc from soy. Fortified infant soy formulas are recommended for infants who are not breastfed [14, 76]. Provided that a child is growing normally, it is suitable to offer him or her full-fat commercial soy milk at age 1 year or older. Not all soy milk is fortified with vitamin D and calcium, so it is important that parents check the label. Cruciferous vegetables, such as broccoli and collard greens, have highly bioavailable calcium. In a 2015 comparison of different plant-based diets, the vegan group was the only group to have mean calcium levels that were insufficient to meet Dietary Reference Intakes for males or females [77]. Calcium intake is often lower in vegans who consume less calcium-rich foods.

Vitamin D

Past research has shown that exposing one's hands and face to the sunlight two or three times each week for 20–30 min provides

enough vitamin D for light-skinned children and adolescents in moderate climates [73]. The most recent literature recognizes that specific age groups require a vitamin D supplement: infants who are exclusively breastfed (especially dark-skinned infants), infants drinking less than 500 mL of vitamin D-fortified milk each day, and children and adolescents who do not receive adequate sunlight exposure (due to climactic conditions, cultural clothing norms, etc.) or do not take a multivitamin containing at least 200 IU of vitamin D [72]. Dark-skinned individuals, especially those living in temperate zones, need more exposure and/or vitamin D supplementation. Vegetarians can choose vitamin D-fortified soy milk, cheese, yogurt, and cereals as dietary sources of this nutrient. Mushrooms exposed to UV radiation can provide vitamin D in the form of ergocalciferol, the form commonly available in supplements.

Vitamin B_{12}

Animal products are considered the only reliable source of vitamin B_{12} or cobalamin, as the cobalamins in algae and seaweeds are nonactive analogues [78]. Because vitamin B_{12} is an essential cofactor in DNA and RNA synthesis, organs with rapid cell turnover such as the bone marrow and the intestine will be the first to exhibit deficiency symptoms. Due to the role of vitamin B_{12} in the maintenance of the nervous system, deficiency in this vitamin can cause potentially irreversible neurological damage. Vitamin B_{12} deficiency can result in megaloblastic anemia. High folate intake, which is likely to occur among vegetarians, can mask the signs of megaloblastic anemia [79].

Lacto-ovo vegetarians may benefit from the high bioavailability of cobalamin from dairy products, which is greater than from meat, fish, or eggs [79]. However, although vegans have a much higher risk of developing vitamin B_{12} deficiency, lacto-ovo vegetarians are also at risk: fish or meat consumption less than once a week predisposes to vitamin B_{12} deficiency. A limited body reserve of vitamin B_{12} at birth exposes infants breastfed by vegan mothers to risk of vitamin B_{12} deficiency between 2 and 12 months of age even in the absence of maternal deficiency [80]. Prevention of vitamin B_{12} deficiency among vegetarians can be achieved by consuming B_{12}-fortified foods or taking a vitamin B_{12} supplement. There exists no clinical evidence for overdosing with vitamin B_{12}.

Omega-3 Fatty Acids

Vegetarian diets can be low in long-chain omega-3 fatty acids if eggs, fish, or large amounts of sea vegetables are not consumed. Sea vegetables provide docosahexaenoic acid, important for vision and cognitive functions. The AHA has confirmed that alpha-linoleic acid, an omega-3 fatty acid of plant origin, can be converted to eicosapentaenoic acid (EPA) by human beings to a limited extent [81]. Because EPA has antithrombotic and cardioprotective effects, vegetarians must consume a reliable source of its precursor, alpha-linolenic acid, in their diet to ensure adequate production of long-chain n-3 fatty acids. Flaxseed, walnuts, chia seeds, soybeans, tofu, and extracted plant oils such as canola oil, soybean oil, and walnut oil contain reasonable amounts of alpha-linolenic acid. Consuming DHA- and/or EPA-fortified food products, if tolerated, is another alternative.

Dietary Fiber

There is very little evidence that fiber in the diets of children in the developed world is harmful. Indeed, with the growing rate of childhood obesity, a reduction in the energy density of the diet may be of great benefit [82]. The new proposed definition for dietary fiber includes many compounds such as resistant starch and oligosaccharides that may be of more benefit to young children. As the gut microflora of the infant develops slowly and in response to diet, it is necessary to understand the implications for the

microflora and potential long-term effects of increasing fermentable components in the diet of the young.

Vitamin Supplementation

All vegetarians, but particularly strict vegans who require dietary vitamin B_{12} supplementation, can benefit from a multivitamin supplement that will help ensure that their nutritional needs are satisfied. Infants require supplementation of at least 400 IU of vitamin D daily, and children require 600 IU to satisfy the adequate intake (AI) values established by the Institute of Medicine [83]. Vitamin B_{12} supplementation (0.4 μ/day for the first 6 months, 0.5 μ/day beginning at 6 months of age) is necessary for breastfed vegan infants if the mother does not take a supplement or if she does not include B_{12}-fortified foods in her diet. Adequate intake of B_{12} in infants is based on the B_{12} content of the breast milk of well-nourished mothers, which approximates 0.42 μ/L [83]. A prospective descriptive study of children and adolescents found that obesity in children and adolescents was associated with an increased risk of low vitamin B_{12} concentration [84]. The authors recommend that dietary assessment of obese children should include an estimation of vitamin B_{12} intake [84]. Although zinc can be low in vegetarian diets, the American Academy of Pediatrics does not currently recommend zinc supplementation [72].

Summary

Among the current recommendations that likely would improve health and the environment, many are increasingly oriented toward increased plant food consumption. Because foods are not consumed in isolation but, rather, as part of a total dietary pattern, more research regarding the use of vegetarian diets in children is required, and studies should be prospective. The available literature on health effects of individual foods and whole lifestyle diets is insufficient and justifies a call for future food-oriented research, including expanding the evidence base for plant-based and vegetarian diets.

Diet and other lifestyle factors are critical determinants of pediatric and adult obesity. Low in energy and rich in nutrients and fiber, the various components of a vegetarian diet may act in concert to reduce the risk of pediatric obesity and attenuate the risks of complications. A well-planned vegetarian diet that includes fruits, vegetables, whole grains, and legumes and limits energy-dense snacks such as foods made with refined flour or refined sugar is most likely to prevent excessive weight gain in children. Approaches to facilitate dietary change include various methods to initiate and increase fruit and vegetable intake among children. Efforts should be made to improve the availability, accessibility, and affordability of healthier food choices to accommodate and support families seeking to improve the health of their children. Policy-level changes are necessary to promote a shift from the current obesogenic food environment to one that facilitates healthy weight maintenance among children.

Editor's Comments and Question

I am a great eater of beef, and I believe that does harm to my wit.
Sir Andrew, in Shakespeare's Twelfth Night

Eat Food. Not too much. Mostly plants.
Michael Pollan, Food Rules: An Eater's Manual

There is considerable evidence that the risks of pediatric and adult obesity and their comorbidities are shaped by *patterns* of dietary intake rather than the intake of any single macronutrient; see Chap. 1 on Childhood Obesity in the Modern Age: Global Trends, Determinants, Complications, and Costs and Chap. 16 on Non-vegetarian Dietary Interventions. In that respect, a well-designed vegetarian diet incorporates low-energy, high-fiber, nutrient-dense plant-derived foods and excludes certain foods now considered toxic, such as processed meats.

The results of the Finnish STRIP study suggest that adoption of such a diet in childhood might reduce the long-term risk of metabolic syndrome. This finding lends support to the potential value of plant-based diets in the prevention and management of childhood obesity.

Yet in our obesogenic environment, the commitment to vegetarianism (or any of its variations) in children requires patience, dedication, and support of the family and, in all likelihood, the material and moral support of the community; maintaining a healthy vegetarian diet is far easier when your parents, relatives, friends, and colleagues understand and model the behavior themselves.

In some (but not all) people, vegetarianism may represent one component of a broader commitment to a healthy lifestyle, which includes avoidance of tobacco and excess alcohol. Other than the study of Greek adolescents cited in your chapter, is there any evidence that adoption of a vegetarian diet is associated with, or promotes, a beneficial change in physical activity or energy expenditure?

Authors' Response

Associations between increased physical activity and vegetarian diets among adults may exist but are most likely explained by the kind of lifestyle choices associated with adopting vegetarian diets, which generally include healthy behaviors such as regular exercise in addition to low fat and high fiber intake. High energy and macronutrient needs for athletic performance can be readily provided by a vegetarian diet so some athletes choose to be vegetarians. Among children and adolescents, there is no existing evidence that adopting a vegetarian diet leads to a beneficial change in physical activity or energy expenditure. Observational studies, however, show that eating a healthier diet—not necessarily vegetarian—clusters with healthy behaviors, i.e., high physical activity, low sedentary behavior, and longer sleep duration[a], and diet quality is associated with vigorous physical activity[b]. Likewise, community-based interventions that focus on increasing fruit and vegetable intake but do not specify the adoption of a vegetarian diet have reported success with managing obesity in children using a holistic approach incorporating exercise[c,d]. There are no known causal pathways by which a vegetarian diet could lead to changes in physical activity or energy expenditure.

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18 Energy Expenditure in Children: The Role of NEAT (Non-exercise Activity Thermogenesis)

Lorraine Lanningham-Foster and James A. Levine

Introduction

By the law of conservation of energy, body fat increases when energy intake is consistently greater than energy expenditure. Excess body fat and obesity are the result of sustained positive energy balance [1]. The pandemic of obesity has spread from the United States to Europe and is now emerging in middle- and even low-income countries [2]. In the United States, for example, since the 1970s, the weight of the average person has increased by ~12 kg; importantly this trend affects all ages, races, and socioeconomic groups [3]. Because of the health [3, 4] and economic costs of obesity [5], the urgency to understand why humans are gaining weight has intensified.

It is accepted that nutritional quality is often poor [6]. However, there is controversy as to whether increased energy intake has accompanied the obesity epidemic. For example, in Britain, obesity rates have doubled since the 1980s yet energy intake appears to have decreased [7]. The NHANES surveys in the United States are difficult to interpret because the method used to examine energy intake changed between surveys [8, 9]. In the absence of firm data that link increased dietary intake to obesity [10], the role of energy expenditure in human energy balance has come under greater scrutiny.

Classically, there are three components of human daily energy expenditure (Fig. 18.1a): basal metabolic rate, the thermic effect of food, and activity thermogenesis. Basal metabolic rate is the energy required for core body functions and is measured at complete rest without food [11, 12]. It accounts for about 60% of daily energy expenditure in a sedentary person. Nearly all of its variability (~80% of the variance) is accounted for by body size—or more precisely lean body mass—the bigger a person, the greater his/her basal metabolic rate [13]. The thermic effect of food (TEF) is the energy expended in response to a meal; it is the energy associated with digestion, absorption, and fuel storage [13, 14]. The thermic effect of food accounts for about 10% of daily energy needs and does not vary greatly between people. The remaining component, activity thermogenesis, can be subdivided into exercise and non-exercise activity thermogenesis (NEAT).

Despite more limited information on energy expenditure in children compared to adults, there are some key differences between children and adults. Children have a higher basal metabolic rate compared to adults [15–17]. As children mature, there is a gradual decrease in energy expenditure with increasing age. The changes in

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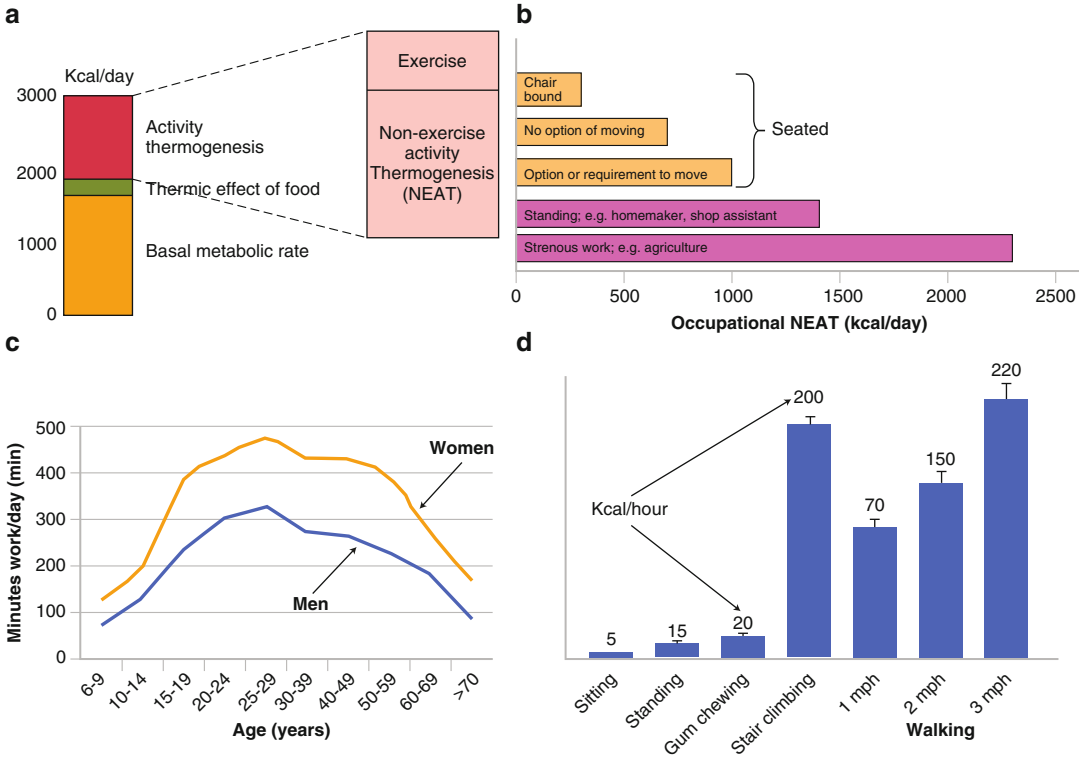

Fig. 18.1 (**a**) Components of total daily energy expenditure (TDEE) in a free-living sedentary adult. (**b**) The effect of occupational intensity on energy expenditure (Data from Black AE, Coward WA, Cole TJ, Prentice AM. Human energy expenditure in affluent societies: an analysis of 574 doubly-labelled water measurements. Eur J Clin Nutr. 1996;50:72–92). (**c**) Work burdens for women and men from the Ivory Coast versus age (Data from Levine JA, Weisell R, Chevassus S, Martinez CD, Burlingame B, Coward WA. The work burden of women. Science. 2001;294:812, and from Levine J, Heet J, Burlingame B. Aging on the job. Sci Aging Knowledge Environ. 2006;2006:pe16). (**d**) Energy expenditure above resting for a variety of activities (Data from Levine JA, Schleusner SJ, Jensen MD. Energy expenditure of non-exercise activity. Am J Clin Nutr. 2000;72: 1451–54)

energy expenditure appear to be related most closely to changes in body composition that occur around the time of puberty. There also appear to be hormonal influences such that there is a larger increase in fat-free mass in boys compared to girls. Energy requirements are thus increased, with the greatest increase for boys, at the start of puberty. Variation in energy expenditure has been explored in relationship to obesity in children. Although obese children spend less time engaged in physical activity, they do not have a reduced resting metabolic rate or thermic effect of food.

Measurement of Energy Expenditure and NEAT

The measurement of energy expenditure associated with rest, activity, the utilization of food, and NEAT has been explained in-depth previously [18, 19]. There are, however, many important considerations for performing these measurements in children compared to adults. General methods for measurement of energy expenditure are described here with emphasis on appropriate procedures used with children.

Basal Metabolic Rate and Resting Energy Expenditure

Basal metabolic rate (BMR) is the energy a fasted person expends at complete rest shortly after awakening in the morning. BMR should be measured in individuals who slept at the site of measurement overnight. For this reason it is generally not practical to routinely perform this measurement in young children. A more common approach would be to measure the energy expenditure associated with rest. Resting energy expenditure (REE) should be performed in the postprandial state, at least 6 h after consumption of any calories or performing any rigorous activity. For children, it is ideal to complete this measurement first thing in the morning after an overnight fast. Children should be fully rested while supine for 60 min prior to the measurement. A common technique is to allow the child to watch an age-appropriate video while resting.

The measurement should be performed with the child supine. A single pillow may support the child's head and/or the head of the bed should be at a 10° vertical tilt. The child should be in thermal comfort and the room should not be brightly lit. Children should be encouraged to lie motionless and should not be allowed to talk. The age of the child may impair their ability to remain motionless for long periods, and researchers often develop creative approaches to encouraging appropriate behavior. For example, a simple technique of giving a child a laboratory timer so that they know how much time they have to lie still may be helpful. The measurement period should last for 20 min.

Thermic Effect of Food

Measurement of the thermic effect of food is also challenging in younger children. However, the measurement may be more ideal in school-age children, ideally at the age of 10 and above. Optimally, a measurement of resting energy expenditure should be performed first; then the child is provided a meal. The energy content of the food should be known precisely and should be 400 kcal or greater. Providing children with food that they prefer to eat is critical. Parent involvement with food choices is preferred over allowing the child to select the foods. Energy expenditure should then be measured for 360 min or until energy expenditure falls to within 5% of the resting energy expenditure. For those using hood-based systems (with response time 2 min), energy expenditure can be measured every 15 min out of 30 min to avoid subject agitation. The thermic effect of food is calculated from the area under a curve describing the energy expenditure above resting energy expenditure (EE-REE) versus time. Some would argue that it is of value to also measure the thermic effect of noncaloric meals.

Energy Expenditure of Physical Activities

Points of reference are important. Resting energy expenditure should be measured first, and then the energy expenditure of the posture of reference should be measured while the child is motionless. For example, for measuring the energy expenditure of desk work at school, sitting energy expenditure should be measured as the point of reference. For measuring the energy expenditure of standing in the school play yard, standing energy expenditure should be measured as the point of reference. A creative approach may be required: standing or sitting motionless is not a natural mode of activity. Distraction is a common technique; children are frequently allowed to watch age-appropriate videos during measurement of activity energy expenditure. Measurement of energy expenditure during the performance of the activity of interest should be performed for 10–15 min if the calorimeter has a response time of 2 min. Where calorimeter response times are longer, the measurement period needs to be prolonged so that steady-state energy expenditure is reached. However, in

working with children, it is ideal to use equipment with lower response times to minimize the length of the measurement period. The energy expenditure for the activity can be calculated as the steady-state energy expenditure for that activity minus (or divided by) either the energy expenditure of the posture of reference or the resting energy expenditure.

Defining Exercise and NEAT

Exercise is defined as "bodily exertion for the sake of developing and maintaining physical fitness," for example, sport or visiting the gym [20]. The vast majority of world-dwellers do not participate in exercise as so defined, and for them, exercise activity thermogenesis is zero. Importantly too, the vast majority of "exercisers" participate in exercise for less than 2 h/week, and for them, exercise accounts for an average energy expenditure of less than 100 kcal/day. *Given that most children do not participate in organized sport activity (see below), their energy expenditure from exercise (as defined above)* per se *is low.*

NEAT is the energy expenditure of all physical activities other than volitional sport-like exercise. NEAT includes all those activities that render us vibrant, unique, and independent beings such as dancing, going to work or school, shoveling snow, playing the guitar, swimming, or walking in the modern mall. NEAT is expended every day and can most easily be classified as NEAT associated with occupation and NEAT associated with leisure. In children, the concept of NEAT may be slightly different compared to adults, as children more commonly engage in NEAT associated with leisurely play. A child's frequent participation in bouts of activity is important for proper development; this is true not only in humans, but across several species. School-age children confined to the limitations of their environments are likely to engage in NEAT associated with leisure and NEAT associated with school. *Indeed, for most children, the total energy expenditure associated with NEAT exceeds greatly the energy expenditure associated with volitional sport-like exercise; see Energy Equivalents of Daily Activity in the Appendix.*

NEAT Energy Expenditure

NEAT is commonly measured by one of two approaches. The first is to measure or estimate total NEAT. Here, total daily energy expenditure is measured using techniques such as the doubly labeled water method [21–23] or gas and/or heat exchange (room calorimetry), and from it resting energy expenditure + thermic effect of food + exercise activity thermogenesis (EAT) is subtracted [TOTAL NEAT = TEE—(REE + TEF + EAT)]. The second approach is the factorial approach whereby the components of NEAT are quantified and total NEAT calculated by summing these components. This approach is frequently used for estimating NEAT in free-living children. First, a child's physical activities are recorded over the time period of interest (e.g., 7 days), for example, using accelerometry [24]. The energy equivalent of each of these activities is determined. The time spent in each activity is then multiplied by the energy equivalent for that activity. These values are then summed to derive an estimate of NEAT. The advantage of this approach is that the components of NEAT can be defined. This final point is critical because the components of NEAT in children and adults are likely different and customization based on the individual's activity patterns is beneficial in more accurately determining NEAT.

NEAT Variability

Daily energy expenditure varies substantially [25]. In fact highly active adults expend three times more energy per day than inactive adults [25], and this marked variability in daily energy expenditure is even greater when data from non-industrialized countries are considered [26, 27]. Overall, for two adults of similar size, daily energy expenditure varies by as much as 2000 calories per day. As noted above, basal metabolic rate is largely accounted for by body size, and the thermic effect of food is small. Thus, activity thermogenesis must vary by as much as 2000 calories per day. Given that volitional exercise

makes only a minor contribution to activity thermogenesis in most people, this wide variation in daily activity thermogenesis must be explained by NEAT.

In adults, occupation is a key determinant of NEAT. For someone of average age, sex, and weight, occupational NEAT varies as shown in Fig. 18.1b [25]. If an average person were to go and work in agriculture, their NEAT could theoretically increase by 1500 kcal/day [27].

Understanding the role of occupation on NEAT is far from straightforward, however, because occupation-related NEAT is overlaid simultaneously by societal *and* biological drives. In Fig. 18.1c [27, 28], the occupational NEAT of more than 5000 dwellers from agricultural regions of the Ivory Coast is shown. Each individual was followed for 7 days by a trained enumerator, and all their daily tasks were recorded using 1 of 200 numeric codes. First, the societal effect of sex on work burdens can be seen; women work more than men. In these societies, the societal construct is that women conduct all (>95%) of domestic tasks and about a third of agricultural tasks. Men work exclusively in agriculture and have greater leisure time than women [27]. Second, these data demonstrate the interaction of aging on work participation, noting that this population is unfettered by retirement policy. As aging occurs, occupational NEAT declines (Fig. 18.1c) [27, 28]. Across all species that have been studied, non-exercise activity levels decline with aging [29]. These data thereby depict the interplay of both society and biology. Other studies [25] and these suggest that occupation is the major predictor of NEAT in adults; active work can expend 1500 kcal/day more than a sedentary job [26, 27].

Variability in leisure [30] also accounts for substantial variability in NEAT. The energy expended in several activities is shown in Fig. 18.1d [31]. Consider that a child returns home from school by parent car at 4 pm. From then until bedtime at 9 pm, the primary activity may be to operate the television remote control or video game control in a semi-recumbent position. For these 5 h, the average energy expenditure above resting would approximate 8%, and the NEAT will thus approximate 25 kcal for the evening (0.08 × 1500 BMR × (5/24) h). Now imagine he/she becomes aware of the soccer tryouts after school, the neighborhood park, and the possibility of walking to school. The child then decides to undertake these tasks. The increase in energy expenditure would be equivalent to walking approximately 1–2 mph for the same period of leisure time (4–9 pm). NEAT then increases to 625–935 kcal for the evening (2 or 3 × 1500 BMR × (5/24) h). Thus, for this hypothetical child, the variance in leisure time NEAT has the potential of impacting energy expenditure by almost 1000 kcal/day. Thus leisure activities range from almost complete rest to those that are highly energized. Since NEAT can vary dramatically among individuals, could NEAT be important in weight gain?

NEAT in Weight Gain and Obesity

In humans, the manipulation of energy balance is associated with changes in NEAT. In one study [32], 12 pairs of twins were overfed by 1000 kcal/day. There was a fourfold variation in weight gain, which by definition must have reflected substantial variance in energy expenditure. Since the changes in energy expenditure were not accounted for by changes in basal metabolic rate or sport-like exercise, changes in NEAT were implicated indirectly. Interestingly, twinness accounted for a substantial minority of the inter-individual variance in weight gain, suggesting that NEAT is under both environmental and biological/genetic influences. When positive energy balance is imposed through overfeeding, NEAT increases [33, 34]. Moreover, the change in NEAT is predictive of fat gain [35]. Those who with overfeeding increase their NEAT the most gain the least fat (Fig. 18.2a) [35]. Those who with overfeeding do not increase their NEAT gain the most fat. Therefore, NEAT is fundamentally important in human fat gain.

If people who fail to increase NEAT with overfeeding gain excess body fat, could there be a NEAT deficit in obesity? To examine this question, we integrated microsensors into undergarments

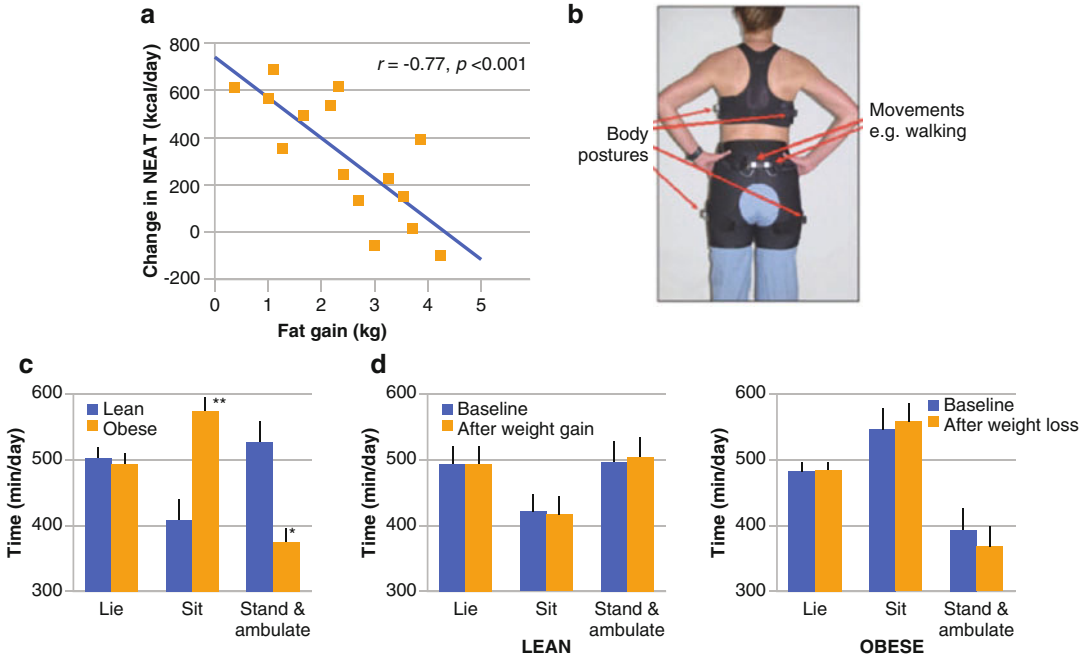

Fig. 18.2 (**a**) Fat gain versus changes in NEAT with 8 weeks of overfeeding by 1000 kcal/day in 16 lean, sedentary volunteers (Used with permission of the AAAS from Levine JA, Eberhardt NL, Jensen MD. Role of nonexercise activity thermogenesis in resistance to fat gain in humans. Science. 1999;283:212–14). (**b**) Posture and activity sensing undergarments. (**c**) Time allocation for components of NEAT in ten sedentary lean and ten obese individuals during weight maintenance feeding (Used with permission of the AAAS from Levine JA, Lanningham-Foster LM, McCrady SK, et al. Interindividual variation in posture allocation: possible role in human obesity. Science. 2005;307:584–86). (**d**) Time allocation for components of NEAT in lean subjects before and after weight gain and obese subjects before and after weight loss (Used with permission of the AAAS from Levine JA, Lanningham-Foster LM, McCrady SK, et al. Interindividual variation in posture allocation: possible role in human obesity. Science. 2005;307:584–86)

(Fig. 18.2b). These sensors allowed body postures and movements, especially walking, to be quantified every half second for 10 days. The data (Fig. 18.2c) [36] demonstrated that obese subjects were seated for 2.5 h/day more than lean subjects. The lean sedentary volunteers stood and walked more than 2 h/day longer than obese subjects. Importantly the lean subjects lived in a similar environment and had similar jobs compared to the obese subjects. Because all the components of energy expenditure were measured, it could be calculated that if the obese subjects were to adopt the same NEAT-o-type as the lean subjects, they might expend an additional 350 calories/day. Thus NEAT and specifically walking are of substantial energetic importance in obesity. Lean individuals exploit opportunities to walk, where the obese find opportunities to sit.

We have also quantified differences in daily standing/walking times between normal-weight and overweight children. These initial studies indicate that normal-weight children stand for longer periods of time each day compared to overweight children; however, the difference is slightly less (90 min compared to 2 h) than that in adults. The significance of this lower difference in standing/walking time in children compared to adults needs to be explored, despite the complexity of performing such evaluations. Our findings suggest that there are developmental influences on NEAT across the life span and that these influences are different in lean compared to obese individuals.

It might seem obvious that because people with obesity are heavier, they sit more than lean people. However, these differences do not reflect

greater body weight alone. When lean adult subjects gained weight through overfeeding, their tendency to stand/ambulate persisted (Fig. 18.2d) [36]. When obese subjects became lighter, their tendency to sit did not change (Fig. 18.2b).

Thus, obesity is associated with a NEAT defect that predisposes obese people to sit [37]. Lean people have an innate tendency to stand and walk. These findings appear to be true in children as well as adults.

NEAT Children

Obesity prevalence among children is at the highest levels measured; presently 15% of US boys and girls aged 6–11 years are overweight [38]. Obesity among children has increased more rapidly in the last 30 years, and this is now occurring worldwide. The situation, however, is projected to get far worse because there are now three times more obese children than there were two decades ago [39–41]. Childhood obesity is a global epidemic with unheralded health consequences [42, 43]. These rising obesity rates have been, in part, blamed upon increasing sedentariness [44–47]. Sitting in front of a television, video game, or computer screen has been consistently associated with low levels of physical activity [47]. Weekly screen time in children is as high as 55 h/week [48], and the average home in the United States has a television on for 8 h/day [49]. Although many programs have attempted to separate children from the screen, these activities are highly valued and children are resistant to giving them up [50]. There is therefore an urgent need to devise approaches that render children active; the school is the obvious place to start.

As to why physical activity became drained from school is uniformly explained by a decrease in the prioritization of physical activity relative to other learning objectives on the school calendar. This occurred concomitantly with decreased fiscal allocation of resources for physical activity. This is equally true in the Unites States, European countries, China, North Korea, and Australia. Interestingly, facilities for physical activity (e.g., gym, playground, or field) are often present, and qualified teachers are available (albeit often few in numbers). However, even elementary schools do not have daily programmed activity; middle schools rarely have compulsory daily activity, and most children report that they do not get regular physical activity. In high schools, the story is even worse, at least in the United States; here many schools offer physical education as a one-semester optional course to meet a minimal state requirement for physical education. Most children do not participate in physical activity most days of the week.

Of course, school systems cannot shoulder the blame for childhood obesity, but schools used to compel daily activity and school is where our children spend most of their weekdays. Furthermore children used to walk or ride their bikes to school, whereas now they invariably ride on a bus or in a car. It only takes a moment of thought to realize that educational standards are irrelevant if children grow up entrained to be sedentary and unhealthy.

It is imperative for both health and fiscal reasons that effective childhood obesity prevention and intervention programs be developed immediately. Previous approaches to reverse low levels of physical activity in children have generally focused on impacting the behaviors that children and their parents engage in at school and/or at home. However, these approaches in general vary in success and overall have failed. Rather than trying to impact behavior, one wonders whether a redesigned physical infrastructure could impact how children behave.

Despite efforts to promote NEAT and activity within the boundaries of the traditional school system, there is a growing realization that these efforts have failed and are likely to continue to do so. That being understood, focus is intensifying as to whether school infrastructure and operational systems can be altered to promote NEAT and daily activity and reverse obesity. By examining this question under the headings of (a) the student, (b) the classroom, (c) the school, and (d) the environment external to school, the conclusion is drawn that a multifaceted approach can be readily applied to effectively change the nature of school from chair imprisoned to NEAT enhanced.

NEAT School

There are four aspects one needs to consider when redesigning the school to promote health. The first is the individual. The second is their immediate space—the classroom. The third is the general space—the school itself. The fourth is the external space—the out-of-school environment. Let us consider these one by one.

The Individual

The individual space of a pupil can most easily be summarized as a desk–chair space or more pejoratively a "desk sentence." Even from preschool, students are conditioned to be desk bound. The focus on educational discipline for centuries has been to maintain children at their desks. This enables a teacher to organize a group of individuals whose natural tendency is to move.

An important question is why we should contemplate changing desk-based learning when this learning approach preceded the obesity epidemic. This argument ignores three issues. The first is that desk-based learning evolved at the time when children would invariably walk to school and be active in their leisure time. For example, many children had documented walk times of more than 4 h/day in their commute to school prior to 1900. The second issue is the assumption that children learn best while seated; the Socratic Peripatetic School in ancient Athens invoked ambulation as the standard form of learning, and a multitude of scholars have worked standing or in motion; Einstein was said to solve the riddle of relativity while riding his bicycle. The third issue is that it is an assumption that children learn best while seated; the evidence for this is absent. There is no education compulsion for children to learn while seated at a desk. In fact our studies indicate that if you give a child a chance to move, they will do so and will learn better. If the notion of a "student sitting at a desk" is dispelled, enormous educational possibilities result.

Examples of NEAT Solutions

1. It is possible for students to use lightweight podium/standing desks that are height adjusted. This enables a student to sit or stand as she wishes and also to define her workspace as she chooses; desks can be moved to where the student wishes to learn.
2. A student can use aluminum lightweight portable personalized white boards that she can move to her chosen workspace. This enables a teacher (in motion too) to write personally for a student and for a student to write on a board in response.
3. Mobile wearable technologies can be deployed. A student using a wireless Ethernet-connected portable computer can gain and deliver knowledge anywhere in the school system. The weight of a portable laptop computer is often less than standard book bags [51]. The technologies allow a student and teacher to communicate privately and at distance. Other mobile technologies (e.g., mobile audio devices) enable a student to receive educational materials while in motion (e.g., audio materials heard while walking or spelling words practiced while playing basketball).
4. Personalized health-sensing technologies can be worn by students. Students already oftentimes wear identity cards. Similarly, students' NEAT and cafeteria food choices can be logged on a portable device and fed back to students to provide them with information and feedback. For example, a student who meets his activity goal for the week could be rewarded, and a student who eats pizza everyday for a week could be sent "an eat cool" advisory.

The Classroom

Once the chairs and desks have been removed from a traditional classroom, it looks very different (Fig. 18.3a, b). In fact, the role of the space itself comes under question. The Merriam-Webster definition of a classroom is "a space where a body of students meeting regularly to study the same subject" [20]. As soon as the desks and chairs are dispensed with, we can consider

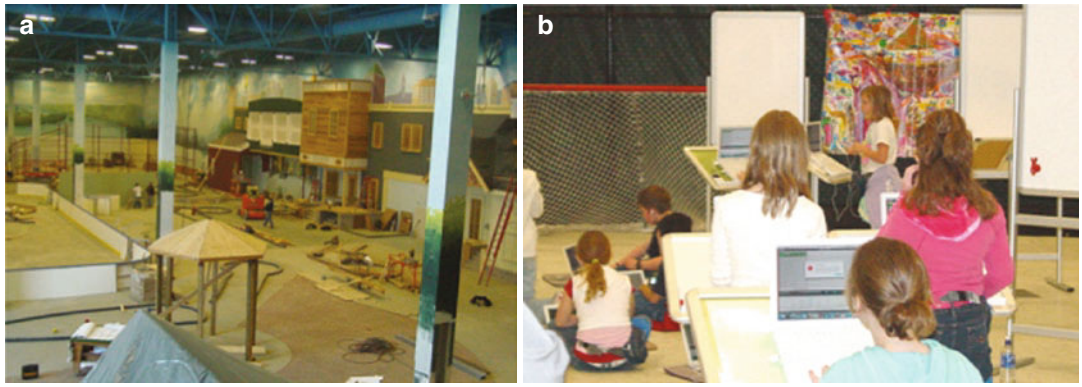

Fig. 18.3 (**a**) A sample, (**b**) NEAT-promoting school of the future

changes in classroom setting. For example, can parkland function as a classroom (San Francisco has city-wide wireless Internet, and so educational materials could be accessed at any time from anywhere in the city)? Can a walking track be a classroom? Once desk and chairs are no longer needed, the answers to these two questions could be "yes."

Examples of NEAT Solutions

1. *Open-format classrooms.* An open-format classroom is a traditional classroom space from which the desks and tables have been removed. An open-format classroom has several advantages over the traditional desk–chair approach. First students can define their own space and their own groupings; some students like to work collaboratively, whereas other students do not. Second, a teacher can direct students within the space so that different educational objectives can be mirrored by different physical layouts. Third, different technologies (such as those described above) can be introduced but only as needed. For example, in a mathematics lesson, a teacher may want to teach students from a white board (wall mounted) at the front of the classroom, and so laptop computers would not be used inside the room. Alternatively, a teacher may want to teach biology using video clips from a local hospital's operating room, and here students would need to have their laptop videocams linked to the hospital.
2. *Un-roomed classrooms.* The theme of mobility can take students out of the traditional four-walled classroom (noting the definition of a "classroom" above). The "classroom" can become a gymnasium, a park, or a walking track. This approach has several advantages as well as drawbacks. A major advantage is that a four-walled space is not needed, so this frees up traditional school classroom "real estate." A consequence of this could be that fewer classrooms are needed for a given school. Also, the un-roomed classroom creates novel educational paradigms; for example, virtual classrooms can evolve to bring geographically separated students under one educational environment and educators with unique skills to students who would not otherwise benefit. Moving-wall systems can be used to "create" classrooms ad hoc in undefined space as the need arises.

Drawbacks that educators report are the issues of acoustics and behavioral issues. Acoustics in free-living space is difficult for three reasons:

(a) Noise transition from source to listener. This can be helped using high-quality mobile transmission systems.
(b) The effect of extraneous noise such as traffic. Theoretically this is helped (but only to a degree) using noise-canceling technology.
(c) Multi-person communication. Even though traditional teaching is from teacher to students

(see (a)), an important part of the educational experience is the vocal interchange between students; this can be challenging even with advanced mobile, acoustic systems.

The second drawback of wall-less learning can broadly be defined as "behavioral issues." This does not necessarily refer to issue of disciplinary control but rather to the nature of group dynamics [52]. There is a general belief that education benefits from the process of group dynamics and this can potentially be stultified by learning either while in motion (e.g., on a walking track) or with virtual learning environments. Although this is intuitively true, evidence is lacking.

The School

When considering how the school itself (Fig. 18.3a, b) can contribute to NEAT-enhanced active learning, two broad categories need to be considered: the first is organizational infrastructure and the second is physical infrastructure. At an organizational level, there are several important areas. For example, are policies in place that promote NEAT and physical activity throughout the school day? Does lesson organization permit or enhance NEAT? Does recess allocation and organization permit and promote physical activity? Does the school week allocate time to physical activity?

Have safety and legal issues been anticipated?

What is important to appreciate is that organizational issues are often inexpensive or even cost neutral.

With respect to physical infrastructure, there are also several considerations. For example, is there adequate space to promote daylong physical activity? Are the resources available to recreate, redesign, and retool classrooms to promote activity? Is the physical infrastructure used wisely to promote daylong physical activity? Are new schools NEAT compliant?

Possible NEAT Solutions

Let us examine NEAT solutions for an entire school first from an organizational perspective and then with respect to physical infrastructure:

1. *Leadership.* The role of school leadership in promoting daylong physical activity and NEAT cannot be understated. The school principal needs to *drive* the initiative for NEAT-enhanced active schooling. Leadership invariably, however, needs to emanate from beyond the individual school itself; there needs to be support from regional and even national school authorities (see below). Within the school, there must be support beyond the principal, including teachers, janitors, kitchen staff, mechanics, and grounds staff.
2. *Lesson organization to promote NEAT.* There are obvious examples of how important lesson organization can be. For example, say a biology teacher wishes to teach her biology class at a local nature reserve; those lessons will need to be scheduled to enable the students to arrive on site in a timely fashion. More radical approaches can be contemplated; for example, several sports- and arts-orientated schools schedule all formal education in the morning to enable students to ski or learn ballet in the afternoon [53, 54]; these students generally exceed educational standards. One could therefore envisage a health promotion school with the same educational organization, where half the day is allocated to healthy pursuits. On a more subtle level, lessons can be organized in such a way as to maximize the distance between the classrooms so that students have to walk the greatest possible distance between lessons. NEAT-based scheduling has tremendous potential power to increase daytime NEAT.
3. *Recess.* In North American schools, recess has contracted to the point where oftentimes it serves only to enable children to eat and use bathrooms. Recreational time during the day is diminishing. This also in part reflects the pressures that many educational systems impose with respect to meeting educational goals. Increasing recess-associated physical activity necessitates that recess time is available to students but also that the time is used efficiently. The timing of recess in relationship to meals may also influence overall activity level. Some schools may consider extending the school day to prolong recess

opportunities. Alternatively, in an extended school day, the first and last 30 min can be designated for promoting activity.

4. *Allocating time in the school week for physical activity.* The obvious opportunity here is to reverse the astonishing decline in compulsory physical education that has occurred in many high-income countries. What should the goal be? The NEAT deficit in children is about 90 min/day. The notion that all children should be active in school for three 30-min sessions per day seems excessive. However, consider a school in North Dakota that engages all children in 30-min walks at the beginning of the school day, after lunch, and at the end of the school day. The walking segments at the beginning and end of the school day are supervised through a volunteer program, and the school bus system is not unduly inconvenienced. In this model, school education time is unaffected. More subtle approaches can also be used; for example, specific school corridors can be preallocated for specific classes so that lesson-time walking is encouraged. Certain classes could even be mandated to be active in nature.
5. *Recognizing nontraditional activities as being health positive is simply a state of mind* [55]. Most children do not engage in formal sports. There is a need to encourage children to pursue activities that they enjoy and that foster lifelong participation. Examples include skateboarding, using rollerblades, dancing, yoga, and talking to friends on the phone while walking. Emphasizing the pleasure of participating over "winning" is often important too.
6. *Contrary to expectations, it is not complicated to devise legal waivers for most activities at school*; this should not be seen as a barrier to promoting daylong, enjoyable, and healthy activities at school.
7. *Using technologies to measure outcomes.* Several modalities of measurement can be used to objectively assess outcomes [56, 57]. The scope of technologies will likely advance activity monitoring to potentially include continuous physiological and metabolic monitoring.

NEAT solutions for an entire school also involve infrastructural considerations:

1. *Adequate space.* A common misconception is that a school needs to be completely rebuilt to render it activity promoting. Oftentimes reallocating preexisting resources and space can create a physical infrastructure to promote NEAT and activity. For example, an old disused play area can be converted into an engaging climbing play ground that invites and stimulates activity. Disused concrete areas can be rebuilt into skateboard parks. An unused wall can become a climbing wall. Parts of walkways can be designated for rollerblade use. Cycle paths can be designated and even mountain bike trails designed. Walks between school areas can be made more engaging using culture and art projects. Unused open spaces can be used as an arena to encourage music and outdoor dancing. Careful review of existing spaces can yield remarkable results at little cost. Safety issues, however, must be considered.
2. *Resource availability is often cited as the key limiting factor for promoting school-based physical activity. This chapter, however, argues strongly against this. Nonetheless, increasing the resources available to a school* can help promote physical activity. Such resources can range from small amounts of money to purchase equipment such as carts containing recess equipment through major grants to convert schools into health-promoting environments. Fund raising from the student body, school districts, funding agencies, and industry are all potential sources of funding. None should be overlooked.
3. *The efficient use of physical infrastructure is important for promoting daylong activity.* If a school elects to build a skateboard park in its concrete area, will this wonderful area be used for only 1 h a day by a small number of students? Could recess times be staggered to give more children more opportunities? Could sports facilities (e.g., gymnasiums) that are normally closed on weekends be opened (often using community volunteers)

to enable children to play in out-of-school hours and weekends? Conversely, could community facilities such as swimming pools be better shared with schools that do not have such opportunities? The efficient use of existing resources can oftentimes triple their use [58, 59].

4. *Building new schools*. New schools are built in every major populous center every year. Without rebuilding existing schools, it is self-evident to build new schools from the "bottom up" (Wi-Fi to bike track) to be NEAT and activity promoting.

The Out-of-School Environment

Understanding the role of the school day in promoting a child's physical activity cannot ignore the role of the external world on the school and vice versa.

Possible NEAT Solutions

The external world affects how a school functions in many ways. Governmental and regional policies, for example, can create mandates to promote physical activity and health. The Australian government in 2009 recommended a ban on all screen time for children under 2 years old and a 1-h limit for 2–5-year-olds in state-funded centers. Resource allocations for children engaged in these programs can be diverted from health promotion budgets rather than school ones. Play areas for out-of-school activities can be rendered safe through police allocation; similarly children can be encouraged to walk or cycle to school assuming city planners recognize the need for walkways and safe cycle paths that override busy streets. In the same way that school-based solutions for obesity may exploit environmental reengineering, so too can compatible programs be derived for adult workplaces.

What is often overlooked is how a school can interface with its external environment. This occurs in two ways. First, a program delivered to children can be complemented by a program delivered to their families. There is widespread potential to use the school premises (and infrastructure) to achieve this goal as well. In so doing, broad-based partnerships between schools and the communities they serve can be strengthened. The second element is even more important. Obese children are likely to become obese adults. What happens in school today affects the nation tomorrow. If children leave the school systems profoundly unhealthy, they are likely to remain this way for life. On the other hand, an education that provides an approach to lifelong activity and fun could be one of the most valuable educational elements a child takes away from the NEAT-enhanced school of tomorrow.

Conclusion

It is recognized that the primary goal of school is to educate children. Since the inception of modern schooling, this mandate has been understood to represent the obligation to provide broad-based education that serves a student lifelong. Examples include the commonplace inclusion of sex education in the curriculum plus the presence of broadening experiences such as drama. It has long been understood that the role of school extends beyond trigonometry and Shakespeare. There is also a universal recognition that childhood obesity is rising unabated at catastrophic rates. Since most children in developed countries attend school, our schools are an obvious place to consider obesity intervention and prevention.

Over the last few decades, the emphasis in the sciences was on changes in nutritional quality being the principal driver in the obesity epidemic. However, the emphasis has shifted over the last 10 years toward the belief that energy expenditure, in particular NEAT, is at the crux of the obesity epidemic.

Exercise is associated with considerable health benefits beyond obesity including diminished rates of diabetes, heart disease, and possibly cancer and is associated with prolongation of life span [60]; the converse appears to be true for inactivity [61]. If so, increasing NEAT might confer health benefit and longer life.

Editor's Comments and Questions

As discussed in Chap. 33 on exercise and childhood obesity, total energy expenditure is normal in obese children when expressed per kg of lean body mass but low when expressed per kg of total body mass. Similar observations have been made in adults[a]. These findings suggest that energy expenditure in overweight people fails to rise adequately or quickly enough to prevent or reverse the accrual of fat mass.

In theory, the lack of a compensatory increase in energy expenditure[b] might be related to subtle defects in hypothalamic function or hormone expression (see Chap. 19 on weight gain in endocrine and metabolic disorders) or innate or acquired deficiencies in mitochondrial metabolism; these in turn could cause reductions (or inadequate increases) in resting energy expenditure, diet-induced thermogenesis, and/or physical activity. Resting energy expenditure appears to be normal in obesity, as it depends largely on lean body mass. Diet-induced thermogenesis has been inadequately studied[a] but might be reduced to some extent, given the relatively low brown adipose tissue activity in overweight adults; see Chap. 7 on brown adipose tissue. However, your studies and others[a,c] suggest that a lack of physical activity contributes to the relative energy deficit.

Regarding daily physical activity, my Israeli brother-in-law Danny Criden likes to say "A dog is a man's best friend, second only to steps." But how best to convince overweight kids to climb stairs, walk to school, and ride their bikes if they have, as you say, an "innate" defect in NEAT that predisposes to sedentary behavior? By "innate," I presume you mean inborn and, from twin studies, inherited.

My questions are:

1. Is there any evidence that babies or young children manifest differences in NEAT that *predict* differences in subsequent rates of weight gain or fat deposition?
2. Are differences in childhood NEAT associated with differences in NEAT among their parents and siblings?

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Authors' Responses

1. No, there is not.
2. The zip code data suggest that this is, but not why (ecology/DNA).

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Part VII

Metabolic Complications of Childhood Obesity

19 Obesity and the Endocrine System, Part I: Pathogenesis of Weight Gain in Endocrine and Metabolic Disorders

Michael Freemark

Metabolic and Hormonal Disorders Causing Excess Fat Deposition

Hormonal disorders commonly associated with adiposity and an increase in the ratio of fat to lean body mass include growth hormone (GH) deficiency, hypothyroidism, glucocorticoid excess, hyperinsulinism, hypogonadism, pseudohypoparathyroidism, polycystic ovarian syndrome (PCOS), and in some cases, hyperprolactinemia. Treatment with synthetic progestins may also cause fat deposition, particularly in females (Table 19.1).

GH Deficiency and GH Resistance

Children and adults with defects in GH production (*GH deficiency*) or GH signaling (*GH resistance*, most commonly associated with mutations in the GH receptor) accrue excess fat in the truncal region and have an increased waist to hip ratio (WHR) [1, 2]. Studies in GH receptor knockout mice show preferential expansion of subcutaneous white adipose tissue and an increase in circulating adiponectin levels [3] (Fig. 19.1). Abdominal adiposity results from heightened insulin sensitivity, decreased rates of lipolysis and fatty acid oxidation, sarcopenia, and induction of 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1), which favors local overproduction of cortisol in visceral and abdominal fat [2–4]. Caloric intake in GH deficiency and GH resistance may be high relative to body weight. A decrease in skeletal muscle mass, which may be mediated by reductions in insulin-like growth factor 1 (IGF-1)-dependent myogenesis and muscle protein synthesis [5], may limit exercise capacity [6] and reduce physical activity energy expenditure; on the other hand, resting energy expenditure is normal or only slightly decreased after adjustment for fat-free mass [7, 8].

Hypothyroidism

Fat accretion in hypothyroidism results from reductions in brown adipose tissue thermogenesis and uncoupling protein 1 (UCP 1) expression and decreases in resting energy expenditure and physical activity [9, 10]. The primary determinant of body weight gain in hypothyroidism, however, is water retention; physiological thyroid hormone replacement acutely increases urinary water excretion and can promote transient, and relatively limited, weight loss.

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Table 19.1 Pathogenesis of weight gain in endocrine and metabolic disorders

Disorder	Pathogenesis of weight gain
GH deficiency/GH resistance	↑ Insulin sensitivity ↑ Lipogenesis, ↓ lipolysis ↑ 11β HSD-1 in abdom/ visceral fat Sarcopenia, ↓ energy capacity
Hypothyroidism	↓ Energy Expenditure ↓ Physical activity Water retention
Glucocorticoid excess	Hyperphagia ↑ Adipogenesis Sarcopenia ↓ Osteocalcin ↓ Energy expenditure
Synthetic progestins	↑ Food intake ↓ Lipolysis
Hypogonadism, males	↓ Myogenesis, sarcopenia ↓ Physical activity ↓ Mitochondrial energy expenditure ↓ Lipolysis in visceral and SQ fat
Hypogonadism, females	↓ Spontaneous physical activity ↓ Lipolysis in SQ and visceral fat
PseudohypoPTH (type 1A)	↓ REE HypoTH, GH deficiency, hypogonadism
PCOS/ovarian Hyperandrogenism	? Hyperinsulinemia ? ↑ 11β HSD-1 abdom/ visceral fat
Hyperprolactinemia	Hypogonadism ? ↑ Food intake ? ↑ Adipogenesis
"Hypothalamic obesity"	Central leptin resistance with hyperphagia ↑ Vagal tone with hyperinsulinemia GH deficiency, hypo TH and/or precocious puberty Hyperprolactinemia Glucocorticoid excess (surgical and post-op)

Glucocorticoid Excess

Glucocorticoid excess is accompanied by increases in visceral fat and reductions in peripheral subcutaneous fat [11]; together with muscle wasting, this explains the central adiposity of Cushing's syndrome. The number of visceral white adipocytes is increased by glucocorticoids while adipocyte size is decreased, suggesting that the effects of glucocorticoids on visceral fat mass are mediated by differentiation of adipocytes from mesenchymal preadipocytes (adipogenesis) rather than hypertrophy of mature adipocytes. Nevertheless, glucocorticoids also act in concert with insulin to promote lipogenesis, in part through increased expression of lipoprotein lipase. Glucocorticoid receptors in visceral preadipocytes are expressed at higher levels in adult males than females; this may contribute to sex-dependent differences in body fat distribution.

Weight gain and adiposity are facilitated by energy imbalance. Glucocorticoids in excess increase hunger and food intake [12] and, through reductions in triiodothyronine [13], inhibit brown adipose tissue expression of UCP 1 [11], the rate-limiting step in thermogenesis. In concert with reductions in skeletal muscle and bone mass, this may reduce resting energy expenditure and thereby promote weight gain.

The molecular mechanisms controlling glucocorticoid action in adipose tissue are complex [11]. Both the glucocorticoid and mineralocorticoid receptors are expressed in white adipose; the affinity of the mineralocorticoid receptor for cortisol exceeds by tenfold the affinity of the glucocorticoid receptor, and the expression of the adipose mineralocorticoid receptor, in contrast to the glucocorticoid receptor, is higher in visceral fat from obese adults. Interestingly, glucocorticoid receptor signaling suppresses production of inflammatory cytokines in white adipose tissue, while mineralocorticoid receptor signaling increases local interleukin 6 (IL6) and plasminogen activator inhibitor 1 (PAI-1) expression. Thus, the metabolic actions of glucocorticoids in visceral adipose, and their systemic effects, might be mediated through binding to the mineralocorticoid as well as the glucocorticoid receptors.

Finally, glucocorticoids reduce dramatically the circulating levels of osteocalcin, an osteoblast protein that increases energy expenditure, limits fat deposition, and increases insulin sensitivity in mice. A recent study [14] found that induction of weight gain and insulin resistance by systemic

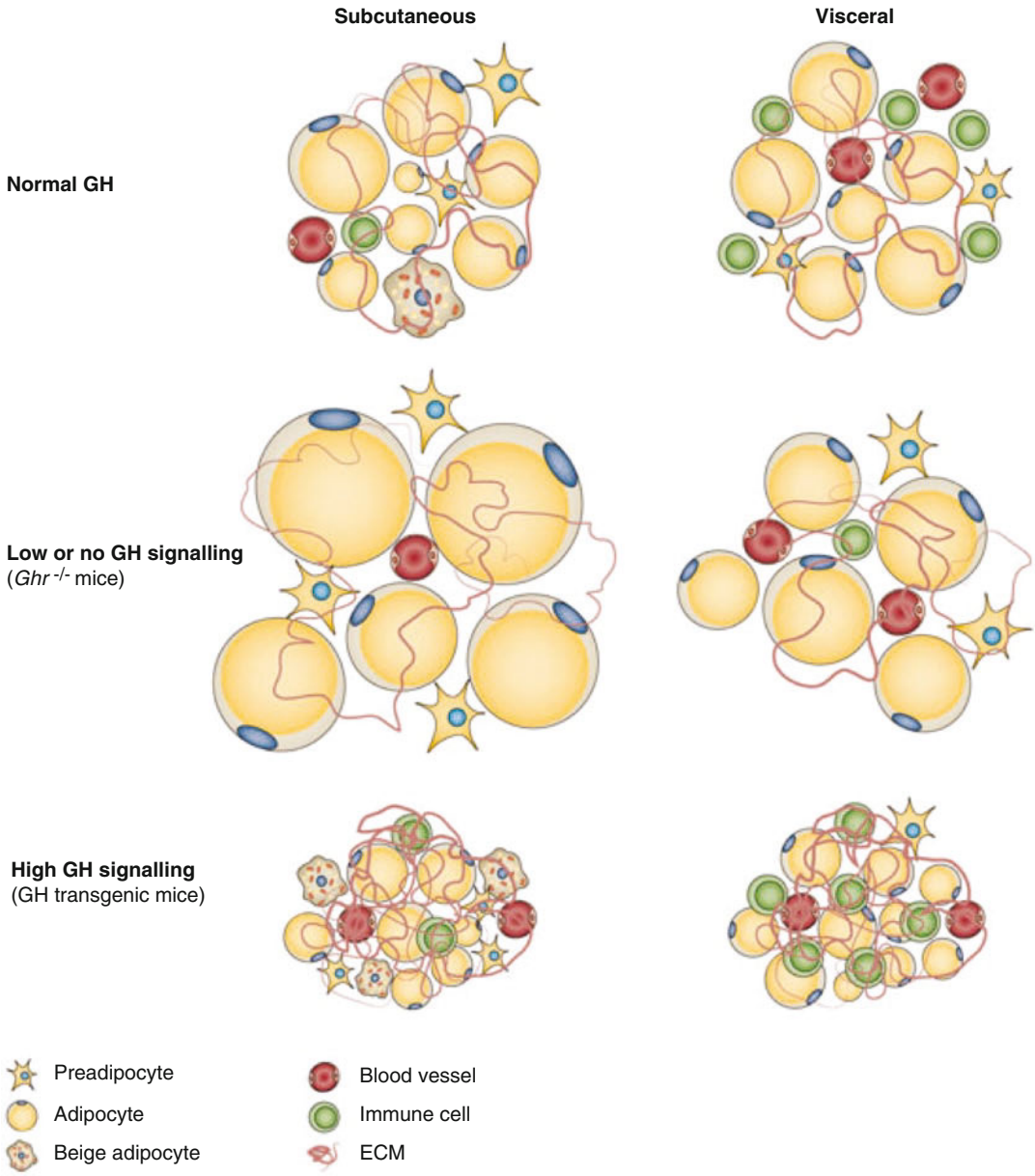

Fig. 19.1 Representation of subcutaneous and visceral adipose tissue in mice with normal GH signaling, GH resistance (Ghr-/- mice), or GH excess (GH transgenic mice). The mass of the subcutaneous white adipose depot expands in GH-resistant mice, with hypertrophy of white adipocytes and a reduction in the number of brown/beige adipocytes; see Chap. 7 on Brown Adipose Tissue. Visceral adipocytes in Ghr –/– mice are normal in size. The mass of WAT and the size of white adipocytes are reduced in transgenic GH-overexpressing mice. Abbreviations: ECM, extracellular matrix; GH, growth hormone; Ghr, GH receptor (Used with permission of Nature Publishing group from Berryman DE, Glad CA, List EO, Johannsson G. The GH/IGF-1 axis in obesity: pathophysiology and therapeutic considerations. Nat Rev. Endocrinol. 2013;9(6):346–56)

glucocorticoids was blunted by concurrent administration of osteocalcin, suggesting that a reduction in osteocalcin may mediate some of the diabetogenic effects of cortisol excess.

Synthetic Progestins

Long-term treatment with synthetic progestins such as Depo-Provera or megestrol acetate [15] can cause fat deposition and weight gain, particularly in females. While some of the drug effects may be mediated through binding to glucocorticoid receptors [16], progesterone promotes food intake [17] and inhibits lipolysis in subcutaneous fat through reductions in hormone-sensitive lipase.

Hyperinsulinism and Central Resistance to Insulin and Leptin

Hyperinsulinemia is associated with macrosomia and adiposity in infants of diabetic mothers, fetal overgrowth syndromes (including Beckwith-Wiedemann), and congenital hyperinsulinism [18]. Beyond the neonatal and infantile periods, excess weight gain is common among insulin- and sulfonylurea-treated patients with types 1 and 2 diabetes. Patients with insulinomas may be overweight or obese but more commonly present with recurrent hypoglycemia and neuroglycopenia [19]; some have multiple endocrine neoplasia type 1 [20]. Finally, children with hypothalamic obesity are often hyperinsulinemic [21]; however, a recent placebo-controlled study [22] in obese children with hypothalamic disease found that while diazoxide reduced insulin secretion, it had no effect on weight gain after 2 months of treatment.

Hyperinsulinemia promotes adipose deposition through induction of adipogenesis, lipogenesis, and triglyceride storage and inhibition of lipolysis and ketogenesis. Food intake may increase in response to insulin-induced hypoglycemia. Interestingly, insulin signaling in the brain reduces food intake and fat storage in experimental animals and increases insulin sensitivity [23, 24]; likewise, intranasal administration of insulin, which appears to gain access to the brain via the olfactory bulb, caused variable short-term reductions in food intake in adult men [23, 24]. Longer-term treatment (8 weeks) caused small reductions in body fat [25].

Insulin exerts a more powerful anorectic effect in males than in females [24–26]. The anorectic effects of insulin as well as leptin are blunted in obesity and other insulin resistant states; this may reflect decreased transport of insulin and leptin into the brain [27, 28] as well as hypothalamic resistance to insulin and leptin action [23, 24, 28, 29]. Central resistance to insulin and leptin is thought to exacerbate weight gain and glucose intolerance in patients with pre-existing obesity.

Hypogonadism

Like the glucocorticoids, the sex steroids have profound effects on adipocyte distribution and function (Table 19.2). Pubertal boys and adult men accumulate fat preferentially in abdominal and visceral regions, while pubertal girls and premenopausal women tend to store fat in gluteal and lower extremity subcutaneous white adipose tissue [30]. Studies in mice [31] find that high-fat feeding in males induces preadipocyte proliferation and differentiation in visceral but not subcutaneous fat depots; in contrast, adipogenesis is induced in subcutaneous as well as visceral fat stores of females. The induction of subcutaneous white adipogenesis is abolished by ovariectomy and can be induced in males by estrogen treatment. Interestingly, adipocyte precursors from male subcutaneous fat depots can be induced to proliferate and differentiate if transplanted to visceral fat, suggesting an important role for the adipose microenvironment in sex-dependent adipose distribution.

Hypogonadism in humans is associated with excess adiposity in females as well as males: classic examples include Turner syndrome [32–34] and Klinefelter's syndrome [35, 36]. Excess fat deposition is also noted in humans and mice with mutations in aromatase or the estrogen receptor

Table 19.2 White adipose distribution, muscle mass, and insulin sensitivity in teenage girls and boys

	Gluteal/low ext fat	Truncal/visceral fat	Muscle mass	Insulin sensitivity
Normal females	Higher	Lower	Lower	Lower in puberty
Normal males	Lower	Higher	Higher	
Hypogonadal females	Variable	↑	Variable	↓
PCOS	Variable	↑	Variably ↑	↓↓
Hypogonadal males	Variably ↑	↑	↓	↓

(ERα) [37–42] and teenagers and adults with idiopathic hypogonadotropic hypogonadism [43, 44]. Adiposity and metabolic dysfunction increase progressively with age in untreated hypogonadal subjects, though accrual of fat mass can be demonstrated even in some peripubertal children [45].

Hypogonadal males have increases in visceral white adipose stores and, to a lesser extent, gluteal and lower extremity subcutaneous fat [46]. Adipogenesis is upregulated and catecholamine-dependent lipolysis decreased. Increases in lipoprotein lipase and acyl-CoA synthase may promote adipose and hepatic free fatty acid uptake and lipogenesis. Insulin resistance is common in hypogonadal men and may be associated with fatty liver disease; androgen treatment may reduce hepatic steatosis [46, 47].

Skeletal muscle and lean body mass are reduced in hypogonadal teenage and adult males [45, 46, 48]. The sarcopenia results in part from defective myogenesis; together with downregulation of skeletal muscle genes controlling mitochondrial oxidative phosphorylation [46, 49, 50], this may limit locomotor activity, exercise capacity, and energy expenditure and thereby contribute to adiposity.

Studies in mice with deletions of the estrogen receptor suggest that adiposity in *female hypogonadism* results, at least in part, from striking reductions in spontaneous physical activity and energy expenditure [40, 51]. There is accumulation of fat in the visceral region, which may reflect increases in visceral adipogenesis and/or decreases in lipolysis. Factors contributing to adiposity may include reductions in brown adipose tissue thermogenesis and sympathetic nervous system activity [37]. In concert, these changes may reduce insulin sensitivity, impair glucose tolerance [33, 52–55], and increase liver fat [56]. As in hypogonadal males, the metabolic function of untreated hypogonadal females deteriorates with age.

Pseudohypoparathyroidism

Early onset obesity is common in children with *pseudohypoparathyroidism type 1A (Albright's hereditary osteodystrophy)*, which results from heterozygous loss-of-function mutations in the maternal allele of the GNAS gene (see Chap. 9 by Drs. Irizarry and Haqq). Associated defects can include resistance to thyroid-stimulating hormone, GH-releasing hormone, and gonadotropins. Rarely, patients with *pseudohypoparathyroidism type 1B*, caused by a deletion mutation of STX16, may also have early onset obesity [57]. Hyperphagia does not appear to cause obesity in pseudohypoparathyroidism type 1A; rather there are significant reductions in resting energy expenditure corrected for fat-free mass [58, 59], even in prepubertal, euthyroid children with normal height z and IGF-1.

Polycystic Ovary Syndrome

Approximately two thirds of adolescents and adults with polycystic ovary syndrome (PCOS) are overweight or obese, with truncal fat deposition and increased WHR [60]. Abdominal adiposity plays a central role in the pathogenesis of insulin resistance in PCOS [61], but its origins are unclear. Possible contributory factors include hyperinsulinemia and upregulation of 11β-HSD1 and cortisol production in visceral and abdominal fat [62, 63]. Androgen-dependent inhibition of

adipogenesis in subcutaneous white adipose tissue [30, 46, 48, 49] may facilitate visceral fat storage. Fatty liver disease is common [64, 65], as androgens promote hepatic lipogenesis in females [47, 64]. Limited evidence suggests that caloric intake and physical activity fall within the normal range in adults with PCOS [66].

Hypothalamic Disease and Hyperprolactinemia

Hypothalamic damage or disease can cause insatiable appetite and progressive weight gain. Reductions in basal metabolic rate and physical activity contribute to hypothalamic obesity; see Chap. 2 by Drs. Haliloglu and Bereket. Deficiencies of GH, thyroid hormone, and glucocorticoids are common in this setting, and some patients have precocious puberty, which can promote fat deposition in girls. The insatiable appetite and obesity associated with hypothalamic disease likely result from central leptin and insulin resistance, loss of αMSH signaling, and heightened vagal tone with hyperinsulinemia. The use of high-dose glucocorticoids around the time of surgery facilitates weight gain; *hyperprolactinemia*, which has been associated with weight gain in adults and children [67, 68], may also play a role. Studies in rodents and birds suggest that prolactin promotes white adipogenesis [69–71] and stimulates food intake, possibly through inhibition of leptin action in the hypothalamus [72–75]. Suppression of gonadotropin secretion may contribute to adiposity in hyperprolactinemic states [76].

Screening for Hormonal Disorders in Obese Children

GH deficiency, hypothyroidism, glucocorticoid excess, and pseudohypoparathyroidism are associated with short stature and/or a reduction in height velocity. In contrast, stature and height velocity are normal or increased in "exogenous" obesity. Laboratory testing in an obese child is unlikely to reveal an underlying hormonal disorder (other than insulin resistance and glucose intolerance) if the height, growth velocity, pubertal development, and menstrual function are appropriate for age and family background. It should be noted, however, that linear growth and bone maturation may not be reduced in Cushingoid children with adrenal tumors that produce androgens as well as cortisol. Moreover, height percentile may be normal or even increased in children with mutations in the leptin or melanocortin 4 receptors or in GH-deficient or hypothyroid patients who also have precocious puberty.

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20 Obesity and the Endocrine System, Part II: The Effects of Childhood Obesity on Growth and Bone Maturation, Thyroid and Adrenal Function, Sexual Development, and Bone Mineralization

Michael Freemark

Introduction

The accumulation of excess body fat has profound effects on somatic development and endocrine function. Here I review the effects of obesity on linear growth and bone maturation, thyroid function, sexual development, adrenal function, calcium homeostasis, and bone mineralization.

Effects of Obesity on Linear Growth and Bone Maturation

Final adult height in otherwise normal obese children generally falls within two standard deviations of parental target height. However, rates of linear growth and bone maturation are often increased in obese pre- and peri-pubertal children despite marked reductions in basal and stimulated plasma growth hormone (GH) concentrations and a reduction in circulating GH half-life [1]. The reduction in GH secretion in obese children and adults has been ascribed to negative feedback by free fatty acids, a reduction in plasma ghrelin (a GH secretagogue produced by the stomach), and nutrient-stimulated increases in IGF-1 production. Total IGF-1 and IGF binding protein (BP)-3 concentrations in obese subjects are typically normal or mildly elevated; this may reflect in part the production of IGF-1 and IGFBP-3 by white adipose tissue [2, 3] and/or an increase in hepatic GH sensitivity, resulting from induction of hepatic GH receptors by hyperinsulinemia (Fig. 20.1).

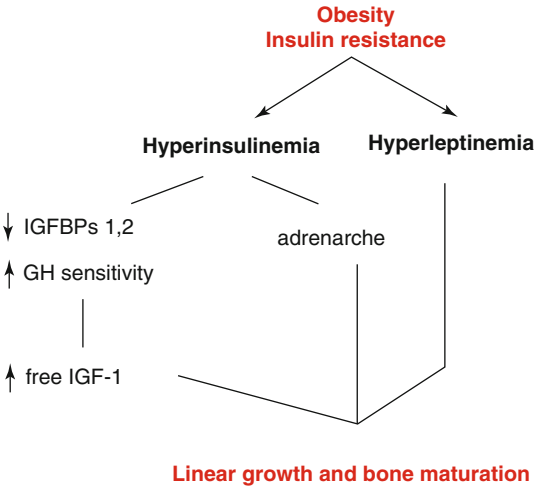

Fig. 20.1 Mechanisms that may explain why linear growth and bone maturation are normal or increased in prepubertal and peripubertal obese children despite a decrease in GH secretion.

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Induction of GH receptor expression in obesity is suggested by an increase in levels of GH binding protein [4], the circulating form of the extracellular GH receptor domain, and by heightened production of IGF-1 following a single dose of GH [5].

Total IGF-2 concentrations were elevated in obese adults in two studies but were normal in a study of obese adolescents [6]. Many investigations have found reductions in serum IGF binding proteins 1 and 2 (IGFBP-1 and BP-2), which correlate inversely with plasma insulin concentrations and liver fat content [7–12]. The decreases in IGFBPs 1 and 2 are postulated to increase the bioavailability of IGF-1, which may maintain or increase linear growth in obesity despite diminished GH secretion [13–15] (Fig. 20.1). "Free" IGF-1 levels have been found to be elevated in some, but not all, studies of obese adults [13, 14]. Interestingly, increased rates of linear growth and reductions in fat mass have been observed in mouse models engineered to make endogenous IGF-1 incapable of binding to IGF binding proteins [16].

Reductions in plasma IGFBP-1 or IGFBP-2 concentrations in insulin-resistant obese subjects may facilitate weight gain because overexpression of IGFBP-1 or IGFBP-2 in transgenic mice reduces adipogenesis and prevents diet-induced obesity. Interestingly BP-1 excess reduces insulin sensitivity but BP-2 excess improves glucose tolerance [8, 17, 18].

Growth and bone maturation in obesity may be potentiated by increases in adrenal androgen production (Fig. 20.1 and below) (see also Fig. 20.3); bone age may be advanced as much as 1–2 years in children with precocious adrenarche, which is more common in obese children. The hyperleptinemia of obesity also appears to play a role (Fig. 20.1). Circulating leptin levels rise in proportion to body (particularly subcutaneous) fat stores and are higher in girls than in boys. Leptin stimulates proliferation of isolated mouse and rat osteoblasts and increases the width of the chondroprogenitor zone of the mouse mandible in vivo. Conversely, leptin deficiency in ob/ob mice reduces cortical bone mass but increases trabecular mass [19]; leptin treatment increases femoral length, bone area, and bone mineral content [20] and may promote the differentiation of osteoblasts from bone marrow stem cells [19]. The effects of leptin may be exerted in concert with IGF-1 because leptin increases IGF-1 receptor expression in mouse chondrocytes [21]. Nevertheless, linear growth is normal in patients with congenital deficiencies of leptin or the leptin receptor [22, 23].

Effects of Obesity on Thyroid Function

Free T4 levels generally fall within the normal range in obese subjects but thyroid-stimulating hormone (TSH) and triiodothyronine (T3) concentrations are mildly, and variably, elevated. The increase in T3 reflects its peripheral conversion from circulating T4 [1, 24] (Fig. 20.2). Higher levels of T3 increase thermogenesis and energy expenditure [25, 26] and may thereby limit further weight gain; see also Chap. 7 on Brown Adipose Tissue. Conversely, caloric restriction and weight loss decrease T3 levels, reducing energy expenditure and thereby facilitating weight regain.

The effects of caloric excess and deprivation on thyroid hormone levels are mediated in part by leptin-dependent effects on hypothalamic TRH production (Fig. 20.2). Thyroid hormone levels

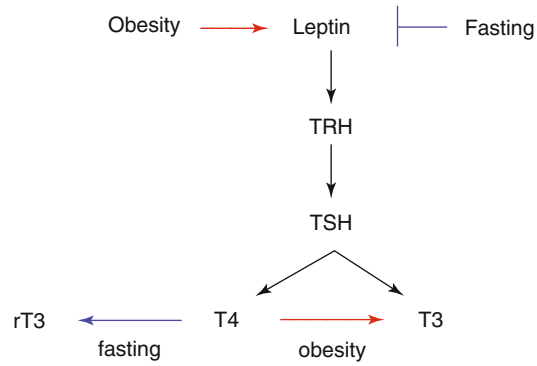

Fig. 20.2 Hyperleptinemia and nutrient-dependent conversion of T4 to T3 can increase T3 levels in obesity; fasting reduces T4 and T3 production and increases the conversion of T4 to inactive reverse T3 (rT3)

are variably low in leptin receptor-deficient humans and are reduced in leptin receptor-deficient db/db mice. Leptin treatment reverses the loss of TSH pulsatility that accompanies short-term fasting and normalizes thyroid hormone levels following longer-term caloric restriction. These actions are mediated by direct effects of leptin/STAT3 signaling on TRH transcription and indirect effects on TRH production mediated by increases in ∝MSH and reductions in agouti-related peptide (AgRP) and neuropeptide Y [27, 28]. By increasing sympathetic nervous system activity and deiodinase expression, hyperleptinemia may also promote peripheral T4 to T3 conversion [29, 30].

Some clinicians consider a mild elevation of TSH (typically in the range of 4.5–7 uIU/mL) in an obese child with normal free T4 to represent a state of subclinical hypothyroidism. However, the elevation of TSH may reflect hyperleptinemia rather than thyroid dysfunction. The author would consider thyroid hormone replacement in a child with elevated TSH if (a) there is a goiter, (b) the child is seropositive for thyroid antibodies, (c) the TSH exceeds 8–10 uIU/mL), (d) the T3 is not markedly elevated, *and/or* (e) the child's symptoms or physical findings (other than obesity) suggest a true hypothyroid state.

Effects of Obesity on Gonadal Function and Pubertal Development

Recent studies show that obesity in early childhood (age 36–54 months) and excessive weight gain between 3–9 years of age increase the risks of precocious thelarche in girls and reduce by ~6–9 months the age of menarche [31]. Since leptin promotes gonadotropin secretion and rises transiently before the onset of puberty in normal weight children, it is possible that the hyperleptinemia of obesity promotes early sexual maturation, at least in girls.

More commonly, obese girls and boys develop precocious adrenarche without true puberty, and obese adolescent females are prone to ovarian hyperandrogenism with mild hirsutism, acne, anovulation, and menstrual irregularity. The pathogenesis of precocious adrenarche and ovarian hyperandrogenism in obesity remains poorly understood (Fig. 20.3). However, insulin and IGF-1 in excess act in synergy with adrenocorticotrophic hormone (ACTH) and luteinizing hormone (LH) to stimulate the production of androgens from adrenocortical cells and ovarian theca cells, respectively. These effects are

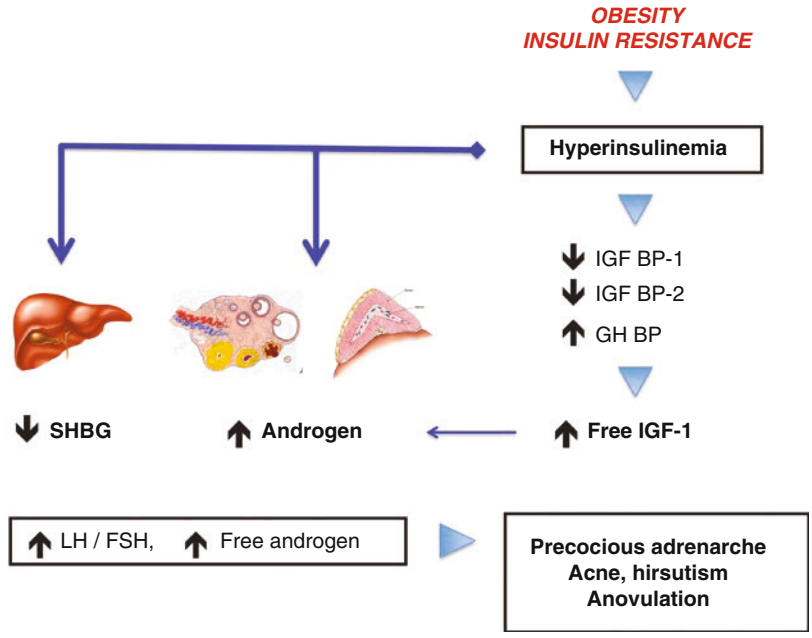

Fig. 20.3 Development of precocious adrenarche and ovarian hyperandrogenism in obese adolescents. IGF, insulin-like growth factor; BP, binding protein; GHBP, growth hormone-binding protein; SHBG, sex hormone-binding globulin; LH, luteinizing hormone; FSH, follicle-stimulating hormone

mediated through induction of P450c17α hydroxylase activity. The biologic availability of ovarian and adrenal androgens is increased because insulin suppresses hepatic sex hormone-binding globulin (SHBG) expression and reduces plasma SHBG concentrations. In obese girls with polycystic ovary syndrome, the free androgens (and, possibly, hyperinsulinemia) increase the frequency of LH pulses [32, 33] and the ratio of LH to follicle-stimulating hormone (FSH), thereby exacerbating thecal androgen production. The increase in free androgens can cause precocious adrenarche in prepubertal girls and boys and anovulation, hirsutism, and acne in adolescent girls and young women. Thus, obesity may mimic and clearly exacerbates the reproductive phenotype of the polycystic ovary syndrome [34–36] (Fig. 20.3); see also Chap. 36 by Dr. Barber and colleagues.

Free and total testosterone levels are generally normal in boys with mild to moderate obesity but decline with dramatic weight gain in association with normal or low gonadotropin levels. Among a group of obese teenage boys [37] aged 14–20 years, free testosterone levels were inversely related to BMI and measures of insulin resistance (HOMA-IR). LH, FSH, and estradiol levels were normal or low, suggesting suppression of the hypothalamic-pituitary-gonadal axis.

The mechanisms driving the fall in testosterone in obese adolescents (and adults) are unclear (Fig. 20.4); potential mediators include hypothalamic resistance to insulin and leptin and increases in circulating proinflammatory cytokines, which in concert reduce gonadotropin releasing-hormone (GnRH) secretion and LH pulse amplitude [38]. In addition, resistance to insulin action in bone may reduce circulating levels of osteocalcin (see below), an osteoblast hormone that in mice promotes Leydig cell testosterone production [39]. Testosterone levels in obese boys and men can be restored with weight loss.

Obesity is now the most common cause of gynecomastia in teenage boys. Aromatization of androgens by adipose tissue likely increases local estrogen concentrations (Fig. 20.4), causing true

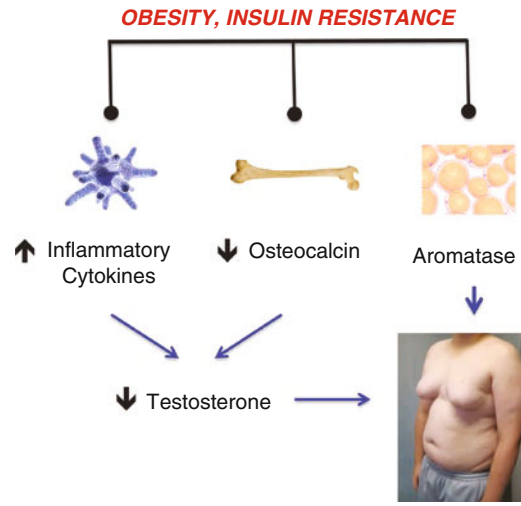

Fig. 20.4 Pathogenesis of testosterone deficiency and gynecomastia in obese males

breast enlargement (commonly superimposed upon adipomastia). In rare cases, gynecomastia in obese boys and ovarian hyperandrogenism in obese teenage girls are caused by hyperprolactinemia. Prolactin levels are typically normal or low in obese children [40]. However, hyperprolactinemia in children with pituitary tumors may be associated with weight gain in children as well as adults [41, 42]. Studies in rodents suggest that prolactin-dependent weight gain derives from increases in food intake and white adipogenesis [43–49]; alternatively, hyperprolactinemia may cause weight gain and fat deposition in pubertal and postpubescent boys and girls by suppressing sex steroid production [50].

Effects of Obesity on Glucocorticoid Production and Turnover

The abdominal weight gain, striae, hirsutism, and menstrual irregularity that may accompany obesity are often confused with Cushing's syndrome. In contrast to "exogenous" obesity, Cushing's syndrome is typically associated with linear growth failure and delayed bone maturation (unless a primary adrenal tumor produces excess androgens as well as glucocorticoids) as well as broad (>1 cm diameter), atrophic, and/or hemorrhagic/violaceous

striae, rather than thin (<1 cm diameter) pink striae. Basal plasma, salivary, and urinary free cortisol concentrations and basal ACTH levels in obese, non-Cushingoid children generally fall within the normal range, and diurnal variation and the response to dexamethasone are maintained [51]. However, body fat mass correlates with total excretion of glucocorticoid metabolites, suggesting that obesity is accompanied by increased cortisol secretion and turnover.

Polymorphisms in the glucocorticoid receptor have been associated with obesity, hypertension, and insulin resistance in some studies in adults. However, in contrast to the mineralocorticoid receptor (which binds cortisol with very high affinity), the glucocorticoid receptor is not overexpressed in white adipose tissue of obese adults [52]. Regulation of tissue glucocorticoid metabolism, rather than circulating cortisol levels per se, may be a critical determinant of fat distribution and peripheral insulin sensitivity in non-Cushingoid obese subjects [53]. Many investigations find overexpression of 11βHSD-1 in visceral adipose tissue of obese adults. In theory, the resulting overproduction of cortisol may either cause or aggravate pre-existing visceral adiposity and insulin resistance. On the other hand, some studies find lower expression of 11βHSD-1 in preadipocytes of obese, nondiabetic adults [54]; the expected reduction in tissue cortisol concentrations is postulated to reduce adipogenesis, stabilize or reverse pre-existing weight gain, and increase insulin sensitivity. Conversely, an increase in 11βHSD-1 expression after weight loss might in theory facilitate adipose cortisol production, adipogenesis, and weight rebound.

Effects of Obesity on Calcium Homeostasis, Bone Mineralization, and Fractures

25-OH Vitamin D, Parathyroid Hormone (PTH), and Vitamin D Binding Protein in Obesity

Adolescents and adults with severe obesity, particularly those with dark skin, often have subnormal circulating levels of 25-hydroxyvitamin D (25-OHD). One study [55] found that 25-OHD levels were less than 20 ng/mL in 78.4% of markedly obese (BMI 43.3) African American teenage girls (mean age 14 years). Reductions in 25-OHD are less frequent in obese white than in black or Hispanic children [56]: in a total of 127 obese adolescents (mean age 13 years, BMI 36.4), low levels of 25-OHD were noted in 43.6% of Hispanics and 48.7% of African Americans but only 10.2% of Caucasians. In that study, levels of 25-OHD correlated inversely with serum parathyroid hormone (PTH). A more recent investigation [57] showed that 17 of 58 obese adolescents (mean 14.9 years, BMI 36, 66% female, 14% black) had 25-OHD levels below 20 ng/mL; however, none had elevated (>65 ng/mL) PTH levels, and bone mineral content and density fell within the normal range.

In theory, the reductions in 25-OHD levels in obese children may be explained by decreased intake of vitamin D-containing dairy products, decreased cutaneous synthesis of vitamin D3 (in persons of color), and/or reduced bioavailability of vitamin D3 owing to sequestration in adipose tissue [58]. However, recent investigations suggest that rates of "vitamin D deficiency" in obese subjects may be drastically overestimated by standard measurements of 25-OHD, which encompass the fraction bound with high affinity to vitamin D binding protein (85–90% of total circulating 25-OHD), the fraction bound with low affinity to albumin (10–15% of total), and the unbound or "free" 25-OHD (<1% of total). A number of investigators consider free and albumin-bound 25-OHD to be "bioavailable" and therefore biologically active. Studies in Italian and American adolescents [59] and American adults [60] found normal levels of "bioavailable" 25-OHD and PTH in obese subjects with low total 25-OHD; moreover, unlike total 25-OHD, the levels of bioavailable 25-OHD did not correlate with either BMIz or the metabolic syndrome. The differences between total and bioavailable 25-OHD in obesity were explained by downregulation of vitamin D binding protein. Interestingly, vitamin D binding protein levels were ~50% lower in African American

than in Caucasian teenage girls and, in contrast to bioavailable 25-OHD, correlated inversely with plasma insulin and HOMA-IR [61]. These findings suggest that levels of biologically active 25-OHD are maintained in obesity and insulin resistance through reductions in vitamin D binding protein. Given that vitamin D treatment neither prevents nor reverses weight gain or insulin resistance in obese subjects [62–64], the widespread treatment of obese children of color with *mild* reductions of (total) 25-OHD should be reconsidered pending development of standard assays for vitamin D binding protein and bioavailable 25OH D.

Bone Density and Fracture Rates in Obese Children

Bone quality depends on sex, age, pubertal development, and nutritional status and is modulated by hormones, growth factors, cytokines, and a variety of genetic and environmental factors including vitamin and micronutrient intake, sun exposure, weight bearing, and physical activity, which promote bone accrual and strength. In general, bone density is more closely related to lean body mass than to fat mass [65]; the increases in lean as well as fat mass in obesity are associated with increased bone mass in boys and with increased bone density and bone mass in girls [66]. Nevertheless, the literature is inconsistent and its findings are highly variable. Some studies show mild reductions in bone mineral content in obese subjects; others find that overweight and obese children have normal or increased bone mass compared with lean controls. One investigative group finds that bone mineral content, bone density, and bone mass are reduced in obese children with insulin resistance or prediabetes but not in otherwise healthy obese children [67].

It is likely that hormones and cytokines produced by adipose tissue and infiltrating immune cells mediate effects of obesity on bone development [65]. High levels of leptin and inflammatory cytokines (including TNF-α and interleukin 6) and low levels of adiponectin and ghrelin in obese subjects with insulin resistance and glucose intolerance act in concert to promote bone resorption and reduce bone density. Resistance to insulin in bone reduces both bone formation and osteoclast differentiation and impedes the release of osteocalcin (see below). These effects are countered by sex steroids, which inhibit bone resorption and promote bone growth by recruiting osteoblast precursors from a common osteoadipogenic stem cell and by inhibiting the trans-differentiation of osteogenic to adipogenic precursors [65]. The effects of sex steroids in males as well as females are mediated by estrogen receptor signaling.

It is unclear if changes in bone density or mass in obesity alter current or future fracture risk. A retrospective review of medical records of more than 900,000 children [68] found that obesity was associated with a modest increase in fracture risk (odds ratio 1.23–1.42). In contrast, a prospective cross-sectional study of 2213 otherwise healthy children [69] found that obesity reduced fracture risk (OR 0.75). Experiments in mice suggest that high-fat feeding increases bone density but reduces bone strength, bending stiffness, and fracture resistance [70].

Osteopontin, Osteocalcin, and the Complications of Obesity

Bone cells produce a number of proteins that appear to play important roles in the pathogenesis of obesity and its metabolic complications. The *osteoclast* matrix glycoprotein *osteopontin* is markedly upregulated in adipose tissue of obese humans and mice [71]. It reduces insulin sensitivity in adipocytes and hepatocytes through recruitment of tissue monocytes and macrophages and local production of inflammatory cytokines [72, 73]. Plasma levels are increased in adults with obesity, insulin resistance, and type 2 diabetes [74, 75]. In contrast, serum osteopontin was not increased in a single study of obese adolescents [76]. It should be noted, however, that circulating osteopontin levels vary widely in the normal population and decline sharply during and after puberty, making comparisons among varying age groups difficult.

Like osteopontin, the plasma levels of the *osteoblast* protein *osteocalcin* decline with age [77]. Plasma osteocalcin is downregulated by leptin and the glucocorticoids; levels are reduced in children as well as adults with obesity, diabetes, and other insulin-resistant states [65, 78–80].

The carboxylated form of osteocalcin is stored in bone matrix; in response to bone resorption induced by insulin or parathyroid hormone, the protein is decarboxylated and released into the circulation, where it boosts energy expenditure through induction of BAT thermogenesis, reduces white adipose mass, increases insulin sensitivity, and improves glucose tolerance [80, 81]. A knockout of osteocalcin or its receptor in mice [80, 81] reduces energy expenditure, increases abdominal fat mass, reduces pancreatic beta cell mass and insulin production, decreases insulin sensitivity, impairs glucose tolerance, and reduces Leydig cell testosterone production. The fall in plasma osteocalcin in obese children and adults would therefore be expected to exacerbate the metabolic and reproductive phenotypes associated with obesity. Potential adaptive benefits of low osteocalcin in obesity might include a reduction in insulin-dependent bone resorption; this would implicate a functional axis with feedback loops involving the bone, pancreas, gonad, and adipose tissue.

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Metabolomic Signatures and Metabolic Complications in Childhood Obesity

21

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Abbreviations

ALA	Alanine
BMI	Body mass index
FAO	Fatty acid oxidation
GLU	Glutamate
HOMA-IR	Homeostasis model assessment index of insulin resistance
HDL	High-density lipoprotein
ILE	Isoleucine
LEU	Leucine
PCA	Principal components analysis
PHE	Phenylalanine
T2D	Type 2 diabetes
TG	Triglyceride
TYR	Tyrosine
VAL	Valine

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Introduction

Childhood obesity is associated with increased risks of glucose intolerance, hypertension, dyslipidemia, insulin resistance, and type 2 diabetes (T2D) [1]. T2D is now a worldwide pandemic projected to affect 300 million people by 2020 with profound consequences for individual and community health and social and economic well-being [2–4].

T2D is caused by complex interactions between genetic and environmental factors and involves dysfunction of multiple organ systems, with impaired insulin action in the muscle and adipose tissue, defective control of hepatic glucose production, and insulin deficiency caused by loss of β-cell mass and function [5–7]. The major determinants of T2D in children and adults are obesity and insulin resistance [8, 9], but BMI explains only 22% of the variance of insulin resistance in the general population [10]. Thus, the pathogenesis of insulin resistance and T2D remains poorly understood. The successful sequencing of the human genome and approaches such as genome-wide association studies (GWAS) have shown that T2D is a polygenic disease with polymorphisms in a wide array of genes, with each individual gene accounting for <1% of disease risk and with all described polymorphisms in aggregate explaining only a small fraction of disease incidence [11]. New and better technologies are needed to explore the

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interaction of genetics with environmental factors such as diet and physical activity in development of T2D.

Comprehensive metabolite profiling, or "metabolomics," defines the chemical phenotype of biological systems and explores their integrated responses to genetic variation and environmental changes [12, 13]. As such this technology has unique potential value for defining biomarkers that predict disease incidence, severity, and progression and generating new insights into disease mechanisms. This chapter seeks to review the application of metabolomics to childhood obesity, insulin resistance, and T2D.

Metabolomic Workflow

Metabolomics is the comprehensive characterization of all the small-molecule metabolites and low-molecular-weight intermediates in a biological system [12]. Metabolite levels respond to genomic, transcriptomic, and proteomic variability and thereby provide an integrated profile of function in biological systems. With new and more sensitive technologies, the number of measurable metabolites continues to expand [14]. There are currently 42,000 metabolites registered in the Human Metabolome Database, of which approximately 4500 have been detected or are expected in the blood [15]. Thus, metabolomic profiling delivers an integrated picture of metabolic activities in multiple organ systems, and a manageable number of analytes compared to estimates of 25,000 genes, 100,000 transcripts, and 1,000,000 proteins.

However, the field of metabolomics is still relatively young, with significant limitations and potential for overinterpretation of data. Wide-ranging concentrations of metabolites within a sample (ranging from sub-nanomolar to millimolar), problems encountered in efficient extraction of metabolites, and the chemical diversity of the analytes remain as challenges for the field [16]. Progress in this area has been advanced by major improvements in instrument technology, most notably in the sensitivity and mass range of mass spectrometers and development of sophisticated chromatography methods. The most advanced systems deployed in a nontargeted mode are now able to detect up to 10,000 independent spectral features in a single biological specimen [14, 17]. However, even in the best of such studies, only about one-third of the detected peaks can be assigned a specific chemical structure.

Targeted and Nontargeted Approaches

Nontargeted metabolomics is used to compare two biological conditions with coverage of as many metabolites as possible regardless of the chemical class of the metabolites. It is best suited as a discovery tool for identifying metabolites that change in response to manipulation of a biological system rather than providing the exact concentration of a known metabolite. In contrast, targeted metabolomics focuses on measurement of known metabolites in clusters with similar chemical structures (e.g., amino acids, organic acids, etc.) and is well suited for studies of biological mechanisms and validation of biomarkers. As this method often involves the use of stable isotope-labeled metabolites (usually ^{2}H or ^{13}C) as internal standards, it provides precise quantification of a targeted analyte relative to labeled standards added at known concentrations [16, 18, 19]. The evolution of static profiling of metabolites (snapshot at one specific time point) has been complemented by advances in metabolic flux analysis, in which heavy atoms from stable isotope-labeled substrates are detected as they label downstream metabolic products [14, 20–22]. When used together, these assembled tools can provide a deep understanding of metabolic status of cells, model organisms, and human subjects.

Current Metabolomic Technologies

Major instrument platforms for detection and identification of metabolites in biological systems include high-resolution proton nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) [23]. MS is typically coupled to a separation technique such as gas

chromatography (GC-MS), liquid chromatography (LC-MS), ultra-performance liquid chromatography (UPLC-MS), or capillary electrophoresis (CE-MS) [24]. MS ionizes chemical species and sorts the ions based on their mass-to-charge ratio. Chromatography techniques help to separate metabolites based on their chemical properties. NMR uses the magnetic properties of certain atomic nuclei and detects spectral features originating from molecules that contain carbon or hydrogen [23]. In general, MS methods have advantages of high sensitivity and small sample volumes, whereas NMR has little chemical bias and can be used directly on the sample with no need for extraction and derivatization [23, 24].

Metabolomic Signatures in Obesity, Insulin Resistance, and Type 2 Diabetes in Adults

Studies in obese adults using metabolomics have consistently identified a metabolomic profile associated with insulin resistance and T2D consisting of increased plasma concentrations of branched-chain amino acids (BCAA) (Val, Leu, and Ile), aromatic amino acids (AA) (Phe and Tyr), C3 and C5 acyl-carnitines, and glutamate and alanine (Glu and Ala) [13, 18], extending earlier observations of elevated BCAA and other amino acids in obese, insulin-resistant adults [25]. In addition, accumulation of incompletely oxidized lipid species in the mitochondria has also been implicated in the development of insulin resistance. However, the association of the BCAA-related metabolic signature with insulin resistance was stronger than observed for other metabolites including several lipid-related clusters [18]. Clustering of Glu, Ala, and C3 and C5 acyl-carnitines with BCAA may reflect altered BCAA catabolic flux in obesity, as Glu and C3 and C5 acyl-carnitines are produced during BCAA catabolism in mitochondria [18]. Interestingly, glycine was found to have a strong negative association with insulin resistance measured as HOMA-IR [18] or by hyperinsulinemic/euglycemic clamp [26]. Positive associations of BCAA and catabolic by-products and negative associations of glycine with insulin resistance have been confirmed in multiple other studies [27–30], including large cross-sectional cohorts [31, 32]. In summary, work from recent years has established that BCAA and related metabolites are associated with insulin resistance and T2D in adult subjects.

Even more importantly, recent work has revealed that BCAA and related metabolites measured at baseline are associated with the risk for future diabetes, even after accounting for established clinical risk factors [33–37]. Furthermore, Rhee and colleagues found that lipids of lower carbon number and double bond content were associated with an increased risk of diabetes, whereas lipids of higher carbon number and double bond content were associated with decreased risk [38]. Wang and colleagues identified 2-aminoadipic acid (2-AAA) as the most strongly correlated metabolite with incident T2D, with subjects in the top quartile for this metabolite having a >fourfold increase in risk of disease [39]. Interestingly, 2-AAA levels were not associated with BCAA or AA, suggesting that 2-AAA reports on a distinct pathophysiological pathway.

Current literature in adults also reveals that BCAA and related metabolites are highly responsive to therapeutic interventions. For example, obese subjects with T2D undergoing gastric bypass surgery had a much larger drop in circulating BCAA, C3 and C5 acyl-carnitines, and other AA than found in response to dietary intervention [40]. Similar findings have been reported for gastric sleeve procedures [41]. These findings implicate BCAA and related metabolites as factors related to improvement of glucose homeostasis, given that surgical methods induce more dramatic improvements in glycemic control than lifestyle interventions despite comparable weight loss [40, 42].

Metabolomic Signatures in Gestational Diabetes and Offspring Outcomes

Metabolomics has also recently been applied to pregnant women in search of biomarkers that assess risk of conversion from gestational diabetes

(GDM) to type 2 diabetes. GDM affects 3–14% of pregnancies, with 20–50% of these women progressing to T2D within 5 years [43]. GDM shares pathophysiological similarities with T2D; thus, metabolite profiles predictive of T2D could have utility for identifying those who will develop GDM. Allalou and colleagues used a plate assay technology to measure 163 metabolites and direct amino acid analysis by LC-MS/MS and fatty acid analysis by GC/MS. A prospective cohort of 1035 women with GDM pregnancy were enrolled at 6–9 weeks postpartum (baseline) and screened for T2D annually for 2 years. A nested case-control design identified 122 incident cases matched to non-cases by age, prepregnancy BMI, and race/ethnicity. Metabolites significantly elevated in women with incident T2D included all three BCAA, Tyr, and 2-AAA, whereas glycine was negatively associated with diabetes risk [43]. However, in another study by Bentley-Lewis and colleagues, metabolomic profiling of 96 women with GDM versus 96 women with normal glucose tolerance matched by age, BMI, gravidity, and parity revealed no differences in BCAA, AA, or glycine. The metabolites that were different between groups included anthranilic acid, alanine, glutamate, creatinine, allantoin, and serine [44]. In parallel to this study, only a few metabolites were associated with fasting plasma glucose levels in 400 pregnant women of European descent from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) cohort [45]. Interestingly many more metabolites were associated with glucose levels at the 1-hour time point of an oral glucose tolerance test, including positive associations with leucine/isoleucine, glutamate/glutamine, phenylalanine, β-hydroxybutyrate, and multiple acyl-carnitines and fatty acids. Subsequently, a recent study identified a novel metabolite, a furan fatty acid metabolite 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF), providing a link between β-cell dysfunction and GDM/T2D. Plasma samples from a cohort of GDM and normoglycemic mothers matched for age, race, family history of diabetes, and prepregnancy BMI revealed a striking (sevenfold) increase in CMPF in subjects with GDM [46, 47]. In addition, CMPF levels were even higher (12-fold) in a subset of subjects with GDM that developed impaired glucose tolerance 1 year postpartum [46].

There are several complex contributing factors—maternal health, nutrition, weight, environmental changes, placental function, and genetics—that affect the growth and well-being of offspring. Application of metabolomics to predict outcomes in offspring is providing novel insights beyond the traditional methods as it integrates all of these genetic and environmental factors. One study compared the offspring of 67 Northern European ancestry mothers with high fasting plasma glucose and 50 mothers with low fasting plasma glucose with comparable BMI; the neonatal sum of skin folds, a measure of body fat, correlated positively with maternal triglyceride, leucine/isoleucine, ketone, and lactate levels and negatively with maternal glycine levels [48]. In another study, children born to obese mothers had a higher BCAA-related component consisting of BCAA, C3 and C5 acyl-carnitines, isovalerylcarnitine, isobutyrylcarnitine, and 3-methyl-2-oxovalerate than their lean counterparts [49]. Remarkably, maternal metabolomic profiling provided an improved ability to predict newborn size outcomes beyond traditional risk factors, including maternal glucose [45]. Future studies evaluating the fetal metabolome and maternal metabolome could provide insight into mechanisms underlying fetal size at birth.

Metabolomic Signatures in Childhood Obesity, Insulin Resistance, and Type 2 Diabetes

Human growth and development is a dynamic process defined by several stages, including the prenatal period (embryogenesis, fetus), infancy, childhood, adolescence, and adulthood. Although most chronic metabolic diseases emerge and are treated in adulthood, pathology often begins in childhood or adolescence. Thus, application of metabolomics to childhood obesity could help in defining biomarkers of future health risk, as well as novel disease mechanisms and targets for early diabetes prevention and treatment.

In contrast to work in adult obesity and T2D summarized above, metabolomic studies in children are more limited, and initial findings have been inconsistent [50]. Nevertheless, in the more recent and larger pediatric studies, associations of BCAA and acyl-carnitine metabolites with disease variables have begun to emerge. Furthermore, unique metabolic signatures of altered fatty acid and steroid metabolism are now being described in pediatric studies.

One of the first cross-sectional cohort studies using metabolomics among obese and normal weight children in Germany provided evidence for obesity-related changes in serum metabolome composition. A plate assay technology complemented with LC-MS/MS was used to measure 163 metabolites in serum samples of 80 obese and 40 normal weight children between 6 and 15 years of age. Fourteen metabolites (acyl-carnitines, amino acids, acyl-alkyl phosphatidylcholines, and lysophosphatidylcholines) were significantly different in obese compared to normal weight children. Interestingly, BCAA were lower in obese youth, in contrast to findings in adults, but this was not significant when adjusted for multiple comparisons [51]. Consistent with adult findings, medium- and long-chain acyl-carnitine (C12:1 and C16:1) levels were higher in obese relative to normal weight children, possibly reflecting a defect in fatty acid β-oxidation capacity. Changes indicative of oxidative stress were prominent among obese children, including lower acyl-alkyl phosphatidylcholine concentrations and higher ratios of saturated lysophosphatidylcholines to phosphatidylcholines. Plasmalogens are a subclass of acyl-alkyl phosphatidylcholines, with antioxidant properties [52]. Thus, lower acyl-alkyl phosphatidylcholines may reflect consumption of plasmalogens during oxidative stress. In addition, lysophosphatidylcholines are derived from phosphatidylcholines during LDL oxidation and have pro-atherogenic, pro-inflammatory, and anti-insulin signaling effects [53]. In this study, none of the metabolite concentrations showed significant association with pubertal stage, even when adjusted for age.

In a study of 64 obese (mean age 13.4 years), 17 type 2 diabetics (mean age 15.3 years), and 39 normal weight adolescents (mean age 13.0 years), fasting plasma samples revealed lower BCAA and BCAA-derived acyl-carnitine species (C3 and C5 acyl-carnitines) in adolescents with T2D [54]. In addition, no significant differences were observed in long-chain acyl-carnitines or free fatty acids among the three groups. Obese youth had lower short- and medium-chain acyl-carnitines, and there was evidence for higher rates of lipolysis and fatty acid oxidation during fasting among obese and type 2 diabetic adolescents. The authors speculate that over time, with continued obesity and aging, an initial compensatory increase in mitochondrial function that provides "early adaptive metabolic plasticity" is lost as the obese individual transitions from youth to adulthood.

The same group also investigated whether increased plasma amino acid concentrations were associated with impaired β-cell function relative to insulin sensitivity. Disposition index was positively associated with BCAA as well as the BCAA-derived intermediates (C3, C4, and C5 acyl-carnitine) and neutrally transported amino acids (Phe and Met), although associations with BCAA-derived intermediates were lost after adjustment for age, race, sex, BMI, and Tanner stage [55]. In both studies, inclusion of subjects who had already progressed to diabetes might have influenced the results. Confounding effects of glycemic control, medications, and possible comorbidities, differences in sample sizes, and subject characteristics including inter- and intra-study variation in age and pubertal status should be considered when interpreting those results.

Recently, studies conducted with larger pediatric cohorts provide evidence of associations of BCAA with insulin resistance that are consistent with adult findings. As such, nontargeted metabolomic profiling was applied to plasma samples of 262 children, age 6–10 years by Perng and colleagues [49]. The 345 metabolites measured were consolidated into 18 factors by Principal components analysis (PCA). Consistent with adult studies, a BCAA-related component consisting of BCAA and C3 and C5 acyl-carnitines (isovalerylcarnitine, isobutyrylcarnitine,

3-methyl-2-oxovalerate) was higher in obese compared to lean children, in agreement with findings in adults. Additionally, obese children had higher levels of the large neutral amino acids (Phe, Tyr, and Trp) that often associate with elevated BCAA in adults, possibly because they compete with BCAA for cellular transport via the large neutral amino acid transporter (LAT1) protein [13]. In addition, a PCA component comprising several androgenic hormones, including dehydroepiandrosterone sulfate (DHEA-S), and their metabolites was significantly higher in obese than lean children. This elevation likely represents increased adrenal androgen synthesis. This component was also related to higher HOMA-IR and lower adiponectin. As early adrenarche associates with, and may increase, the risk of future cardiometabolic disorders, studies exploring the relation of specific metabolites within this androgen cluster with changes in metabolic risk may help to identify preventive strategies.

The largest pediatric cohort study by Butte and coworkers combined GC-MS and UPLC-MS analyses on fasting plasma samples of 353 non-obese and 450 obese Hispanic children [56]. Consistent with adult findings, BCAA and their catabolites, propionyl-carnitine and butyrylcarnitine, were significantly elevated in obese children. Together with the alterations in BCAA catabolism, higher α-hydroxybutyrate, propionyl-carnitine, and pyruvate levels and lower citrate levels among obese children were indicative of mitochondrial dysfunction, seemingly discordant with the hypothesis of "enhanced mitochondrial function and adaptive metabolic plasticity" suggested in previous pediatric studies [54, 55]. Strikingly, a strong signature of reduced fatty acid catabolism was unique to obese children. Despite higher long-chain fatty acids, long-chain acyl-carnitines (generated during the import of long-chain fatty acids into the mitochondria for catabolism), lysolipids and dicarboxylated fatty acids (intermediates of ω-oxidation), 3-hydroxy fatty acid (readout of β-oxidation), and β-hydroxybutyrate (ketone body) were all lower in obese children. Finally, increased androgen derivatives were observed in the obese children, in agreement with previous findings [49]. As noted above, elevated androgen derivatives can induce premature adrenarche, which is linked to unfavorable metabolic features including metabolic syndrome and PCOS [57].

A recent study of 69 healthy children and adolescents (8–18 years) observed no association between BCAA and HOMA-IR at the time of recruitment. However, in a subgroup of 17 participants (8–13 years) with complete data, higher BCAA at baseline predicted worsening of insulin resistance during 18 months of follow-up [58]. These relationships held when adjusted for race, ethnicity, caloric intake, physical activity, family history of T2D, Tanner stage, and IGF1 level.

Newbern and coworkers used PCA to consolidate an array of metabolites into 17 components in a study of obese adolescents (ages 12–18 years) [59]. HOMA-IR, adiponectin, and the TG to HDL ratio were used as markers of insulin resistance. HOMA-IR correlated positively with a BCAA-related metabolic signature (BCAA, C3 and C5 acyl-carnitines, and glutamate/glutamine and uric acid) and negatively with by-products of complete fatty acid oxidation (Fig. 21.1a, b). Furthermore, the ratio of C2 to (C3 + C5) also correlated negatively with HOMA-IR. C2 (acetyl) carnitine is an end product of complete FAO, whereas C3 and C5 (propionyl, α-methylbutyryl, and isovalerylcarnitine species) carnitines are by-products of BCAA and methionine catabolism. Thus, increased BCAA, increased BCAA catabolism, and decreased complete fatty acid oxidation were associated with higher HOMA-IR.

Sex differences also contribute to changes in metabolic function and outcomes in pediatric obesity. In the previous study [59], BCAA levels and by-products of BCAA catabolism were higher in obese teenage boys than girls of comparable BMI *z*-score. Interestingly the BCAA-related metabolic signature correlated positively with HOMA-IR only in males, only with TG to HDL ratio in females, and inversely with adiponectin in males but not females. Likewise, by-products of fatty acid oxidation associated inversely with HOMA-IR in males but not females (Fig. 21.1a, b). Another study by Zheng and coworkers

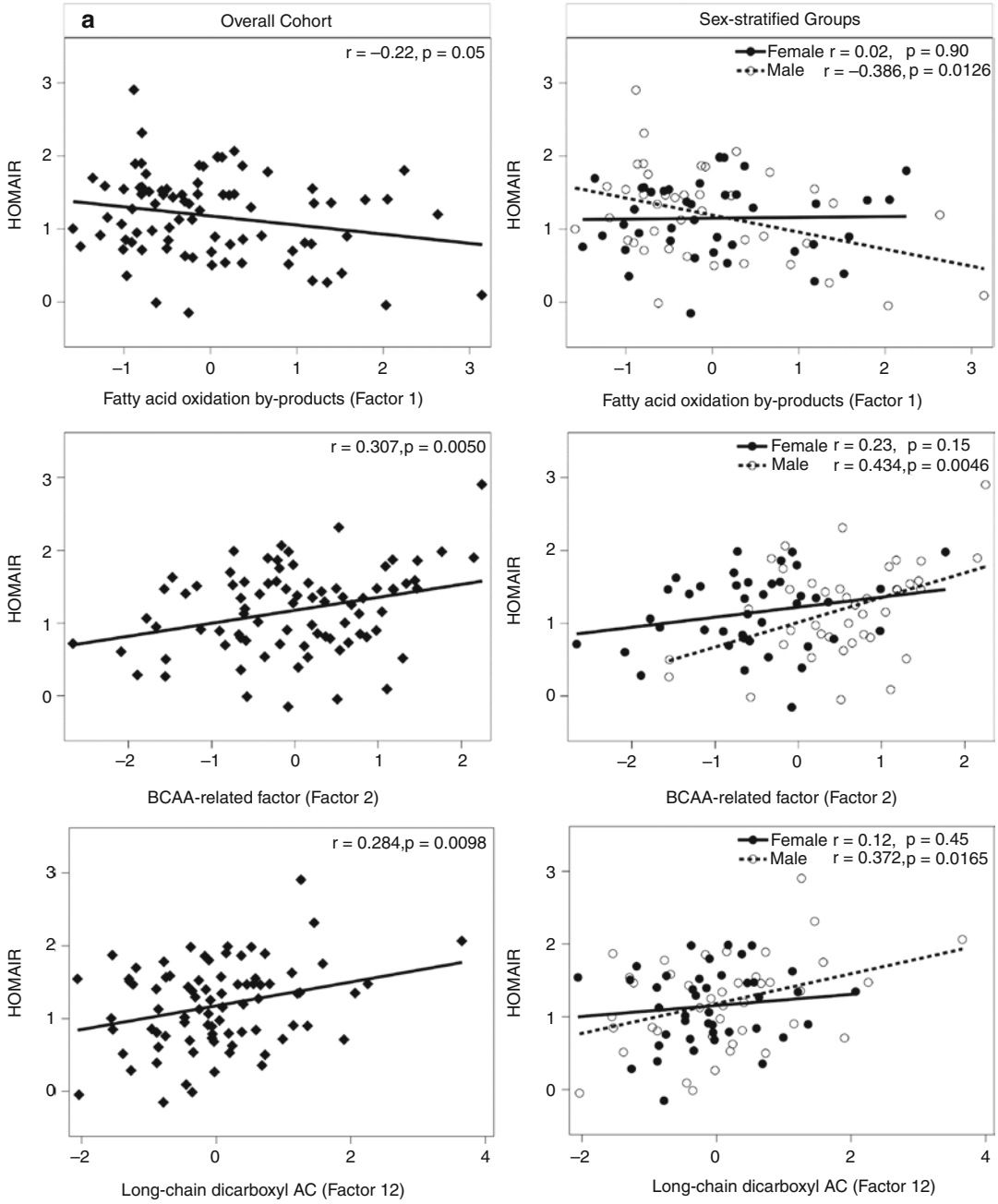

Fig. 21.1 (**a**) Correlations between HOMA-IR and fatty acid oxidation by-products (factor 1), BCAA-related factor (factor 2), and long-chain dicarboxyl acyl-carnitine (factor 12). (**b**) Correlation between adiponectin and BCAA-related factor (factor 2). Correlations are shown for the overall cohort (*left side*) and sex-stratified groups (*right side*). HOMA-IR values and adiponectin are natural log-transformed (Used with permission of Endocrine Society from Newbern D, Gumus Balikcioglu P, Balikcioglu M, Bain J, Muehlbauer M, Stevens R, Ilkayeva O, Dolinsky D, Armstrong S, Irizarry K, and Freemark M. Sex differences in biomarkers associated with insulin resistance in obese adolescents: metabolomic profiling and principal components analysis. J Clin Endocrinol Metab. 2014;99:4730–4739)

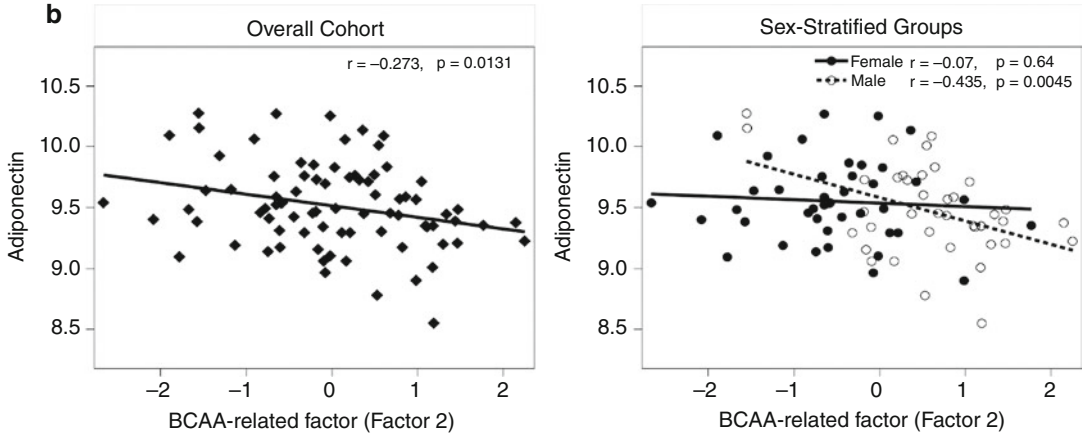

Fig. 21.1 (continued)

examined the plasma and urine metabolome of 192 overweight 12–15-year-old adolescents in Denmark using proton NMR spectroscopy [60]. The concentrations of citrate and creatinine were significantly higher in girls, while urea content was lower in girls compared with boys. Girls had a relatively higher urinary excretion of hippurate and phenylacetylglutamine than boys. These results suggest that sex differences in the metabolome are already manifested in childhood, some of which persist in adolescents and adults. The pathogenesis of sex-dependent differences in amino acid and fatty acid metabolism are poorly understood. Possible factors include differences in sex steroid and/or growth hormone production and action and variations in body fat content and distribution.

Prospective metabolomic studies in children with greater potential to identify biomarkers predictive of future disease risk and obesity interventions outcomes are emerging. A prospective study by Lee and coworkers identified baseline BCAA concentration as a predictor of future risk of insulin resistance and metabolic syndrome, in agreement with the adult studies [61]. Plasma metabolites from 109 Korean boys (age 10.5 ± 0.4 years) were analyzed at baseline and at 2-year follow-up. Obese boys showed significantly higher levels of BCAA, Tyr, Phe, 2-AAA, and several acyl-carnitines and lower levels of acyl-alkyl phosphatidylcholines. Baseline BCAA were positively correlated with both HOMA-IR and continuous metabolic risk score at the 2-year follow-up. This score was constructed using z-scores for five components (waist circumference, systolic blood pressure, TGs, HDL-C, and HOMA-IR). Hellmuth and colleagues performed a longitudinal analysis of 80 obese children before and after a 1-year lifestyle intervention [62]. Tyr was the only metabolite significantly associated with HOMA-IR at baseline and after 1-year intervention. Changes of Tyr over time were also positively associated with changes of HOMA-IR. The authors suggested that "Tyr rather than the BCAA was associated with insulin resistance." Interestingly, in a recent study, Tyr was the highest-ranked metabolite on the basis of its contribution to the obesity classification in a random forest analysis [56]. They found no association between HOMA-IR and BCAA, either at baseline or after the intervention. The authors suggest that prolonged elevations in Tyr may ultimately contribute to increased BCAA levels, since BCAA and AA compete for the same LAT1 for cellular uptake. Most recently, a 7.5-year longitudinal study by Wiklund and colleagues examined serum amino acid profiles by NMR among a total of 396 nondiabetic Finnish girls (aged 11.2 ± 0.8 years at baseline) [63]. Serum Leu and Ile correlated significantly with future triglyceride levels, independent of baseline triglyceride level. In early adulthood (at the age of 18 years), these amino acids were significantly associated with hypertriglyceridemia, whereas fat mass and HOMA-IR were not. Leu was the metabolite that most clearly

discriminated subjects with hypertriglyceridemia from those with normal triglyceride level.

Two studies from Germany applied metabolomics to search for predictors and effects of weight loss during a 1-year intensive weight loss program [64, 65]. Children who lost weight had increases in glutamine, methionine, some lysophosphatidylcholines, and acyl-alkyl phosphatidylcholines, all of which had been previously reported to be lower in obese relative to normal weight children [51]. In addition, the baseline levels of glutamine, methionine, and acyl-alkyl phosphatidylcholines were all lower in the obese children who had substantial weight loss during the intervention compared to those who did not lose significant amounts of weight [65]. Lower serum concentrations of long-chain unsaturated phosphatidylcholines and lower waist circumference were identified as significant predictors of weight loss [64]. These results are difficult to interpret, given that acyl-alkyl phosphatidylcholines were low in obese children but also low in the best responders to the weight loss program. The authors speculate that the phosphatidylcholine profile predicting better weight loss is representative of reduced endogenous choline synthesis, while lower waist circumference is associated with a more beneficial adipokine profile [66]. Indeed, abdominal adipose tissue has been implicated in weight regulation via adipokine secretion and subclinical inflammation [67]. However, the adipokines were not measured in this study.

In summary, on balance, current literature suggests that BCAA and related metabolites are associated with insulin resistance and T2D and that they predict future risk of insulin resistance, metabolic syndrome, and hypertriglyceridemia in pediatric subjects. The results also suggest that changes in the metabolome are already manifested in childhood, some of which persist in adolescents and adults. Furthermore, there may be novel metabolic signatures that are unique to childhood. Prospective studies with larger pediatric cohorts are warranted to extricate temporality and causality of the BCAA and other metabolites with childhood obesity, insulin resistance, and T2D.

Metabolomics Applied to Mechanisms of Insulin Resistance

Metabolomics has recently provided insights into mechanisms underlying development of insulin resistance [13, 16]. For example, metabolic profiling of muscle samples from obese rodents revealed accumulation of a broad array of acylcarnitine species, which originate from the pool of mitochondrial acyl-CoA metabolites and the β-oxidative pathway [68, 69]. In the setting of genetic or diet-induced obesity, high levels of fatty acids cause induction of genes of β-oxidation, but with no effect or a decrease in expression of enzymes involved in the tricarboxylic acid (TCA) cycle and electron transport chain [68]. This "disconnect" between fatty acid oxidation and the TCA cycle results in incomplete fatty acid oxidation, leading to accumulation of incompletely oxidized mitochondrial lipid species. This in turn may contribute to mitochondrial stress and ultimately to insulin resistance [70, 71] (Fig. 21.2).

Evidence from animal models also supports a role for BCAA in disease pathogenesis. Wistar rats fed a high-fat (HF) diet supplemented with BCAA (HF/BCAA) develop insulin resistance despite a reduction in food intake and lesser weight gain than rats fed HF diet alone [18]. On the other hand, feeding obese rodents a BCAA-restricted diet improves insulin sensitivity [72, 73], normalizes muscle glycine levels [72], and increases excretion of acyl-glycine in the urine [72]. These findings demonstrate a direct connection between BCAA and glycine levels and may help to explain the consistent observation of high BCAA levels and low glycine levels in obese and insulin-resistant subjects. Formation of acyl-glycine adducts may constitute a means by which BCAA restriction lowers muscle acyl-CoA levels and restores muscle insulin sensitivity.

Application of metabolomics to rodent models involving overexpression of the transcriptional coactivator peroxisome-activated receptor-gamma coactivator-1α (PGC-1α) identified two BCAA-derived metabolites that may participate in regulation of metabolic homeostasis: β-aminoisobutyric acid (BAIBA) and 3-hydroxyisobutryate (3-HIB).

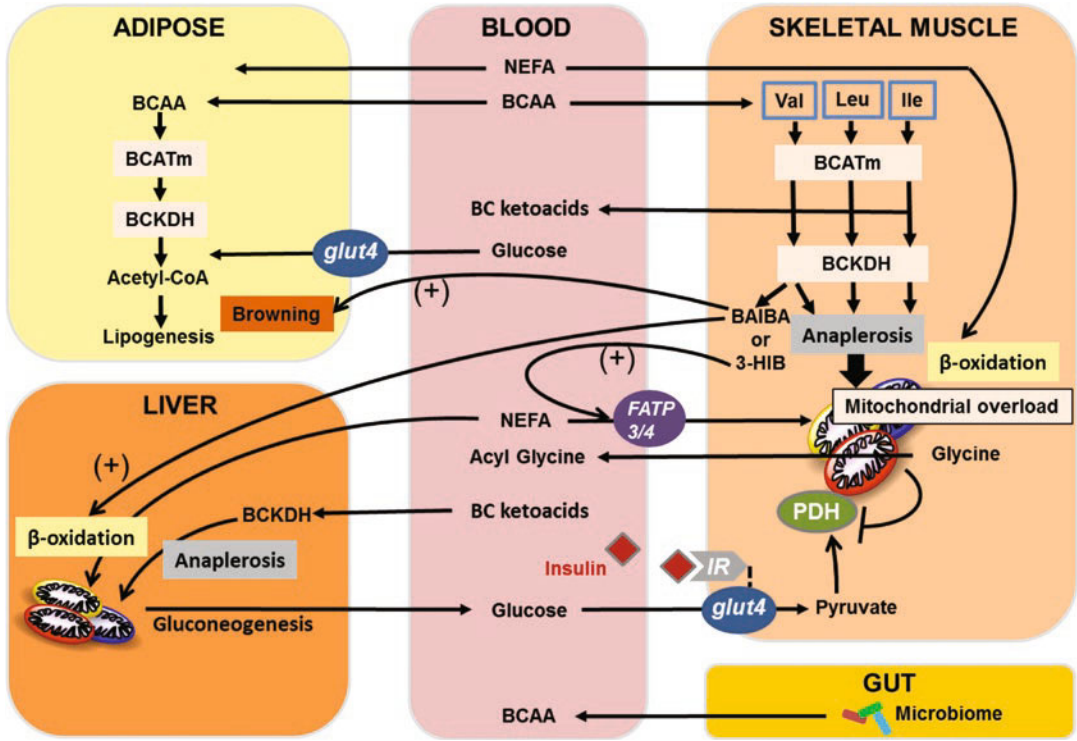

Fig. 21.2 Emergent mechanisms of branched-chain amino acid metabolism in cardiometabolic disease pathogenesis unveiled with metabolomics. Several mechanisms contribute to the accumulation of branched-chain amino acids (BCAAs) in plasma of obese, insulin-resistant humans, including increased de novo production of BCAAs by the gut microbiome and reduced utilization of BCAAs in liver and adipose tissue. BCAA utilization does not appear to be suppressed in skeletal muscle, and under obese conditions, elevated BCAAs induce a decrease in skeletal muscle glycine levels, removing a potential escape valve for excess acyl CoAs. The combination of substrate pressure from elevated BCAAs and lipids in obesity contributes to accumulation of incompletely oxidized fatty acids in mitochondria ("mitochondrial overload") and reduced efficiency of glucose disposal. In addition, valine catabolism yields two new BCAA-derived factors that contribute to energy balance and metabolic homeostasis: β-aminoisobutyric acid (BAIBA), which stimulates thermogenesis and browning of white fat, and 3-hydroxyisobutryate (3-HIB), which stimulates transendothelial and muscle uptake of fatty acids (Used with permission of Elsevier from Newgard C.B. Metabolomics and Metabolic Diseases: Where Do We Stand? Cell Metab. 2017;25(1):43–56)

PGC-1α overexpression in skeletal muscle mimics the effects of exercise by inducing thermogenic genes within white adipose tissue. Profiling of media from cultured myocytes by LC-MS identified BAIBA as one of four metabolites significantly increased by forced overexpression of PGC-1α. Among these, only BAIBA, which is derived from valine metabolism, increased expression of PPARα in white adipose and liver, induced thermogenic genes in adipose tissue (browning), and activated fatty acid oxidation in hepatocytes. Administration of BAIBA to mice limits weight gain, enhances glucose tolerance, and induces browning of white fat. Exercise increases circulating BAIBA concentrations in rodents and humans, and it is proposed that BAIBA represents an endocrine factor that modifies liver and adipose metabolism during exercise [74]. In a second study, another valine metabolite, 3-HIB was also induced by PGC-1α overexpression and shown to function as an activator of transendothelial fatty acid transport [75]. In contrast to BAIBA, 3-HIB levels were found to be elevated in ob/ob mice and in humans with T2D. Furthermore, the administration of 3-HIB to rodents resulted in lipid accumulation in the muscle and development of insulin resistance. Sedentary mice with muscle-specific overexpression

of PGC-1α fed with a high-fat diet actually have impaired glucose tolerance relative to non-transgenic littermates [76], and mice of the two genotypes exhibit similar improvements in body weights and glucose control in response to a combined caloric restriction/exercise intervention [77]. These studies in aggregate may suggest that increases in Val levels in sedentary and metabolically unhealthy subjects are preferentially metabolized to yield 3-HIB rather than BAIBA, thus promoting lipid storage and impaired insulin action in the muscle.

Genetic regulation of BCAA homeostasis may also contribute to accumulation of BCAA in obesity. Recent evidence from a large-scale human genetic and metabolomic study by Lotta and coworkers [78] suggests a causal role of BCAA metabolism in the etiology of T2D. In meta-analysis of 16,596 individuals, a strong association was found between BCAA levels and a SNP 21 kb upstream of the PPM1K gene, which encodes the phosphatase that dephosphorylates and activates the branched-chain keto acid dehydrogenase (BCKDH) complex. BCKDH complex is responsible for the rate-limiting step in BCAA catabolism (Fig. 21.2). In further analysis of 47,877 T2D cases and 267,694 controls, a change of 1 standard deviation in Ile, Leu, or Val levels was associated with odds ratios of 1.44, 1.85, and 1.54 for T2D, respectively. Metabolome-wide association analyses of BCAA-raising alleles revealed high specificity to the BCAA pathway and an accumulation of metabolites upstream of branched-chain alpha-keto acid oxidation, consistent with reduced BCKDH activity. It should be noted that the possibility of pleiotropic associations cannot be entirely excluded, while the association of genetic variants were highly specific. Also, genetic scores used in the study captured a limited proportion of the heritability in BCAA levels [78].

The Microbiome and the Metabolome

The role of the gut microbiome in development of insulin resistance and obesity has been intriguing, as many bacterial species are capable of de novo synthesis of BCAA. The first direct evidence of such an effect emerges from a recent study in which fecal microbiota from human adult female twin pairs discordant for obesity were transplanted into germ-free mice [79]. Mice harboring the transplanted microbiomes from the obese twins demonstrated significant increases in circulating BCAA, as well as increases in short-chain, medium-chain, and long-chain acyl-carnitines in skeletal muscle [79]. These findings are similar to those reported in obese, insulin-resistant versus lean, insulin-sensitive humans [18]. Furthermore, cohousing mice harboring an obese twin's microbiota with mice containing the lean co-twin's microbiota prevented the development of this obesity-associated metabolic phenotype. "Rescue" was driven with invasion of specific members of *Bacteroidetes* from the lean microbiota to obese microbiota and was diet dependent. These findings reveal "transmissible, rapid, and modifiable effects of diet-by-microbiota interactions" [79]. More recently, another group has investigated the impact of human microbiome on metabolome and insulin sensitivity. Metabolomic and microbiome profiling was performed in 277 nondiabetic Danish subjects, and findings were validated in 75 subjects with T2D [80]. A strong correlation between BCAA levels and insulin resistance was confirmed in this study, and the specific bacterial species *Prevotella copri* (*P. copri*) and *Bacteroides vulgatus* (*B. vulgatus*) were proposed to drive BCAA biosynthesis in insulin-resistant subjects. In support of this idea, transplantation of *P. copri* into germ-free mice raised circulating levels of BCAA and caused insulin resistance and glucose intolerance.

The significance of the microbiome in early life and its implications for future health and disease has been a recent area of interest in pediatrics [81–83]; see also Chap. 4 by Anita Kozyrskyj and colleagues. Several studies in children have identified associations between altered gut microbial composition early in life and increased risk for future disease development including obesity and T2D. For example, in a study of 1255 children with body composition measured at 3 years of age, cesarean section was associated with a higher risk of obesity, higher mean BMI *z*-score, and higher sum of triceps + subscapular skinfold thicknesses [84]. Another study conducted in Finland among 6114 healthy boys and

5948 healthy girls at age 2 found that antibiotic exposure before 6 months of age or repeatedly during infancy was associated with increased body mass [85]. Yet a recent study among 163,820 children aged 3–18 years suggests that antibiotic use may influence weight gain throughout childhood and not just during the earliest years [86]. However, studies investigating the structure, the composition, and the function of the microbiota and its role in disease pathogenesis are more limited in children. A recent study conducted by Riva and colleagues among 42 obese and 36 normal weight Italian children aged 6–16 demonstrated an altered gut microbiota characterized by elevated levels of *Firmicutes* and depleted levels of *Bacteroidetes* in obese children [87]. The elevated *Firmicutes*/*Bacteroidetes* ratio was replicated in a group of obese children from Belgium [88]. Short-chain fatty acids (SCFAs), the main fermentation products from fiber breakdown by gut bacteria, were higher in obese children [87], suggesting elevated substrate utilization in agreement with previous studies among obese adolescents [89–91]. SCFA provides an additional source of energy for the body: propionate is a precursor for lipid production, gluconeogenesis, and protein synthesis by the liver, acetate is used in cholesterol synthesis, and butyrate acts as the main energy supply for epithelial cells in the colon [92, 93]. SCFA also activates hormones that inhibit gut motility, increases nutrient absorption, and stimulates appetite [94], contributing to a state of increased "energy harvest." In another study by Michail and coworkers, stool specimens were subjected to 16S rRNA gene microarray, shotgun sequencing, mass spectroscopy for proteomics, and NMR spectroscopy for metabolite analysis from 13 obese children with nonalcoholic fatty liver disease (NAFLD), 11 obese children without evidence of NAFLD, and 26 normal healthy children [95]. Children with NAFLD had more abundant *Gammaproteobacteria* and *Prevotella*, bacterial strains known to play a role in carbohydrate fermentation, producing SCFA [96] and enhancing alcohol production [97]. Interestingly, adding complexity to the relationship between gut microbes and metabolites, differential effects were observed among the SCFA: formate, acetate, and valerate were less abundant; butyrate and propionate were unaffected, and none of the SCFA measured were elevated in the NAFLD group. However, the NAFLD subjects had significantly higher levels of ethanol. Metagenomic and proteomic data showed more bacterial pathways devoted to energy production and conversion, further supporting the idea of enhanced energy harvest in the NAFLD group. Future research with detailed functional analyses of the metabolic activity of the gut microbiota will be needed to define the role of the microbiome in childhood obesity and insulin resistance.

Conclusions and Future Directions

Early childhood factors may play an important role in the pathogenesis of T2D. Application of metabolomics in childhood obesity can define novel disease mechanisms and targets for early diabetes prevention and treatment. Current literature suggests that metabolomics has promise for characterizing biomarkers that predict disease incidence, severity, and progression and generating new insights into disease mechanisms. Remarkably, changes in the metabolome are already manifested in childhood, some of which persist into adolescence and adulthood. Furthermore, there seem to be novel metabolic signatures that are unique to childhood. Prospective studies with larger pediatric cohorts are warranted to extricate temporality and causality of implicated metabolites and development of pediatric obesity, insulin resistance, and T2D.

Editor's Comments and Questions

Studies pioneered by you and your colleagues[a,b] have demonstrated that branched-chain amino acids (BCAA) and their metabolites are associated with and appear to predict the development of insulin resistance and type 2 diabetes mellitus in children and adults.

1. Does the elevation in BCAA in obese, insulin-resistant subjects reflect an increase in dietary intake or a decrease in BCAA tissue uptake and catabolism?

2. Does the macronutrient composition of the diet affect BCAA levels in children or adults?
3. Are there genetic determinants of BCAA catabolism that could modulate the risk of T2D?
4. Do the sex differences you describe in BCAA levels reflect effects of the sex steroids on BCAA metabolism?

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Authors' Responses

1. BCAA are essential amino acids, and their levels in the blood are controlled by multiple factors including dietary intake, rate of use for anabolic processes (protein synthesis), catabolism through transamination and the branched-chain keto acid dehydrogenase complex (BCKDH), and protein turnover. Moreover, recent studies have documented a significant contribution of the gut microbiome for regulation of BCAA homeostasis [78, 79]. In both cross-sectional [28] and longitudinal studies [33], associations of BCAA and related metabolites with insulin resistance and risk for diabetes were not influenced by protein consumption, as estimated by feeding questionnaires. Thus, the elevation in BCAA cannot simply be explained by an increase in dietary intake.

   Obesity is associated with differential regulation of BCAA catabolism across key metabolic tissues and organs [13]. In obese states, BCAA uptake and catabolism is decreased in the adipose tissue[a,b,c] and liver[a] while it is enhanced in skeletal muscle [72]. This differential regulation may contribute to elevations in circulating BCAA and generation of anaplerotic substrates from BCAA catabolism in the muscle "filling up" the TCA cycle.
2. Yes, the macronutrient composition of the diet affects BCAA levels. Fontana and coworkers recently demonstrated that a moderately protein-restricted (PR) diet improves markers of metabolic health in humans accompanied by a significant decrease in plasma levels of BCAA [73]. More importantly, they found that feeding mice a diet specifically reduced in BCAA improves glucose tolerance and body composition equivalently to a PR diet, via metabolically distinct pathways. These findings are consistent with studies of BCAA restriction in rodent models, for example, the Zucker fatty rat [72].
3. A very recent study provides new evidence of genetic regulation of BCAA homeostasis.[d] In a meta-analysis of 16,596 individuals, a strong association was found between BCAA levels and a SNP near the PPM1K gene, which encodes the phosphatase that dephosphorylates and activates the BCKDH complex. In subsequent analysis of 47,877 T2D cases and 267,694 controls, a 1 standard deviation increase in Ile, Leu, or Val levels was associated with odds ratios of 1.44, 1.85, and 1.54 for T2D, respectively.
4. Sex steroids might play an important role in the pathogenesis of sex-dependent differences in BCAA metabolism. However, other possible factors including GH production and action, variations in body

fat content, and distribution should also be considered. Estrogen increases insulin sensitivity and limits body fat deposition, while progesterone opposes these effects in genetically engineered mouse models.[e,f] On the other hand, a study in adolescents found no relationship between sex steroid levels and measures of carbohydrate metabolism during puberty.[g] Likewise, a longitudinal investigation in boys and girls found no correlation between pubertal changes in insulin sensitivity and changes in levels of estrogens and androgens.[h] Future prospective studies investigating the role of sex steroids and possible other factors on BCAA metabolism are warranted to further delineate pathogenesis of sex-dependent differences in metabolic function and outcomes in pediatric obesity.

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Immune Function in Obesity

22

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Abbreviations

EAE	Experimental autoimmune encephalomyelitis
IBD	Inflammatory bowel disease
IFN-γ	Interferon-γ
IL	Interleukin
JNK	c-Jun N-terminal kinase
MCP-1	Monocyte chemotactic protein 1
MS	Multiple sclerosis
NF-κB	Nuclear factor kappaB
NKT cells	Natural killer T cells
PPARγ	Peroxisome proliferator-activated receptor gamma
TCR	T cell receptor
Th1	T helper type 1
Th17	T helper type 17
TNF-α	Tumor necrosis factor-α
Treg	Regulatory T cells
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus

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Introduction

The immune system is a host defense system that provides protection against invading pathogens as well as cancer immunosurveillance. Encompassing a wide range of immune cells with protective functions, the immune response can be divided into non-specific innate immunity and antigen-specific adaptive immunity; the latter creates an immunologic memory to provide specific and long-term protection against select pathogens seen in repeated exposures.

White adipose tissue is composed largely of adipocytes along with other cells including preadipocytes, fibroblasts, endothelial cells, and immune cells. Adipose tissue cells secrete hormones, cytokines, and other factors that can influence one another (in a paracrine manner) or send signals to distant cells throughout the body (in an endocrine manner). White adipose tissue is altered in obesity, leading to increases in adipocyte volume as well as adipocyte lipid content. These alterations in fat volume and lipid content are associated with changes in adipose tissue-resident immune cells, as well as circulating immune cells, and promote a pro-inflammatory phenotype. This obesity-associated inflammatory response, in turn, influences protective immunity and mediates aspects of obesity-driven metabolic disease. In this chapter we review changes in immune cell number and function in obesity, the influence of obesity-associated inflammation on

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obesity-related pathologies, and the effects of obesity on protective immunity, autoimmunity, and cancer immunosurveillance.

Adipose Tissue and Immune Cell Interactions

Adipocytes communicate with immune cells residing within adipose tissue, with immune cells in the circulation, and with immune cells located in other tissues throughout the body. Adipocyte-immune cell communication can occur via cell-to-cell contact, through the paracrine action of adipocyte-secreted factors, or by secretion of a variety of signaling molecules that alter immune cell function in an endocrine manner. Here we discuss some of the key immune cells and adipocyte-secreted factors that are altered in obesity.

Immune Cells in Obesity

Macrophages are the most abundant immune cell found in adipose tissue and comprise 40–60% of adipose tissue-resident immune cells in obese states [1]. Macrophages can be polarized toward either an M1 or M2 phenotype. In lean individuals, most adipose tissue macrophages are polarized toward the M2 phenotype (also known as alternatively activated macrophages) and support an anti-inflammatory environment by secreting cytokines such as interleukin-10 (IL-10), IL-4, IL-1 receptor agonist, and the metalloprotease arginase-1 [2]. In obese subjects, adipose tissue macrophages are predominantly pro-inflammatory M1 macrophages (also known as classically activated macrophages). M1 adipose tissue macrophages are responsive to the pro-inflammatory cytokine interferon-γ (IFN-γ) and, following activation, express substantial quantities of inflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-6, IL-12, IL-1β, and the chemokine monocyte chemotactic protein 1 (MCP-1) [2].

In addition to macrophages, there are also several populations of lymphocytes residing within the adipose tissue, including T lymphocytes (T cells), B lymphocytes (B cells), and natural killer T (NKT) cells. In fact, *T cells* are the second most abundant immune cell in adipose tissue after macrophages [3]. T cells can be broadly characterized as either CD4+ T helper cells or CD8+ cytotoxic T cells. The primary role of the CD4+ T helper cell is to secrete cytokines that facilitate the responses of other immune cells to antigens, whereas the primary role of the CD8+ cytotoxic T cell is to kill infected cells or tumor cells. Obesity is accompanied by an increase in adipose-resident CD4+ T helper 1 (Th1) cells and CD8+ cytotoxic T cells, both of which secrete the pro-inflammatory cytokine IFN-γ upon activation. Increased circulating pro-inflammatory CD4+ T helper 17 (Th17) cells have also been observed in obesity, as well as increased serum IL-17 which may be secreted by Th17 as well as other immune cells.

In contrast to Th1 and Th17 cells, regulatory T (Treg) cell numbers are decreased in obesity. Treg cells play a major role in maintenance of self-tolerance and in dampening the pro-inflammatory influence from other immune cells, such as Th1 and Th17 cells. Treg cells suppress inflammation, in part, by secreting the anti-inflammatory cytokine IL-10, activating M2 macrophages, and expressing peroxisome proliferator-activated receptor gamma (PPARγ) which is required for Treg cells to maintain their anti-inflammatory function [3, 4]. In the lean state, Treg cells are abundant in adipose tissue; the reduction in Treg cells in obesity contributes to a pro-inflammatory adipose environment.

In addition to increased CD4+ and CD8+ T cells, *B cells* are lymphocytes that also accumulate in adipose tissue in obesity [5]. In this context, B cells promote inflammation, albeit to a lesser degree than T cells and macrophages, by producing pro-inflammatory cytokines such as IL-2 and IL-12 that influence the inflammatory state by inducing the differentiation of naïve T cells into Th2 and Th1 cells, respectively [6]. *Natural killer T (NKT)* cells are another type of lymphocyte found in adipose tissue [7]. NKT cells express an invariant form of the T cell receptor that interacts with CD1d, a lipid

antigen-presenting protein expressed by many types of cells. Depending on the type of lipid antigen that is presented by the CD1d complex, NKT cells can respond by secreting different types of cytokines. Adipocytes express a large quantity of CD1d protein and thereby promote NKT cell activity [8]. In general, NKT cells have an important role in modulating immune response in adipose tissue and producing anti-inflammatory cytokines such as IL-4 and IL-10 [9]. These cells, however, are decreased in obese individuals [9].

Multiple other immune cells are detected in altered numbers in the adipose tissue of obese subjects (Table 22.1). Both pro-inflammatory *neutrophils and mast cells* are activated in obesity [10]. Conversely, *eosinophils* are decreased in adipose tissue in obesity. Eosinophils typically regulate allergic responses and play a central role in immunity against multicellular parasites such as helminths. Within adipose tissue, eosinophils secrete IL-4, which maintains the adipose tissue macrophage M2 phenotype [11].

Immunosignaling Molecules Altered in Obesity

Adipocytes secrete several types of hormones, cytokines, and chemokines, many of which are also secreted by immune cells [12]. These secreted factors can influence immune cells localized in adipose tissue as well as in circulation. Moreover, levels and proportions of these adipocyte-secreted immunosignaling molecules vary in obesity.

Leptin is secreted from white adipose tissue in proportion to adipocyte mass. In addition to its critical role in regulating body weight, appetite, and energy expenditure [13], leptin also provides a key link between nutritional status and immune cell activation and functions as a pro-inflammatory cytokine [14]. Several types of immune cells express the full-length leptin receptor, and mutations or deletions in either leptin or the leptin receptor can result in immunodeficiency characterized by decreased total T cells, decreased CD4+ T helper cells, and altered cytokine production leading to increased susceptibility to intracellular infections [15, 16]. In general, leptin has been found to increase the survival of immune cells, promote immune cell proliferation, and protect against apoptosis [14]. In T cells, leptin induces Th1 and Th17 polarization, leading to increased IFN-γ and IL-17 production [17, 18]. As leptin levels are markedly increased in obesity, leptin may play a major role in promoting obesity-associated inflammation.

In contrast to leptin, the levels of *adiponectin* are inversely correlated with body fat percentage

Table 22.1 Changes in immune cells during obesity

Leukocyte population	Lean adipose tissue	Obese adipose tissue
Macrophages	Alternatively activated (M2) macrophages express IL-10	IFN-γ-activated (M1) macrophages express TNF-α, IL-6, IL-1β, and IL-12
CD4+ T cells	Predominantly Th2 and Treg cells	Predominantly Th1 and Th17 cells; express IFN-γ and IL-17, respectively
CD8+ T cells	Not detectable in lean adipose tissue	Increased in number; express IFN-γ
Treg cells	Express IL-10 and inhibit the pro-inflammatory action of other immune cells	Decreased in number
B cells	Breg phenotype (B1a) express IL-10 and IgM antibodies	B2 phenotype increased in number; express IgG antibodies
NKT cells	Express IL-2, IL-4, and IL-10	Decreased in number
ILC2 cells	Express IL-5, MetEnk, and IL-13	Decreased in number
Neutrophils	Low numbers	Increased in number and produce elastase
Mast cells	Inactive	Express TNF-α, IL-6, and IFN-γ
Eosinophils	Express IL-4 and IL-13	Decreased in number

in adults [19]. The adiponectin receptor is expressed by several classes of immune cells, including monocytes, B cells, NK cells, and select populations of T cells [20]. Adiponectin primes macrophage polarization toward the anti-inflammatory M2 phenotype and inhibits lipopolysaccharide-induced IFN-γ production by NK cells [21, 22]. As adiponectin has anti-inflammatory actions, the reduction in adiponectin levels in obesity results in a shift toward a pro-inflammatory phenotype.

Adipocytes also produce many types of cytokines, several of which are also secreted by immune cells (Table 22.2). Due to their potent pro-inflammatory nature and their role in obesity-associated insulin resistance, *tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6)* have received considerable attention in obesity research. *TNF-α* is secreted by adipocytes, macrophages, and a wide variety of other cells. Studies from the 1990s demonstrated that TNF-α expression is increased in obesity [23]. Increased circulating TNF-α promotes systemic inflammation and, along with other cytokines, stimulates the acute phase reaction. TNF-α has a broad role in inflammation, most notably as a potent attractant that recruits neutrophils to adipose tissue and as an inducer of C reactive protein production in the liver [24].

Not long after the initial finding that TNF-α was increased in obesity, other pro-inflammatory cytokines were found to be nutritionally altered. One example is *IL-6*, which is secreted by adipocytes, pre-adipocytes, T cells, and macrophages in response to trauma or other tissue damage leading to inflammation [25]. Circulating IL-6 levels are significantly increased in obesity. Importantly, secretion of IL-6 by adipocytes leads to the accumulation of adipose tissue macrophages through trans-signaling, whereby IL-6 binds to a soluble version of the IL-6 receptor, and the IL-6/IL-6R complex binds to gp130 on

Table 22.2 Adipose tissue-secreted immunosignaling molecules

Molecule	Class	Immune function	Reference
Leptin	Adipokine	Induces Th1 and Th17 polarization	[17, 18]
Adiponectin	Adipokine	Polarization of macrophages into M2 phenotype	[22]
Resistin	Adipokine	Stimulates the production of TNF-α and IL-12 in macrophages	[29]
Visfatin	Adipokine	Stimulates the production of TNF-α, IL-1β, and IL-6	[30]
TNF-α	Cytokine	Neutrophil chemotaxis	[31]
IL-1β	Cytokine	Stimulates macrophage activity	[32]
IL-6	Cytokine	Recruitment of macrophages	[26]
IL-8	Cytokine	Induces neutrophil chemotaxis	[33]
IL-10	Cytokine	Broad anti-inflammatory function	[34]
IL-33	Cytokine	Maintains adipose tissue-resident Treg function	[35]
IL-1RA	Cytokine	Inhibits IL-1α and IL-1β activity	[36]
MCP-1	Chemokine	Macrophage recruitment	[27]
MIF	Chemokine	Inhibits macrophage migration	[37]
MIP-1α	Chemokine	Enhances macrophage migration	[38]
MIP-1β	Chemokine	Enhances macrophage migration	[38]

the surface of macrophages, leading to downstream signaling and activation [26].

Adipocytes also secrete several types of chemokines that promote the chemotaxis of immune cells directly into adipose tissue. *Monocyte chemotactic protein-1 (MCP-1)* is secreted by adipose tissue and binds to the chemokine (C-C motif) receptor 2 (CCR2) on macrophages. Local MCP-1 expression is thought to contribute to the influx of macrophages into adipose tissue in obesity [27]; high levels of the secreted protein in obese individuals may also promote adipose recruitment of CD4+ T cells [28].

See also [29, 38], through as noted in Table 22.2.

Immune Cell Metabolism and Function

Activated immune cells have a very high metabolic demand that is needed to fuel growth, proliferation, and function [39]. To meet this increased energy demand, the metabolic profile of immune cells is altered upon activation [40]. Pro-inflammatory M1 macrophages, activated effector CD4+ T helper cells (including Th1 and Th17 cells), and effector CD8+ cytotoxic T cells upregulate glucose metabolism (glycolysis) to promote growth, survival, and cytokine production. To do so, these pro-inflammatory cells increase expression of the glucose transporter Glut1, which is required for inflammatory immune cell glucose uptake, growth, and survival [40, 41]. In contrast, M2 macrophages, Treg, and naïve and memory T cells require upregulation of fatty acid oxidation to fuel suppressive function and immune surveillance [42, 43]. We now understand that the regulation of nutrient uptake and utilization is critically important for the control of immune cell differentiation and function [40]. Further, the pathways that control immune cell subset function and metabolism are intimately linked. Increases in circulating lipids and non-esterified fatty acids are, therefore, likely to have a significant impact on immune cell function by altering immune cell metabolism and thereby driving inflammation.

Obesity-Mediated Changes in Gut Microbiota Promoting Inflammation

There is now evidence that the gut microbiome is altered in obese adults and children [44]. Changes in microbiome composition can influence both the innate and adaptive immune systems and lead to changes in immune cell distribution that promote inflammation. For example, dysbiosis in the gut may lead to a rise in the levels of bacteria that produce lipopolysaccharide (LPS), providing a trigger for low-grade inflammation [45]. Conversely, there is also evidence that altering the gut microbiome in infancy or childhood can lead to increased risk of obesity and obesity-associated diseases, such as diabetes, later in life. Conditions that may adversely alter the microbiome in early life include mode of delivery (C-section versus vaginal delivery), formula-feeding versus breast-feeding, and early antibiotic exposure [46–49].

Role of the Immune System in Obesity Pathogenesis

As discussed above, obesity is associated with both systemic inflammation and an influx of pro-inflammatory immune cells into adipose tissue (Fig. 22.1a, b). Both the influx of immune cells and the increase in inflammatory cytokines have been shown to promote insulin resistance and the development of type 2 diabetes [25, 50]. This was first described in studies of the pro-inflammatory cytokine TNF-α. In addition to finding that TNF-α expression is increased in obesity, loss of TNF-α in obese animals was found to improve insulin sensitivity, whereas exogenous administration of TNF-α to lean animals led to insulin resistance [23, 51].

Not long after these initial findings with TNF-α, other pro-inflammatory cytokines were implicated, and both C-reactive protein (CRP) and IL-6 levels were found to predict the development of type 2 diabetes in obese patients [52]. These early studies led to subsequent discoveries implicating multiple immune cells, chemokines, and cytokines in the network of inflammation that lead to insulin resis-

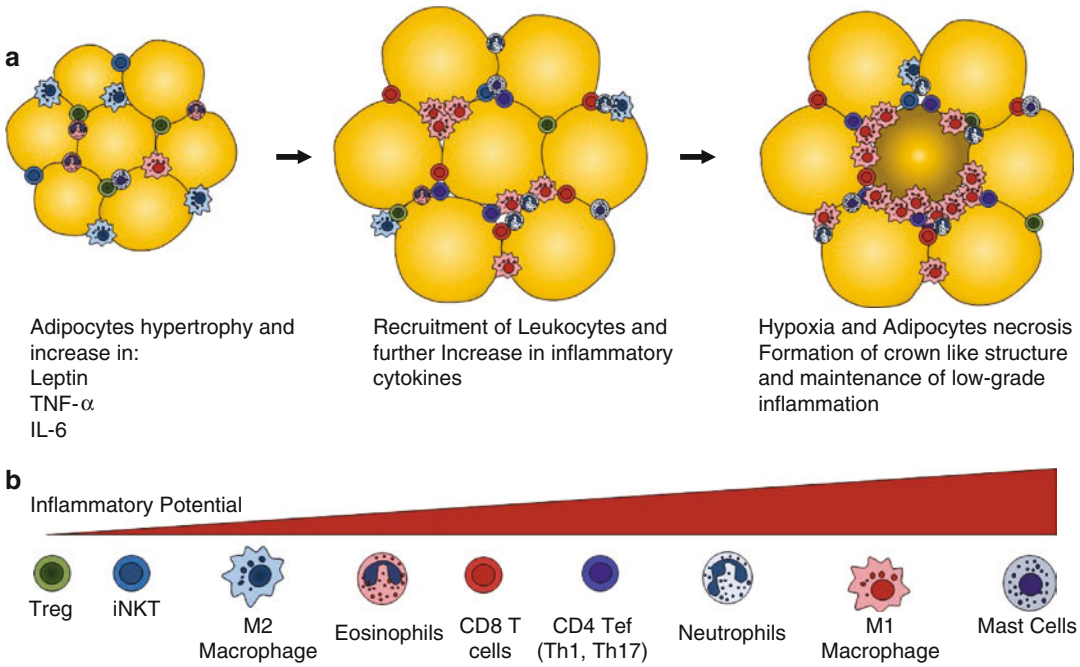

Fig. 22.1 (**a**) Adipose tissue is altered in obesity. Early changes include adipocyte hypertrophy followed by recruitment of pro-inflammatory leukocytes and increased secretion of inflammatory cytokines. This can progress to hypoxia and adipocyte necrosis. Macrophages surrounding dead or dying adipocytes are referred to as crown-like structures. (**b**) Several adipose tissue leukocyte populations are altered during obesity, with recruitment of pro-inflammatory cells into adipose tissue

tance and the metabolic syndrome. For example, obese animals lacking IFN-γ expression produced less adipose tissue TNF-α and MCP-1, had decreased inflammatory cell accumulation in adipose tissue, and had improved insulin sensitivity compared to animals with normal IFN-γ expression [53, 54]. Moreover, weight loss in obese patients was found to be associated with a decrease of inflammatory biomarkers (including CRP, TNF-α, and IL-6) and improvement of metabolic parameters, particularly insulin sensitivity.

The role of adipose tissue macrophages in metabolic disease is now established; many studies have demonstrated a role for classically activated M1 macrophages in promoting insulin resistance [55]. Indeed, numerous animal studies have confirmed that disabling the macrophage inflammatory response pathway in obesity can protect against the development of insulin resistance [56, 57]. In addition to macrophages, other innate immune cells also appear to contribute to insulin resistance. Both pro-inflammatory neutrophils and mast cells are activated in obesity, and mice lacking these innate inflammatory cells are protected against insulin resistance [10]. Interestingly, the activation of NKT cells in obese mice was found to induce weight loss, increase glucose tolerance, and improve insulin sensitivity, highlighting the potential role of NKT cells as a therapeutic target for obesity-associated comorbidities [9].

It the last decade, it has become clear that adaptive immune cells also play important roles: the accumulation of pro-inflammatory lymphocytes (B cells and T cells) in adipose tissue promotes insulin resistance in obesity [3]. For example, T cell receptor beta (TCRβ)-deficient mice, which lack T cells, are protected against obesity-induced adipose tissue macrophage infiltration as well as insulin resistance, whereas adoptive transfer of Th1 cells into the high-fat diet-fed TCRβ-deficient mouse led to increased muscle and adipose tissue inflammation as well as increased insulin resistance [58]. As noted previously, obese humans have decreased proportions of anti-inflammatory Treg in adipose tissue. In studies where Treg were depleted acutely,

mice showed increased inflammatory gene expression in adipose tissue as well as decreased insulin sensitivity. Depletion of CD8+ T cells in diet-induced obesity resulted in decreased accumulation of macrophages into obese adipose tissue as well as improved insulin sensitivity [59]. Conversely, adoptive transfer of CD8+ T cells into CD8-deficient mice increased infiltration of macrophages into adipose tissue, increased expression of the inflammatory cytokines IL-6 and TNF-α, and promoted insulin resistance following high-fat diet [59]. Additionally, diet-induced obese mice that lack B cells are protected against insulin resistance, despite weight gain on a high-fat diet [60]. Treatment of these B cell-deficient mice with IgG antibodies from wildtype obese mice restored insulin resistance [60], which indicates a role for both B cells and B cell-secreted antibodies in driving insulin resistance in obesity.

How do these inflammatory cytokines and signals promote insulin resistance? One potential mechanism is elevated inflammatory signals inducing the c-Jun N-terminal kinase (JNK) and nuclear factor kappaB (NF-κB) signaling pathways. Both JNK and NF-κB activation have been reported to decrease insulin action in adipocytes and hepatocytes [61, 62].

Understanding the mechanisms by which immune cell inflammation promotes insulin resistance in obesity opens up new possibilities for treatment of type 2 diabetes using immunotherapy. To date, a handful of targets of inflammation have been tested in small clinical studies and show some potential as novel therapeutic targets for type 2 diabetes: these include TNF-α, NF-κB, and IL-1R signaling [63–67]. Intervening in the early steps of obesity-associated inflammation, perhaps as early as childhood, may help to prevent the onset of diabetes in predisposed patients.

Obesity Effects on Immune Function

The inflammatory response to obesity is different than a typical immune response in several ways. First, it is not an immune response to infection or tumor, nor is it a classical autoimmune response. Second, the inflammation associated with obesity is a chronic low-grade inflammation, as opposed, for example, to the acute and robust immune response seen following infection. Third, while the immune response to infection or tumor is usually beneficial to the organism, the chronic inflammation seen in obesity is harmful. We have already discussed how obesity-associated inflammation can promote insulin resistance and type 2 diabetes. In addition, obesity-associated inflammation has other deleterious effects on immune function which include: (1) an increased risk of select autoimmune diseases; (2) abnormalities in protective immunity that increase morbidity and mortality from select infections and decrease vaccine response; and (3) a potentially altered immune response to cancer. We will discuss each of these in turn.

The Relationship Between Obesity and Autoimmunity

Over the last few decades, the rates of autoimmune diseases in developed countries have risen in parallel with obesity [68]. In fact, obesity has been found to be associated with increased risk for multiple sclerosis (MS), inflammatory bowel disease (IBD), thyroid autoimmunity, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriasis and psoriatic arthritis, and type 1 diabetes [68–71]. Onset of obesity in childhood may play an important role in these diseases. For example, recent clinical studies suggested a correlation between the increased prevalence of childhood obesity in adolescent girls and young adult women over the last few decades and the increased incidence of MS [72–75]. Moreover, childhood obesity is associated with increased risk of developing autoimmune thyroiditis [76], and factors including increased birthweight, early weight gain, and childhood obesity may either increase the risk, or promote the earlier development, of type 1 diabetes [77–79]. Obesity may also increase autoimmune disease severity and decrease response to treatment; correlations between obesity and disease severity as well as treatment efficacy have been found in RA, IBD, psoriasis, and psoriatic arthritis [68, 80–83].

Multiple mechanisms may explain the ability of obesity to promote autoimmune disease. Much

of the association may be due directly to obesity-associated increases in pro-inflammatory cytokines and adipokines IL-6, TNF-α, and leptin, as well as to decreasing adiponectin levels, all key players in the interaction between adipose tissue and immune cells. Moreover, both Th17 number and Th17 secretion of IL-17, which are increased in obesity, have been found to exacerbate autoimmune disease in animal models [84]. Both IL-6 and leptin have been shown to promote Th17 differentiation [17, 18], providing a potential pathway from obesity to inflammatory cytokine production to autoimmunity.

The observation that circulating levels of leptin are increased in obesity is particularly important here, as leptin has been shown to directly promote the pathogenesis of multiple autoimmune diseases in humans and animals, in large part by altering the ratio of Th17 to Treg cells [85]. For example, in mouse models of SLE, leptin was shown to promote disease and increase Th17 response [86], whereas leptin blockade with neutralizing antibodies or leptin deficiency inhibited Th17 number, decreased IL-17 production, increased the number of Treg cells, and improved autoimmune disease [86–88]. Leptin has also been shown to have a role in the pathogenesis of MS in humans and in a mouse model of MS, experimental autoimmune encephalomyelitis (EAE). Leptin injections worsened EAE and increased disease susceptibility in mice while promoting inflammatory cytokine release [89]. Moreover, leptin-deficient *ob/ob* mice were found to be resistant to EAE, but this protection was lost when mice were treated with recombinant leptin [90]. Leptin neutralizing antibodies likewise protected against T cell response and EAE in mice [91]. In humans, leptin levels were increased in patients with MS in both serum and cerebrospinal fluid and associated with increased inflammatory cytokines [92–94].

Studies have also pointed to a role for leptin in IBD. Whole body leptin-deficient mice or mice treated with a leptin antagonist were found to be protected from induced colitis, while leptin replacement reversed this protection [95–97]. Serum leptin levels did not always correlate with IBD disease pathogenesis [98], but were found to be increased in patients with exacerbations of ulcerative colitis in comparison with ulcerative colitis patients in remission [99]. In Hashimoto's thyroiditis, leptin levels correlated with Th17 cell number [100], and increased leptin levels correlated with thyroid autoantibodies in non-obese males independent of obesity [101].

The innate immune system may also play a role in promoting autoimmune disease in obesity, as the NLRP3 inflammasome, a complex innate cell protein complex that has recently been shown to be activated in obesity, and which secretes pro-inflammatory cytokines IL-1β and IL-18, is implicated in the pathogenesis of multiple autoimmune diseases [102]. Other factors may also contribute, such as changes in the microbiome as influenced by a high-carbohydrate, high-saturated fat Western diet, which may alter immune cell populations to favor inflammatory processes.

Consequences of Obesity for Protective Immunity

During the 2009 pandemic, obesity was identified as an independent risk factor for increased morbidity and mortality from H1N1 influenza infection [103, 104]. Subsequently, obesity was also found to increase risk from seasonal influenza, and obese individuals were found to have impaired immune responses to influenza vaccination [105]. Indeed, at 1 year postvaccination, obese subjects displayed a greater decline in influenza antibody titers than healthy weight subjects and had abnormally decreased T cell activation and inflammatory cytokine production when stimulated with influenza virus or antigen in culture. Similar findings have been described in animal studies, where influenza infection of obese mice led to increased mortality, increased recovery time, increased lung inflammation, and altered immune cell (particularly T cell) activation and function [106]. When compared to lean mice, influenza-infected obese mice had reduced memory to infection over time, which resulted in increased mortality following secondary infections [107].

Obesity may increase susceptibility to other respiratory infections in addition to influenza, particularly in children. A study from Poland reported that overweight pre-adolescent children are more predisposed to respiratory infections [108]. A more recent study reported that obesity prolonged disease duration in children with respiratory syncytial virus [109]. Increasing body weight and BMI were also associated with increased periodontal infections, *Staphylococcus* colonization, herpes simplex virus 1 seropositivity, and colonization with *Helicobacter pylori* [110, 111].

Obesity may also reduce vaccine response to other infections in addition to influenza. Obesity has been shown to predict poor vaccine response to hepatitis B vaccination [112, 113]. In overweight children, reduced response to tetanus vaccine has also been observed [114]. This poor response to vaccination has important public health implications, particularly as two thirds of the US is currently classified as overweight or obese. Worldwide, the approximately 500 million individuals who are obese are at increased risk of morbidity and mortality during influenza epidemics and in response to other infections that are recurring threats to global public health.

Immune Contribution to Increased Cancer Risk in Obesity

Cancer is a complex disease influenced by multiple factors including health, genetics, environment, and lifestyle. For example, it is well-known that factors such as tobacco smoke and sun exposure increase risk of cancer. Over the last couple of decades, it has become apparent that overnutrition and obesity are also associated with increased risk of certain malignancies including cancers of the esophagus, breast, endometrium, colon and rectum, kidney, pancreas, thyroid, and gallbladder [115, 116].

Many mechanisms have been proposed to explain how obesity may increase cancer risk [117]. As obesity is associated with insulin resistance and type 2 diabetes, it has been suggested that high serum glucose may favor the pro-glycolytic metabolism of cancer cells [118], whereas elevated insulin levels (seen in insulin resistance) and elevated insulin-like growth factors (also observed in obesity) are potentially cancer-promoting via their growth stimulatory and anti-apoptotic effects.

However, there may also be several immune mechanisms by which obesity promotes the development and/or growth of select cancers. First, both systemic and adipose tissue inflammation, which skew toward a pro-inflammatory phenotype in obesity, produce cytokines that are tumor-promoting. One example is TNF-α, which has been found to enhance cancer cell survival and proliferation through NF-κB and JNK activation [119]. Pro-inflammatory responses in obesity have also been proposed to alter the functional and metabolic state of immune cells leading to poor tumor surveillance, not dissimilar to the impaired protective immunity against infection observed in obese individuals. Additionally, in the colon, obesity can shift the gut microbiome and alter gut permeability. Promotion of select microflora which produce pro-carcinogenic metabolites has been suggested as another potential mechanism by which an altered immunity and microbiome can promote cancer pathogenesis [120].

Summary

It is now clear that obesity results in changes in hormones, cytokines, and immune cells that support a pro-inflammatory phenotype. This inflammatory response promotes insulin resistance leading to diabetes and metabolic disease; increases the risk of select autoimmune diseases; decreases protective immunity to several infections, particularly influenza; and increases the risk of developing several types of cancer. Given the high proportion of obese individuals in the US and other developed countries, obesity-associated immune dysfunction has become a major public health concern. Immunotherapies that target obesity-associated inflammation may have broad applicability in preventing many forms of obesity-related disease.

Editor's Comments and Questions

1. Obesity and insulin resistance are associated with immune cell infiltration of tissues other than white adipose, including the pancreas, liver, and skeletal muscle. In addition, animal models demonstrate microglial accumulation in the hypothalamus. Inflammatory cytokine production appears to contribute to beta cell dysfunction in those with type 2 diabetes and to the pathogenesis of steatohepatitis and hypothalamic insulin and leptin resistance.
2. It is interesting that macrophages tend to accumulate around dying white adipocytes.[a] This finding suggests that that immune activation in obesity may originate with adipocyte apoptosis emanating, perhaps, from adipocyte hypertrophy, adipocyte oxidative and ER stress related to nutrient overload, and/or damage from toxins released by a dysbiotic and leaky GI tract; see also Chap. 6 by Antje Korner and her colleagues. The fact that insulin resistance, fatty liver disease, and type 2 diabetes can be reversed by weight loss suggests that tissue immune activation might be a consequence, or propagating force, rather than proximate cause of white adipose dysfunction. Do you agree with this premise?
3. The infiltration of various tissues with pro-inflammatory immune cells and subsequent tissue damage suggest that obesity and insulin resistance are associated with loss of self-tolerance and heightened immune responses to self-antigens. On the other hand, you present evidence that obesity is accompanied by relative defects in the immune responses to viruses and cancer cells. Can you suggest mechanisms that could mediate selected changes in the immune responses to foreign and self-antigens? Can this be explained by an increase in the ratio of CD4+ to CD8+ cells or a change in the ratio of Treg to Th17 cells?
4. *Potential adaptive roles of insulin resistance:* Several lines of evidence suggest that immune responses associated with insulin resistance may (at least in some cases) be adaptive rather than destructive. The best example is pregnancy, in which development of maternal insulin resistance is essential for the transplacental delivery of nutrients to the growing fetus.[b] Likewise, the insulin resistance of severe acute malnutrition[c] and cancer cachexia is essential for maintaining glucose availability to critical organs including the brain and red blood cells. Interestingly, the white adipose tissue of late pregnant mice, as in obese nonpregnant humans, is hypertrophic and infiltrated with M1-polarized macrophages and expresses high levels of inflammatory cytokines including TNF-α, PAI-1, MCP-1, and IL-6.[d]

   The question then arises: what possible adaptive mechanisms might be served by the development of insulin resistance in obesity? Hibernating mammals and migrating birds deposit fat in excess during the feeding season and become insulin resistant during the winter or in flight in order to maintain blood sugar in the absence of nutrient intake.

   But this is seasonal and reversible; what about the insulin resistance of chronic obesity in humans? One possibility is that resistance to insulin-dependent glucose uptake may limit tissue lipotoxicity that derives from glucose-dependent lipogenesis.[e] However, a recent paper[f] suggests another important adaptive role. High fat feeding in mice in vivo, and saturated fatty acids in vitro, acutely downregulates Glut-1 expression in brain endothelial (blood brain barrier)

cells and reduces brain glucose uptake. Glut-1 expression and brain glucose uptake are restored by compensatory induction of vascular endothelial growth factor (VEGF) in perivascular macrophages. In the absence of VEGF, brain glucose uptake remains impaired in the obese mice, with consequent reductions in cognitive performance. These observations suggest that inflammatory processes inherent in obesity and insulin resistance, which limit glucose uptake by skeletal muscle, increase hepatic glucose production, and activate macrophage VEGF expression, insure glucose availability for, and uptake by, the brain in order to maintain cognitive function.

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Authors' Responses

1. High-fat diet exposure leads to impaired intestinal barrier and altered microbiome along with other factors that may contribute to inflammation. In contrast with your premise, it has been shown that adipocyte hypertrophy following high-fat diet does not occur without the pro-inflammatory cascade.[a] The current prevailing view is that obesity-associated inflammatory changes in the adipose tissue are responsible for adipocyte damage and death and thus lead to the formation of crown-like structures and adipose tissue insulin resistance.[b] Adipocyte insulin resistance and death lead to lipid storage in other tissues such as muscle and fat which then promotes systemic insulin resistance.

   Interestingly, weight loss may be harder to achieve in an inflammatory state. In a report published in *The Journal of Clinical Endocrinology & Metabolism* in 2014, the presence of increased inflammation, as measured by inflammatory cytokine levels, prior to bariatric surgery, led to decreased body mass index reduction following weight-loss surgery.[c]
2. The immune response in obesity is disordered in ways that both promote general-

ized inflammation and autoimmunity while simultaneously decreasing protective immunity against select pathogens, such as influenza. Indeed, the lymphocyte (T and B cell) response in obesity can be described as occurring too late and being overly robust, as well as insufficient in building adequate memory against subsequent infections. Obesity is fundamentally a metabolic disorder, and there are a number of studies, including our own, that demonstrate immune cell function is highly dependent on immune cell metabolism. We are, therefore, exploring the hypothesis that immune cell dysfunction in the obese state is related to altered immune cell glucose and lipid metabolism, which alter lymphocyte function and memory response, as described above. These cellular metabolic changes could promote pro-inflammatory T and B cell subsets including Th1, Th17, and T follicular helper cells (which in turn support B cell development and activation) while downregulating numbers of Treg cells.

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Pathogenesis of Insulin Resistance and Glucose Intolerance in Childhood Obesity

23

Ram Weiss and Emilia Hagman

Introduction

The prevalence of obesity in childhood seems to have plateaued in some parts of the world yet is still increasing in others [1, 2]. Obesity in children and adolescents presents a major public health concern due to its related comorbidities, some of which present in childhood and others which emerge later in life [3]. The mechanistic link between obesity and the majority of its related comorbidities lies in resistance to the effects of insulin on its target organs [4].

"Insulin resistance" is difficult to measure and has multiple definitions. From a biological point of view, "insulin resistance" refers to a reduced effect of insulin in one or more of its target tissues, resulting in a compensatory elevation of the concentration of the hormone in order to achieve the original intended biological effect. Insulin receptors are present in multiple tissues, and the downstream reactions they mediate are involved in a variety of metabolic processes ranging from glucose and lipid metabolism to cell proliferation and neurotransmitter reuptake in synapses. The main metabolic pathway governed by insulin, and the one that dictates its circulating concentrations, is the regulation of plasma glucose through continuous orchestration of fuel selection. In addition to the pancreas, the source of insulin, the main peripheral tissues involved in this process include the liver (which governs glucose metabolism in the fasting state), skeletal muscle (the largest insulin-responsive organ and the one that modulates glucose metabolism in the postabsorptive state), and fat (as a source of free fatty acids in fasting and as a storage depot during the postabsorptive state). Resistance to the effects of insulin in these tissues results in reduced suppression of hepatic glucose production, reduced glucose uptake in skeletal muscle, and increased adipose tissue lipolysis, together resulting in elevated circulating glucose and free fatty acids, the typical markers of the insulin resistant state [4]. In order to maintain homeostasis of glucose metabolism, there is a compensatory increase in circulating insulin concentrations resulting from upregulated pancreatic insulin secretion and reduced hepatic insulin clearance.

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Importantly, insulin resistance is not uniform across tissues and metabolic pathways. For example, the liver becomes resistant to insulin suppression of gluconeogenesis but remains sensitive to insulin induction of lipoprotein (VLDL) synthesis, manifesting as elevated plasma triglycerides [5]. The ability of insulin to suppress production of certain proteins, including IGF-binding proteins 1 and 2 and sex hormone-binding globulin, is also preserved. In skeletal muscle, resistance to the effect of insulin reduces glucose uptake. In contrast, exposure of ovarian theca cells to hyperinsulinemia results in increased androgen production and secretion [6]. Thus, the effects of compensatory hyperinsulinemia on tissues and signal transduction pathways not directly involved in glucose metabolism (including the liver, kidneys, ovaries, and skin) result in the typical manifestations of insulin resistance, namely, dyslipidemia, hypertension, hyperandrogenism, and acanthosis nigricans; see also Chap. 1.

Obesity in childhood can drive insulin resistance. Yet additional factors are critical modulators that determine the degree and extent of such resistance. For example, genetic factors related to the metabolic pathways governing glucose metabolism are major determinants of insulin resistance [7]. These are evident by the strong familial propensity to develop conditions such as type 2 diabetes mellitus (T2DM) and by the differences in insulin sensitivity among ethnic groups in individuals with similar body proportions. In addition, epigenetic effects imposed in utero (such as in infants born small for gestational age) and in the postnatal period are major determinants of insulin action [8]. Developmental states such as puberty and pregnancy are accompanied by transient resistance to the effects of insulin aimed at facilitating growth and fetal survival, respectively [9]. Importantly, exercise is a potent sensitizer of skeletal muscle glucose uptake via insulin-independent GLUT-4 translocation to the myocyte membrane and is thus a cornerstone in the management of conditions characterized by insulin resistance [10].

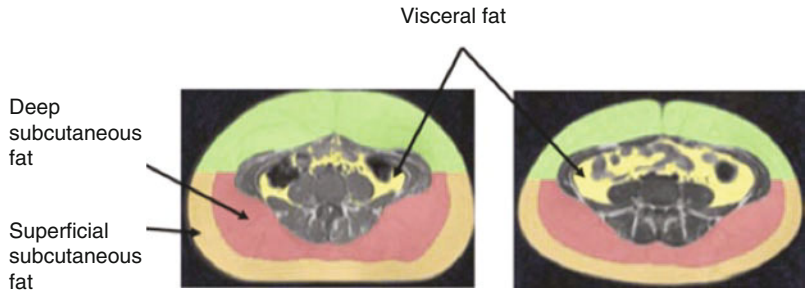
Pathophysiology of Insulin Resistance

Lipid Partitioning

Obesity is a major cause of insulin resistance in childhood, yet it is important to emphasize that the degree of insulin resistance varies quite widely in obese children and adolescents. Moreover, the metabolic impact of increased fat relates more strongly to its distribution in the body rather than to its absolute amount. This distribution is referred to as "lipid partitioning" (Fig. 23.1) and describes the relative deposition of subcutaneous fat, intra-abdominal fat, fat surrounding specific organs such as pericardial adipose tissue, and deposition of fat within specific organs (such as the liver, muscle, and the pancreas itself) [11]. Specific extra-organ fat depots may differ significantly in their metabolic characteristics and respond differently to major hormonal regulators such as insulin and the catecholamines, resulting in varying secretory profiles of free fatty acids and adipose-derived hormones (adipocytokines). In addition, the propensity of different fat depots to harbor cells of the immune system such as macrophages is highly variable [12, 13]. The impact of intra-organ fat deposition is determined by its effects on metabolic signal transduction pathways [14]. While the amount of fat deposited within insulin-responsive organs may be very small compared to subcutaneous and intra-abdominal depots, its systemic effects may be detrimental to whole-body metabolism.

Subcutaneous tissue is considered the natural depot for excess fat and probably has the least deleterious metabolic effects when increased in conditions like obesity. Subcutaneous fat in itself has multiple components differing between abdominal and hip areas. It has been suggested that the deep and superficial layers of abdominal subcutaneous fat have different metabolic profiles and that an increased deep layer may have adverse metabolic effects, unlike the superficial layer [15].

Intra-abdominal fat is normally deposited around vital organs such as the kidneys



Visceral (Visc)	28 cm^2	58 cm^2
Subcutaneous (SQ)	518 cm^2	338 cm^2
Visc / SQ	0.05	0.15
Deep / Superficial	1.15	1.39
Insulin sensitivity	1.90	0.27

Fig. 23.1 Representative MRI images of Caucasian female subjects with low and high levels of visceral fat. Note the inverse relationship between visceral fat and insulin sensitivity (Matsuda index) (Adapted with permission of American Diabetes Association from Taksali SE et al. High visceral and low abdominal subcutaneous fat stores in the obese adolescent: a determinant of an adverse metabolic phenotype. Diabetes 2008;57(2):367–71)

(perinephric fat) and vital blood vessels of the omentum. Below a certain threshold, intra-abdominal fat has little impact on insulin-related metabolic pathways. On the other hand, expansion of intra-abdominal fat is associated with whole-body insulin resistance [16]. The uniqueness of intra-abdominal fat relates to its propensity to be infiltrated by macrophages and its selective drainage via the portal system into the liver.

Hepatic Insulin Resistance (See Also Chap. 26)

Transport of fatty acids to the liver, in combination with hyperinsulinemia, promotes intrahepatic lipid deposition (steatosis), which is associated with hepatic insulin resistance. Insulin action in the liver requires a well-coordinated transmission of intracellular signals that involve a series of synchronized phosphorylation and dephosphorylation events [17]. Binding of insulin to its receptor activates its kinase activity, resulting in phosphorylation of insulin receptor substrate-2 (IRS-2). This reaction promotes the generation of binding sites for substances such as phosphatidylinositol-3 kinase, which promotes Akt recruitment and activation. Akt suppresses hepatic glucose production by decreasing expression of gluconeogenic enzymes and reducing activity of glycogen synthase. Increased hepatic steatosis is typically associated with increased diacylglycerol (DAG) and protein kinase Ɛ (PKCƐ) content within hepatocytes. PKCƐ has been shown to translocate to the cell membrane and inhibit the kinase domain of the insulin receptor [18]. This results in lower insulin-induced activation of PI3K and Akt via IRS-2, impairing the ability of insulin to suppress gluconeogenesis and induce glycogen storage. The end result of such processes is increased hepatic glucose production, manifesting clinically as elevated fasting glucose and reduced early suppression of hepatic glucose output in the post-absorptive state.

Skeletal Muscle Insulin Resistance

Like hepatic insulin resistance, skeletal muscle insulin resistance is associated with increased intra-myocellular lipid deposition. Insulin action in muscle following binding to the receptor involves similar activation of PI3-kinase, leading eventually to translocation of the transporter

GLUT-4 from an endosomal compartment to the myocyte membrane. This is the rate-limiting step for entry of glucose into the cell. Following cellular uptake, glucose is phosphorylated by hexokinase to glucose-6-phosphate, which can either enter the glycolytic pathway or be used for glycogen synthesis.

Following excess lipid accumulation within the myocyte or acute exposure to free fatty acids, the insulin signal transduction pathway is attenuated in a manner that reduces GLUT-4 translocation to the cell membrane [19]. This phenomenon is accompanied by reduced insulin receptor substrate-1 (IRS-1)-induced PI3-kinase activity and a significant increase of protein kinase C Θ. It is postulated that acute exposure to free fatty acids leads to accumulation of fatty acid derivatives such as fatty acid acyl-CoA or diacylglycerol; this in turn leads to activation of serine phosphorylation and reduced tyrosine phosphorylation of IRS-1 by protein kinase C Θ and thereby limits activation of PI3-kinase and impedes GLUT-4 membrane translocation [20].

Adipocyte Insulin Resistance

Adipocytes represent an important insulin-responsive tissue, taking an active part in whole-body glucose and lipid metabolism. Insulin stimulates adipose glucose uptake and lipogenesis while suppressing lipolysis. These effects are mediated by upregulation of lipoprotein lipase (LPL), acetyl-CoA carboxylase (ACC), and fatty acid synthase (FAS), which promote lipogenesis, and inhibition of phosphorylation of hormone-sensitive lipase (HSL), which decreases lipolysis. In insulin-resistant adipose tissue, the effects of insulin on LPL and HSL are attenuated [21]. This manifests as decreased lipolysis of chylomicron-rich triglyceride by LPL and attenuated inhibition of lipolysis by HSL. Thus, an exaggerated release of adipose tissue free fatty acids (FFA), particularly in the postabsorptive state, is the main manifestation of adipose insulin resistance (IR) [22].

As indicated earlier, circulating FFAs play a major mechanistic role in the development of reduced insulin sensitivity in muscle and liver and may also induce β-cell dysfunction. The reduced uptake and storage of FFAs in adipose depots in the postabsorptive state lead to preferential partitioning and deposition of lipids into extra-adipose organs [23]. It has been suggested that intra-abdominal fat is less sensitive than subcutaneous fat to the effects of insulin and more sensitive to lipolytic adrenergic signals. Yet elegant studies using tracer isotopes have shown that the contribution of the intra-abdominal fat depot to whole-body FFA flux is in proportion to its mass [24]. Infiltration of adipose tissue depots by macrophages or other cells of the immune system may be the source of elevated levels of cytokines characteristic of the subclinical inflammatory state commonly observed in obese children. These may include interleukin-6, interleukin-1, and TNF-α, as well as acute-phase reactants such as c-reactive proteins. In contrast, the levels of adiponectin, which has anti-inflammatory properties, are reduced. A significant association has been shown between adipose tissue insulin resistance and a pro-inflammatory adipocytokine profile, suggesting that the two may be interlinked mechanistically.

Lipid Partitioning and Insulin Resistance in Children

Resistance to the action of insulin in the liver and muscle is most probably mediated by derivatives of FFA metabolism. The obese, insulin-resistant adolescent has increased lipid deposition in the muscle and liver; this intracellular lipid accumulation could derive from increased flux of plasma FFA and/or reduced lipid utilization. Postprandial free fatty acidemia exposes skeletal muscle to a surplus energy supply when FFAs are not needed as an energy source. At the same time, fat oxidation in the mitochondria of individuals with insulin resistance is impaired [25]. The combination of excess FFA supply along with reduced utilization results in increased intracellular lipid accumulation, a by-product of which may be the release of toxic FFA metabolites that activate PKCs and thereby hamper the insulin signal transduction pathway.

Obese children and adolescents may have wide variation in lipid partitioning patterns for any given BMI and age. It is well established that

worsening glucose tolerance in this age group is associated with increasing deposition of lipid in the skeletal muscle and liver as well as a greater amount of intra-abdominal fat [26]. Specifically, differences between equally obese insulin-sensitive and insulin-resistant adolescents have been shown in the ratio of intra-abdominal to subcutaneous abdominal fat [27] (Fig. 23.1). A higher ratio is associated with increased intrahepatic lipid deposition and with lower insulin sensitivity. In addition to its association with adverse metabolic phenotype in childhood, the ratio of intra-abdominal to subcutaneous fat in adolescence correlates with the presence of atherogenic dyslipidemia in young adulthood [28] and predicts the clinical and metabolic responses to surgically induced weight loss [29]. The subcutaneous fat depot probably serves as a "metabolic sink" that accumulates fat in states of excess energy intake/low energy output and grows in proportion to its capacity to expand. Inability to expand this depot results in ectopic lipid deposition in the intra-abdominal compartment as well as within and around tissues.

Pancreatic steatosis has been identified in a significant proportion of obese children, specifically among those with increased intrahepatic fat, yet its functional implications are still debated [30]. Similarly, *epicardial fat deposition* has been shown to be increased in insulin-resistant obese children and adolescents [31]. Thus, the subcutaneous fat depot—particularly that localized in the lower body rather than in the upper body—seems to be the optimal lipid storage depot with the least adverse metabolic impact. Individuals with the ability to store excess fat in lower body subcutaneous depots appear to be able to gain substantial amounts of excess weight without developing significant insulin resistance. In contrast, those with low capacity to store excess lipid in subcutaneous depots tend to accumulate fat in visceral depots and in insulin-responsive tissues such as the muscle and liver, leading to the development of insulin resistance. The latter unfavorable pattern of lipid partitioning is associated with an adverse metabolic phenotype characterized by the presence of several cardiovascular risk markers and alterations of glucose metabolism.

Pathophysiology of Impaired Glucose Metabolism in Obese Children (Table 23.1)

Normal glucose levels vary within a narrow range during fasting as well as postabsorptive conditions. Maintaining this normal narrow glucose range depends upon the delicate coordinated interplay of insulin and glucagon action in all their target organs. The islets of Langerhans are the source of both insulin and glucagon, secreted from β- and α-cells, respectively. The balance between insulin secretion and insulin action results in clearance of excess glucose from plasma, preventing the development of hyperglycemia.

Insulin secretion is described as having two phases, the first and second, both of which are crucial for a normal physiological responses. *First-phase secretion* is the early response to increasing plasma glucose and is thought to reflect the release of prepackaged insulin from secretory granules. *Second-phase secretion* is the response to persistent elevated glucose and involves the longer process of trafficking of insulin from the Golgi system to secretory granules. Both have been described in response to a non-physiological intravenous glucose stimulus and cannot be easily detected in response to an oral glucose load, yet their measurement is important as defects in first-phase secretion in subjects with altered glucose metabolism generally precede the development of overt diabetes [32]. Children and adolescents with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) have been shown in hyperglycemic clamps to have primary defects in first-phase insulin secretion compared to those with normal glucose tolerance (NGT). Glucose sensitivity of first-phase insulin secretion declines progressively as children progress from isolated IFG or IGT to combined IFG/IGT [33]. Studies using c-peptide modeling of oral glucose tolerance tests reveal that defects in second-phase insulin secretion occur only in those with IFG/IGT or diabetes [34], indicating that the double defect is a marker of "diabetic" beta cell dysfunction prior to the appearance of overt diabetes.

When prediabetic and diabetic conditions have been evaluated in adults, using different

Table 23.1 Clinical metrics of insulin secretion and action and glucose tolerance

	Calculation	Fasting glucose (mg%)	2-h or random glucose (mg%)	HbA1C
Insulin resistance[a]	*HOMA-IR*: Fasting insulin (μU/mL) × fasting glucose (mM)/22.5[b] *TG/HDL*: Fasting TG/HDL[c] *Matsuda index*: 10,000/$\sqrt{}$fasting glucose × fasting insulin[d]			
Disposition index[a]	$\Delta I_{0\text{-}30}/\Delta G_{0\text{-}30} \times 1$/fasting insulin			
Impaired fasting glucose		100–125		
Impaired glucose tolerance			140–199	
"Prediabetes"		100–125[e]	140–199[e]	5.7–6.4
Diabetes		≥126	≥200	≥6.5

[a]These can be calculated from glucose and insulin levels obtained after an oral glucose administration. See http://mmatsuda.diabetes-smc.jp/MIndex.html
[b]Values in insulin-resistant subjects exceed 2.5 when insulin is in μU/mL and glucose is in mmol
[c]Values in insulin-resistant subjects commonly exceed 2.3 if both TG and HDL are in mg%
[d]Values in insulin-resistant subjects are commonly <4.3
[e]Prediabetes includes impaired fasting glucose and/or impaired glucose tolerance

methodologies for assessment of insulin secretion and sensitivity, it has been shown that IFG is associated with reduced hepatorenal insulin sensitivity. This increases hepatic and renal glucose production [35], which in combination with insufficient basal insulin secretion results in elevated fasting glucose levels. In contrast, IGT is mainly due to marked skeletal muscle insulin resistance and a relative inadequacy of the first-phase insulin response [34, 36]. The differences in the pathophysiology of altered glucose metabolism between obese children and adults are in line with the accelerated pace at which glucose metabolism deteriorates in severely obese children in contrast to the subtle insidious development of this phenomenon in adulthood.

Insulin Sensitivity, Secretion, and Clearance: The Disposition Index

Insulin sensitivity defines insulin action in all relevant target organs. Across the spectrum of glucose metabolism in obese children, it is well established that whole-body insulin sensitivity declines from normal to impaired glucose tolerance [16, 34]. Importantly, while those with IGT are uniformly very insulin resistant, those with NGT have a wide range of insulin sensitivity ranging from very sensitive to very resistant, similar to those with IGT [26]. Whole-body insulin sensitivity measured using the "gold standard" euglycemic-hyperinsulinemic clamp is tightly linked to the lipid partitioning profile described earlier. Lower insulin sensitivity in obese, prediabetic children is associated with increased intra-abdominal, intrahepatic, and intra-myocellular lipid deposition [27] (Fig. 23.1). The ability of the obese child with reduced insulin sensitivity to compensate by increasing circulating insulin concentrations determines the level of glucose tolerance.

In order to increase insulin concentrations, two compensatory mechanisms come into play: increases in insulin secretion and reductions in first-phase hepatic insulin clearance. It has been shown that those with NGT and very low insulin sensitivity probably reduce hepatic clearance to the minimal trough beyond which hepatic insulin action would be compromised and are left with increasing insulin secretion in order to maintain euglycemia [37]. Failure to appropriately increase insulin secretion results in worsening glucose tolerance [38]; see also Chap. 24 on Youth-Onset Type 2 Diabetes.

The relationship between insulin sensitivity and secretion is hyperbolic, such that the product of insulin sensitivity X insulin secretion equals a constant [39] (Fig. 23.2). The product of the two has been named "disposition index" (DI) and reflects beta cell function in the context of ambient insulin sensitivity. The DI has been shown to be the strongest predictor of the development of diabetes over time [40]. Obese children with impaired glucose metabolism have lower DI than their NGT counterparts, reflecting defects in beta cell function that precede development of diabetic range hyperglycemia [33, 41]. Importantly, even appropriate beta cell compensation requires a continuous stimulus to maintain enhanced insulin secretion. For a given DI, exposure to lower insulin sensitivity (i.e., being on the left of the hyperbolic DI curve) is accompanied by slight yet significant increases in both fasting and 2-h glucose [42]. These may still be within the "normal" glucose tolerance range yet reflect an increased demand upon the stressed beta cell.

It should be noted that "normal glucose tolerance" in obese children represents a continuous spectrum, reflected in the worsening DI that accompanies increases in postprandial glucose levels that nevertheless remain in the "normal" range [41]. The DI is likely shaped by genetic/epigenetic factors that govern the ability of the obese child to compensate for insulin resistance. Indeed, it has been shown that intrauterine exposure to gestational diabetes, manifesting exposure to both the genetic background of T2DM and to hyperglycemia, results in a lower DI for a given degree of obesity in childhood and predicts deterioration of glucose tolerance over time [43].

Glucose Effectiveness

Glucose has the ability to facilitate its own uptake via a mass effect in peripheral tissues and to suppress hepatic glucose production depending on basal insulin concentrations [44]. This property of glucose is known as "glucose effectiveness"

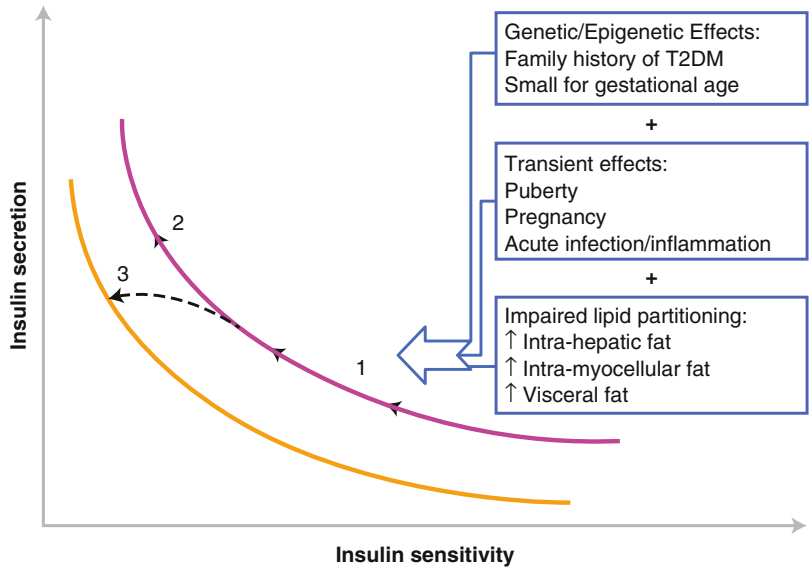


Fig. 23.2 The disposition index in obese children and adolescents. Genetic/epigenetic factors along with transient metabolic conditions and an adverse lipid partitioning profile conspire to reduce insulin sensitivity. Initially, the obese child with normal glucose metabolism moves left on his/her DI curve (1) by increasing insulin secretion as a compensation for reduced insulin sensitivity. Increased insulin secretion allows adequate maintenance of glucose metabolism and a stable DI (purple) in the face of very low insulin sensitivity (2). Failure to compensate appropriately over time by increasing insulin secretion (3) results in a new DI representing a lower DI (yellow), indicating the presence or the early future development of prediabetes and later overt diabetes

(GE) and tends to increase with greater insulin concentrations [45]. The contribution of GE to glucose disposal in fasting conditions (with basal insulin concentrations) is estimated at ~70% of total, while at typical postabsorptive insulin concentrations imposed during a euglycemic-hyperinsulinemic clamp, the contribution of GE to whole-body glucose disposal drops to ~30%. It is thus estimated that the contribution of insulin-independent glucose disposal (GE) to the maintenance of glucose homeostasis is similar to that of insulin.

When glucose tolerance deteriorates, GE is impaired and is unable to reduce blood glucose levels via suppression of hepatic glucose production or acceleration of muscle glucose uptake independent of increased insulin concentration. In combination, the defects in GE and beta cell insulin secretion promote a further rise in circulating blood sugar. Lower GE has been demonstrated in adult patients with T2DM [46] and in children and adolescents with altered glucose metabolism [47]. Of note, baseline levels and the dynamics of GE are independent predictors of changes in 2-h glucose levels over time, emphasizing the role of this factor in the development of altered glucose metabolism in obese children.

The Role of Glucagon

Glucose metabolism is governed by glucagon as well as insulin. The mechanisms regulating glucagon secretion from α-cells remain poorly understood. It is, for example, unclear in humans if α-cells can directly sense and respond to fluctuations in plasma glucose [48] or react only to signals from the autonomic nervous system that sense glucose elsewhere [49]. It is assumed that regulation of glucagon secretion depends on ambient glucose, paracrine and endocrine hormonal stimuli from neighboring cells within the islet and gastrointestinal tract, and parasympathetic activation [50]. In obese children fasting glucagon levels tend to be elevated in association with decreasing insulin sensitivity [51]. The elevated fasting glucagon levels observed in obese insulin-resistant adolescents with normal glucose tolerance and low insulin sensitivity and in those with IGT seem inappropriate in the context of elevated fasting insulin levels. As insulin inhibits glucagon secretion [52], this may imply that α-cells are resistant to the suppressive effect of insulin [53].

Taken together, altered glucose metabolism in obese children is preceded by early defects in insulin secretion in the face of low insulin sensitivity as well as inadequate suppression of glucagon. These defects can be detected within the "high-normal" range of normal glucose levels, emphasizing that glucose tolerance represents a continuous spectrum. A combination of low insulin sensitivity tightly linked to adverse lipid partitioning patterns, along with inadequate beta cell compensation, impaired glucose effectiveness, and elevated basal glucagon secretion, drives deterioration of glucose tolerance that may be progressive and culminate in overt diabetes.

The Role of Gut-Derived Incretins

Incretins are hormones that are released from the gastrointestinal tract in response to food intake and regulate islet hormone secretion. At present, the two major incretins are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). Both of these potentiate glucose-induced insulin release and decrease the release of glucagon from the pancreatic islets [54]. This is manifest as an enhanced insulin response to oral glucose in comparison to the response to intravenous glucose administration when both are matched for plasma glucose concentrations. Obesity and altered glucose metabolism in obese children are associated with reduced fasting and variable postprandial GLP-1 levels [55]. When the incretin effect is calculated, obese children with IGT and T2DM manifest a significantly reduced incretin effect compared to those with normal glucose metabolism in the face of comparable GIP and GLP-1 concentrations [56].

Moreover, obese African American children seem to have reduced GLP-1 response during an oral glucose tolerance test compared to Caucasians [57]. The role of GIP is less clear in the context of altered glucose metabolism in childhood, as it has been shown to be released in comparable amounts in lean and obese children at euglycemia and in postprandial hyperglycemic conditions [58].

Fasting GLP-1 has been shown to be associated with increased resting energy expenditure and fat oxidation in humans [59] (see also Chap. 7 on Brown Adipose Tissue); thus, the lower concentrations observed in obese youth may provide a mechanistic link to development of obesity as well as T2DM; see also Chap. 3. Indeed, preliminary studies have shown that GLP-1 receptor agonists induce weight loss in obese youth [60]. The application of incretin-based therapies for childhood obesity and diabetes is still in its early phases, yet the promising results from adult studies indicate that agents affecting the incretin axis may be beneficial in childhood as well; see Chap. 35 by Drs. Kelly and Fox.

IFG, IGT, and the Progression to T2DM

T2DM is preceded, as described earlier, by prediabetes, with impaired fasting glucose (IFG) levels, impaired glucose tolerance (IGT), and, in many cases, mildly elevated HbA1c (5.7–6.4%). Even though prediabetes is a high-risk state for developing diabetes, many people with prediabetes will not progress to severe glucose intolerance [61, 62]; see also Chap. 24 on Youth-Onset T2DM. Indeed, the prevalence of prediabetes and diabetes in the obese pediatric population varies dramatically across different countries and ethnicities [63–67].

Estimates of prevalence rates are made more difficult by some differences in classification of prediabetes. For example, there are two glucose cutoffs used to define IFG: the American Diabetes Association suggests 5.6 mmol/L [61], while the World Health Organization promotes 6.1 mmol/L [62]. European studies report prevalence rates of IFG in obese children ranging from 1% in Italy [68] and 4% in Germany to 17% in Sweden (all using the ADA criteria) [69]. American studies have reported prevalence rates ranging from 2–9% (WHO criteria) to 15–47% (ADA criteria) [63, 67, 70]. Other countries, including India, China, and Mexico, report only a few percent of patients with IFG in the obese pediatric population [65, 71, 72], whereas 28% of obese adolescents in Taiwan are reported to have IFG [73]. The United Arab Emirates (UAE), which has among the highest adult prevalence of T2DM, reports that 12% of overweight and obese children have IFG [74]. Several challenges arise when attempting to compare and interpret these prevalence rates since different methods (e.g., population based vs obesity clinic) were used to recruit the sample populations.

Rates of progression of IFG to overt T2DM appear to be lower in the pediatric obese population than in adults [75]. On the other hand, the transition from IGT to T2DM has been shown to be more rapid in children and adolescents than adults [76]. The prediabetic stages IGT and IFG may not necessarily coexist [66, 68, 74], which emphasizes that these two conditions are distinct metabolic abnormalities [33]. Therefore, subjects with both IFG and IGT have additive metabolic defects and are more likely to progress to overt T2DM [77].

Prediabetes in adolescents seems to be more common in males [68, 69], whereas T2DM is more common in females [75, 78]. The reasons for this are poorly understood.

Reduction of the degree of obesity in childhood and adolescence improves insulin sensitivity, and individuals who are obese in childhood and become nonobese in adulthood have the same risk for T2DM as subjects who were never obese [79]. Unfortunately, as the success rate of weight loss programs in childhood is modest, the future health of obese children is not looking bright. In year 2025 the worldwide prevalence in school-aged children of prediabetes is estimated to be 12 million and, of T2DM, 4 million [80].

Editor's Comments and Questions

1. Visceral adipose tissue is said to be more "metabolically active" than subcutaneous tissue with higher rates of lipolysis; this is said to explain the heightened fat deposition in the liver and skeletal muscle. Given the overall mass of the visceral fat depot, however, some investigators argue that the majority of circulating FFA are derived from non-visceral stores. In your opinion, why does visceral fat play such an important role in the pathogenesis of insulin resistance?
2. The relative amount of visceral fat in obese African American teenagers is significantly less than that in BMI-matched Caucasians. Yet the rates of type 2 diabetes in African American adolescents are at least two- to fourfold higher than those in Caucasians. How do you explain this apparent paradox?

Authors' Responses

1. As shown by Jensen, visceral fat contributes free fatty acids to the circulation in proportion to its overall size in comparison to total fat.[a] The difference is that these free fatty acids reach the liver via the portal and not via the systemic circulation. It is postulated that free fatty acids reach the liver in high concentrations and have a local effect in various signal transduction pathways. Moreover, visceral fat seems to have a different secretion profile of adipocytokines and of inflammatory cytokines in comparison to subcutaneous fat. The pro-inflammatory molecules secreted from visceral fat act locally in the liver as well as systemically.
2. Indeed, African American children tend to have less visceral fat in comparison to their Caucasian peers yet have a greater prevalence of diabetes. This paradox can be explained by the fact that the relation of insulin secretion and insulin sensitivity (i.e., the disposition index) is different between these groups. This translates to a greater insulin response in the face of the same degree of insulin sensitivity in African American lean and obese children in comparison to Caucasians. That means in the face of marked insulin resistance characteristic of severe obesity, African Americans must produce more insulin to maintain glucose tolerance. This greater beta cell demand predisposes them to earlier beta cell failure. In addition, dietary constituents may differ between these groups favoring a greater "glycemic" diet in African Americans.

Reference for Authors' Responses Section

(a) Jensen MD. Role of body fat distribution and the metabolic complications of obesity. J Clin Endocrinol Metab. 2008;93(11 Suppl 1):S57–63.

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Youth-Onset Type 2 Diabetes

24

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Pathophysiology of Youth-Onset T2D (YO-T2D)

Glucose homeostasis is maintained by the balance of insulin secretion from the β-cells of the pancreas and insulin sensitivity in skeletal muscle, adipose tissue, and liver [1]; when insulin sensitivity declines, insulin secretion must increase to maintain normoglycemia. In the presence of sufficient compensatory insulin secretion, glucose homeostasis remains normal despite increasing insulin resistance. This relationship between insulin sensitivity and secretion can be described by the disposition index (DI), which is the product of insulin sensitivity and β-cell function and will be constant irrespective of changes in insulin sensitivity, as long as there is sufficient compensation. However, when β-cells are no longer able to secrete sufficient insulin to compensate, DI falls and glucose homeostasis is lost. Prediabetes and type 2 diabetes (T2D) occur when there is a mismatch between insulin sensitivity and insulin secretion, such that there is progressive insulin deficiency relative to that required for metabolic stability (i.e. falling DI) [2, 3]; see also Chap. 23 on the pathophysiology of insulin resistance and glucose intolerance in childhood obesity.

Obese adolescents with YO-T2D have severe peripheral and hepatic insulin resistance along with substantially decreased insulin secretion, leading to an approximately 85% reduction in DI compared to nondiabetic matched obese youth. This results in elevated fasting hepatic glucose production and decreased peripheral glucose uptake [4–8]. Once YO-T2D is established, a strong relationship remains between β-cell function and degree of glycemic control [9].

In the transition from normal glucose tolerance to T2D, there is an intermediate state associated with an increased risk for the future development of T2D [10]. This state of prediabetes is defined by the American Diabetes Association (ADA) as

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either impaired fasting glucose (IFG) [fasting plasma glucose 100–125 mg/dL] or impaired glucose tolerance (IGT) [OGTT 2-h values 140–199 mg/dL], or hemoglobin A1(HbA1c) 5.7–6.4% [10] (Table 24.1). Studies in obese youth with varying degrees of glucose tolerance (normoglycemia, prediabetes, and YO-T2D) show that there is some decrease in insulin sensitivity as glucose rises [11]; however, it is predominately β-cell failure (i.e., failure to compensate for changes in sensitivity) that determines the development of dysglycemia in high-risk youth, as has been previously shown in adults. Most important, even prior to reaching the ADA-defined glycemic cut-points for prediabetes, obese youth have declining β-cell function relative to insulin sensitivity (i.e. falling DI) as fasting and stimulated glucose concentrations rise [4, 11–18]. Similarly, youth with HbA1c in the prediabetes range demonstrate impaired β-cell function compared with youth with normal HbA1c [19].

Table 24.1 American Diabetes Association Classification of prediabetes and diabetes

	Prediabetes	Diabetes
Fasting plasma glucose[a]	100–125 mg/dL (IFG)	≥126 mg/dL[b]
2-h plasma glucose in a 75-g OGTT	140–199 mg/dL (IGT)	≥200 mg/dL[b]
Random glucose		≥200 mg/dL with symptoms of hyperglycemia or hyperglycemic crisis
Hemoglobin A1c	5.7–6.4%	≥6.5%[b,c]

IFG impaired fasting glucose, *IGT* impaired glucose tolerance

[a]No caloric intake for at least 8 h

[b]In the absence of symptomatic hyperglycemia, results must be confirmed by repeat testing

[c]The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay

Data from [10]

YO-T2D typically occurs in adolescents at mid puberty; the mean age of diagnosis was 14 years in the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial and the SEARCH for diabetes in youth study [20, 21] and the condition is exceedingly rare prior to Tanner stage 2 (Fig. 24.1). This close association with puberty appears to reflect puberty-related insulin resistance; insulin sensitivity declines by 25–30% as youth transition from pre-puberty to puberty [22–24]. In the presence of normally functioning β-cells, puberty-related insulin resistance is compensated by increased insulin secretion/hyperinsulinemia and DI remains unchanged. However, in some youth β-cell compensation is inadequate due to impaired β-cell function and a

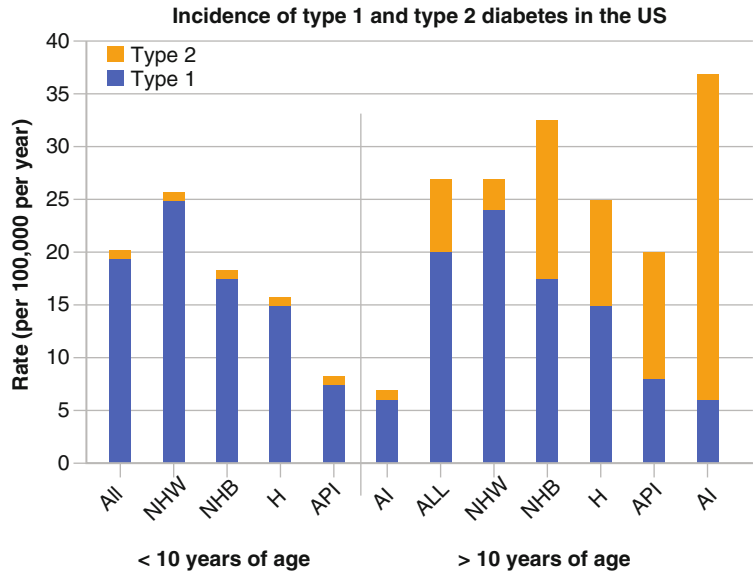

Fig. 24.1 Incidence of type 1 and type 2 diabetes in the US in the SEARCH for Diabetes in Youth Study (Data from [21])

progressive decline in DI ensues, ultimately resulting in dysglycemia [24, 25]. Thus puberty, like pregnancy, is a high-risk phase for diabetes development in susceptible individuals. Furthermore, reminiscent of gestational diabetes, diabetes onset during puberty may be reversible in some youth due to the dynamic nature of the underlying insulin resistance.

Abnormalities in other hormones, such as lack of suppression of glucagon with nutrient intake and decreased insulin secretory response to incretins (GLP-1, GIP), contribute to insulin resistance, impaired insulin secretion, and hyperglycemia in adults [3, 6, 26–29]. In a study of obese youth along the spectrum from normoglycemia through prediabetes to YO-T2D, OGTT-stimulated glucagon concentrations were highest in T2D and lowest in NGT, suggesting progressive hyperglucagonemia with worsening dysglycemia [3]. Similarly, glucagon concentrations were higher in obese prediabetic compared to nonobese youth before and after a hyperinsulinemic-euglycemic clamp [29]. Longitudinal observation of subjects in this study demonstrated that individuals who converted from normoglycemia to prediabetes increased their fasting glucagon concentrations. Finally, obese youth with T2D have reduced incretin effect without reduction in serum concentrations of GLP-1 or GIP [3]; see also Chap. 3 on gastrointestinal hormones.

The Course of Glucose Intolerance in Obese Children and Adolescents and the Progression to T2D

Unlike in adults, dysglycemia may be transient in youth even in the absence of intervention, likely related to the transient nature of pubertal insulin resistance. A study of 79 obese children and adolescents (mean age 13 years) with IGT showed that 66% reverted to normal glucose tolerance in 1 year [30]. Predictors of normalization of IGT included lower weight and 2-h OGTT glucose at baseline, and reduction of weight and later stage of puberty at follow-up, confirming the important role that puberty plays in adolescent dysglycemia. Children with persistent IGT had higher baseline HbA1c (6.0% vs. 5.4%). Similarly, the transient nature of IFG in adolescents was demonstrated in a population-based study of 2501 students (mean age 14.3 years, BMI 23.1 kg/m^2); 7% of participants had IFG on initial screen but less than 10% of these had persistent IFG on a second test [31].

In another study of 117 obese youth (mean age 12.7, BMI 35.5 kg/m^2), 33 (28%) participants had IGT at baseline. Eight participants (24%) with IGT developed T2D at f/u 20 months later, but a similar number reverted to normoglycemia. Participants who reverted to normoglycemia maintained BMI, whereas those who developed T2D did not [32]. Similarly, in a study of 20 patients with IGT at baseline, the 20% who progressed to T2D over 2 years had higher baseline HbA1c [13]. Likewise, an analysis of 218 youth showed that those with baseline HbA1c ≥5.7% had a greater chance of having diabetes or prediabetes at follow-up (mean 1.7 years), with an odds ratio of 5.7 [33]. Finally, a longitudinal study of 1604 American Indian youth aged 5–19 years reported that 5.7% developed T2D at follow-up (mean 5.5 years). Predictors of diabetes were 2-h glucose, BMI, and HbA1c at baseline [34].

In a recent investigation, we retrospectively evaluated the course of dysglycemia in a population of more than 10,000 overweight and obese youth. In this predominantly Hispanic White and Non-Hispanic Black cohort, 32.7% of obese and 23.6% of overweight youth had dysglycemia as assessed by HbA1c. Thus, prediabetes was very common in this high-risk population. Among those noted to have dysglycemia initially, the rate of progression to diabetes-range HbA1c during a relatively short follow-up depended on the initial HbA1c and was twice as high (8%) for adolescents with HbA1c of 6–6.4% as those with HbA1c of 5.7–5.9% (4%). Therefore, HbA1c values in the ADA-defined prediabetes range represent a continuum, with highest risks for progression to T2D among those with HbA1c ≥6.0%. The annualized progression rates of ~2.5% per year for those youth with low-range prediabetes and 5% per year for patients with high-range prediabetes are approximately 3.7 and 7 times, respectively, the baseline diabetes incidence in this population [35]. Nevertheless,

the majority of youth with initial HbA1c in the 6.5–7.9% range did not persist in having diabetes-range HbA1c, at least during the period of follow-up in this study. Thus, the progression rate to diabetes in our population of youth, while similar to other studies in youth, was much lower than has been reported in adults. Taken together, these studies indicate that only a minority of youth with dysglycemia will progress to T2D during adolescence. Higher initial HbA1c and BMI, and increasing BMI during follow-up, predict continued or progressive dysglycemia. However, whether individuals who have transient dysglycemia during adolescence will have increased risk for T2D in early adulthood, particularly if they remain obese, is unclear.

Factors Predicting the Development of T2D

There is a strong association of YO-T2D with family history of T2D in first- or second-degree relatives [20, 21] and minority race/ethnicity [36]. Even in the first decade of life impaired insulin sensitivity and reduced DI are present in otherwise healthy youth with a family history of T2D [37]. Adolescents with YO-T2D generally come from families in which the parents are also obese and tend to have insulin resistance or overt T2D themselves. In a published series, 60–90% of adolescents with YO-T2D had a family history of T2D in one first-degree relative [38]. Maternal effects are stronger than paternal ones [39]. The impact of parental influence reflects genetic components, maternal obesity during pregnancy, maternal T2D during pregnancy, and the shared lifestyle environment.

Adults who have one or both parents or a sibling with T2D have a heightened risk of developing T2D. Genome-wide association studies in adults have identified more than 100 genetic variants associated with T2D or glycemia, most related to β-cell function [40, 41]. However, only 10% of heritability of adult-onset T2D is accounted for by currently identified genetic variants [42–44]. In the Oji-Cree Native Canadians, a genetic variant of hepatic nuclear factor-1α (HNF1A) strongly predisposes to diabetes in children and adults [45]. Common variants in the transcription factor 7-like 2 (TCF7L2) gene have been shown to increase the odds for YO-T2D nearly 2-fold in non-Hispanic Black youth [46]. Polygenic susceptibility, combined with obesity and a sedentary lifestyle, likely contribute to the risk for T2D. In a study of obese youth, a genetic risk score based on five SNPs known to modulate insulin secretion was associated with progressive worsening of insulin secretion and increased risk for progression from normoglycemia to prediabetes and T2D [47].

There is also an increased risk of YO-T2D in youth who are offspring of pregnancies complicated by diabetes; see Chap. 13 by Dabelea and Sauder. Evidence from animal and human studies indicates that both maternal obesity and gestational diabetes mellitus (GDM) contribute to the risk for T2D in youth [48, 49]. Data from SEARCH demonstrated that exposure to maternal obesity was associated with a 2.8-fold risk for YO-T2D and that exposure to maternal diabetes in utero was associated with a 5.7-fold risk [50]; an estimated 47% of the risk for YO-T2D could be attributed to intrauterine exposures [50]. In TODAY, 33% of participants were born to a pregnancy complicated by preexisting diabetes or GDM [20]. Those exposed to maternal diabetes during pregnancy were diagnosed at younger ages, had lower DI at diagnosis, and increased likelihood of loss of glycemic control [51, 52]. In a study of Japanese youth, 68% reported at least one parent with diabetes. Diabetes was more frequent among mothers than fathers of probands ($P = 0.020$) [39]. Thus, fetal exposure to aberrant metabolism may have long-term deleterious effects.

The incidence and prevalence of YO-T2D is highest among minority youth [36, 53]. This is most likely multifactorial, comprising genetic, cultural, environmental, economic, and stress-related factors and metabolic characteristics. For example, there are significant racial differences in insulin sensitivity and secretion that may contribute to the risk of YO-T2D in non-Hispanic Black adolescents compared with their non-Hispanic White peers [9, 54–58].

The major modifiable risk factors for T2D include obesity, excess caloric intake, and physical inactivity leading to decreased energy expenditure. Together, these factors promote visceral and ectopic fat accumulation and insulin resistance. The most prominent clinical risk factor for YO-T2D appears to be early onset and severe obesity. In SEARCH, the prevalence of obesity among youth with YO-T2D was 79.4%; an additional 10.4% were overweight but not obese. The average body mass index (BMI) of patients with YO-T2D in published reports ranges from 35 to 39 kg/m^2. About one-third of individuals with YO-T2D have BMI greater than 40 kg/m^2 and 17% have BMI greater than 45 kg/m^2. Furthermore, abdominal obesity was present in 90% of females and 68% of males [59].

The association of birth weight with YO-T2D in children was studied among 259 Japanese children (9–17 years of age). Eleven percent of 195 patients had low birth weights (<2500 g) and 10% had high birth weights (> or =4000 g). The frequencies of low and high birth weights were higher among patients with YO-T2D than among a control group, producing a U-shaped distribution [60].

Girls are more susceptible to YO-T2D than boys, with an overall female-to-male ratio approximating 2.0; for American Indians, it is estimated to be as high as 4–6:1 [52]. The only exception is found in a study of 4,337,836 children and adolescents in China [61, 62], where the prevalence of YO-T2D in males was higher than in females. This may reflect the higher prevalence of obesity in Chinese boys. The reasons for the sex-specific susceptibility to YO-T2D are unknown; similar sex differences are not observed in adult-onset T2D [53].

T2D is more common among youth and adults with psychiatric disorders; see also Chap. 37 by Reeves and Sikich. The increased risk has been attributed both to unhealthy lifestyle behaviors and to treatment with antipsychotic medications. In a meta-analysis of T2D risk in antipsychotic-exposed youth, the unadjusted, cumulative risk and incidence of T2D, respectively, were 2.6-fold and 3.0-fold higher than in healthy controls and 2.1-fold and 1.8-fold higher than in psychiatric controls [63]. Cumulative T2D risk was significantly greater in youth treated with olanzapine than with other antipsychotics, in males than in females, and in those with longer duration of follow-up.

The prevalence of metabolic syndrome in YO-T2D at diagnosis in TODAY was 76%. Metabolic syndrome was more common in females (83%) than males (62%) and was similar among ethnic groups [59]. Nevertheless, there was no overlap between metabolic syndrome and impaired glucose tolerance (IGT) in an unselected group of adolescents who underwent OGTT in the National Health and Nutrition Evaluation Survey. Thus, the metabolic syndrome per se is not a reliable indicator of risk for T2D [64], likely because abnormalities in the components of metabolic syndrome are much more common than T2D in the obese adolescent population.

Chronic stress and/or depressed mood [65, 66] likely contribute to risk for T2D, though the biological mechanisms are unclear. In obese youth, depressive symptoms, particularly negative mood, anhedonia, and negative self-esteem, are associated with higher fasting and OGTT-stimulated glucose concentrations and lower DI [66]. Sleep-related disorders may also increase the risk of T2D [67–69], though it is unclear if improved sleep quality or treatment of obstructive sleep will decrease risk for T2D.

The Epidemiology of YO-T2D

Over the last three decades, a global rise occurred in the incidence of YO-T2D in children and adolescents [70]; see Chap. 1. The incidence and prevalence of YO-T2D in children and adolescents differ widely according to ethnicity, country, age, gender, and study methods [71]. However, several commonalties can be identified from the various epidemiological studies. The lowest prevalence of YO-T2D is in non-Hispanic White youth, whereas in the US among adolescents the highest prevalence is in American Indians, followed by non-Hispanic Black, Hispanic, and Asian Pacific Islander youth [36]. Similarly, high rates of YO-T2D have been documented among the First Nations people in Canada and among the Maori

children in New Zealand [2]. Immigrants are also disproportionately affected by YO-T2D. Data from Austria, the United Kingdom, and the Netherlands indicate that up to 40–50% of reported patients are from immigrant Asian and North-African groups (Pakistan, Turkey, Asian, India, Middle East, Tunisia, Morocco). The prevalence and incidence of YO-T2D also increase significantly with age. Accordingly, the highest incidence documented in the SEARCH for Diabetes in Youth study was among Navajo adolescents aged 15–19 years; rates were 38.2 and 32.4 per 100,000 in female and male subjects, respectively [72]. Among non-Hispanic Black youth aged 15–19 years, annual incidence was 20.1 in females and 13.8 in males [73]. In comparison, the incidence among non-Hispanic Whites was only 4.1 per 100,000. Similarly, in a population-based study conducted between 2001 and 2008 in youth aged 10–18 years in Australia [74], the incidence was almost seven times higher in Indigenous compared with non-Indigenous youth.

The SEARCH study estimated the prevalence of type 2 diabetes in US adolescents to be 2.8 cases per 1000 [8]. Prevalence varied greatly by ethnicity and was more common in ethnic minorities. Twenty-eight cases of T2D were identified in a community health population of 3940 largely minority obese youth (7 per 1000) [9]. A study of 468 severely obese children (mean age 12.5 years, BMI 34.4 kg/m^2) found 9% to have IGT and 2% T2D, while a European study of 102 obese high risk youth (mean age 12 years, BMI 33 kg/m^2) found that 36% had IGT and 6% had T2D [10].

Clinical Presentation

The clinical presentation of YO-T2D can range from mild asymptomatic hyperglycemia to severe ketoacidosis [75]. Approximately 20% of adolescents with T2D present with classical signs of polyuria, polydipsia, and weight loss, while the remaining present with a variety of complaints including infection (osteomyelitis, pharyngitis), obesity, dysuria, and enuresis. Twenty-five percent of girls with T2D have a vaginal monilial infection as their chief complaint at presentation. About one-third of YO-T2D patients are diagnosed by routine laboratory screening (usually urinalysis) as part of a school physical, rather than as a result of specific complaints [76, 77]. In the Pediatric Diabetes Consortium (PDC) T2D Clinic Registry, which enrolled T2D participants from eight American pediatric diabetes centers, 11% presented with diabetic ketoacidosis (DKA) and 2% with hyperglycemic hyperosmolar state (HHS) [77].

Diabetic Ketoacidosis

Although traditionally considered the hallmark of T1D, adolescents with YO-T2D, particularly non-Hispanic Black patients, may present with DKA. In one series, 25% of non-Hispanic Black adolescents presented with DKA and 42% with ketonuria [78]. In another study, about a third of Hispanic adolescents presented with ketonuria. Temporal changes in the prevalence of DKA at diagnosis of YO-T2D were estimated among 1425 youth. DKA prevalence significantly decreased from 11.7% in 2002–2003 to 5.7% in 2008–2010 [79]. Higher prevalence was associated with younger age at diagnosis, minority race/ethnicity, and male gender. Possible explanations for declining rates of DKA include improved access to care and enhanced early diagnosis in at-risk individuals.

Hyperglycemic Hyperosmolar State (HHS)

HHS is characterized by severe hyperglycemia (serum glucose level >600 mg/dL), hyperosmolality (effective serum osmolality >350 mOsm/kg), and absence of or minimal ketosis or acidosis [80]. HHS commonly occurs after prolonged and gradually increasing polyuria and polydipsia, resulting in profound dehydration. Males, non-Hispanic Blacks, and patients with developmental delay have been reported to be at highest risk. Patients with HHS are vulnerable to a number of serious complications, including severe

electrolyte imbalances, thrombosis, cerebral edema, malignant hyperthermia, rhabdomyolysis, renal failure, and pancreatitis [81]. The mortality rate of HHS in children is high: up to 33% of cases do not survive, with multiple organ failure being the most common cause of death. Although HHS is a distinct clinical entity from DKA, the two conditions may occur simultaneously. The Pediatric Endocrine Society has published recommendations for the management of HHS in pediatric patients [82].

Screening for T2D in Youth

Screening for YO-T2D is controversial. The ADA recommends screening of overweight or obese (BMI ≥85th and 95th percentile, respectively) youth who have at least two additional T2D risk factors (family history of T2D in first or second-degree relatives, high risk ethnicity, signs or conditions associated with insulin resistance, maternal history of diabetes or GDM during the child's gestation) starting at the age of 10 years or at the onset of puberty, if it occurs earlier. Re-screening of nondiabetic subjects is recommended every 3 years [10, 83]. However, the validity of these recommendations is in question. Unlike the identification of diabetes in youth with moderate or high level of clinical suspicion, screening refers to broad-based testing of a population or testing of individuals meeting certain general criteria. While case identification is necessary in the evaluation of individual patients, screening is only justifiable in certain circumstances.

First, the condition selected for screening should be sufficiently common to justify the cost of the testing. It is not clear that this is the case for glucose intolerance in most populations. For example, in the US, screening using fasting and post-challenge glucose in asymptomatic high-risk minority adolescents at the peak age of T2D diagnosis identified <1% with T2D [83]. If the disorder has low prevalence, most abnormal tests will be false positives and require additional testing, which must be included in the determination of cost. Whether there are specific populations (i.e. American Indians) in which there is sufficient prevalence of undiagnosed T2D among adolescents to justify testing remains unclear.

Second, the selected condition should have a prolonged latency period without symptoms, during which abnormalities in function can be detected and treatment can prevent morbidity. While prediabetes has been identified in at-risk youth, there is currently no evidence that interventions beyond that which would be delivered to any obese youth (weight loss, exercise, diet change) are efficacious. It is true that hypertension, dyslipidemia, and microalbuminuria have been identified in youth with prediabetes, but that is also true in obese youth without diabetes. Therefore, the prevalence of these disorders argues for monitoring and appropriate treatment of hypertension, dyslipidemia, and microalbuminuria in at-risk youth, not identification of dysglycemia.

Finally, there should be an available test that is sensitive and accurate with acceptable specificity. However, as discussed previously, none of the currently available tests (fasting glucose, random glucose, 2 h post-challenge glucose, HbA1c) are sufficiently sensitive and specific to function well given the low prevalence of T2D even in high-risk populations. Furthermore, there remains substantial uncertainty regarding the normal ranges and meaning of abnormal values in each of these measures of glycemia in adolescence.

Taken together, accumulating data indicate that generalized screening to identify diabetes in asymptomatic youth has a low yield and further research is required to determine the optimal strategy for testing, including the frequency of testing. Therefore, for now, the best evidence suggests that screening for T2D [84] outside of research settings is not cost effective in most populations and, in general, testing should be limited to the highest-risk individuals and those with symptoms consistent with hyperglycemia.

The laboratory diagnostic criteria for DM and prediabetes are the same for youth and adults, regardless of type of diabetes (Table 24.1) [10]. There are a few important points that should be considered. First, glucose criteria require measurement in a laboratory assay and not by point of care or home glucose monitor. Second, in

asymptomatic patients, the diagnosis of diabetes using any measures of glucose requires confirmation on a different day, either by the same or by an alternate test. Third, the HbA1c criteria assume measurement by a DCCT aligned laboratory HbA1c assay, not a point-of-care machine.

Several studies have questioned the validity of HbA1c as a screening tool in the pediatric population, and suggest that more definitive testing with the oral glucose tolerance test (OGTT) or fasting plasma glucose are more suitable diagnostic tests. In one study [84], an HbA1c of 6.5% had sensitivity of 75.0% (CI 30.1%–95.4%) and specificity of 99.9% (CI 99.5–100%) to diagnose diabetes. The authors examined the diagnosis of prediabetes based on FPG as well and noted a low sensitivity but a good specificity for HbA1c of 5.7%, and 6.0% (specificity 98.3% and 99.4%, respectively). Similarly, Nowicka and colleagues [33] compared HbA1c to OGTT in more than 1000 obese patients and concluded that HbA1c has relatively low sensitivity and specificity for diabetes when diabetes is defined by OGTT results; 9 of 893 patients with an HbA1c less than 5.7% were determined to have diabetes using OGTT criteria. Thus, about 1% of the patients in the sample of obese patients referred to a specialty center had diabetes on an OGTT that would have been "missed" if HbA1c less than 5.7% alone had been used to exclude further testing. However, a larger number of cases of prediabetes defined by OGTT were not identified using an HbA1c cutoff of 5.7%; 240 of the 347 (69%) cases of prediabetes (2 h glucose 140–199 mg%) in this high-risk population had HbA1c <5.7%. In another cross-sectional study of 254 overweight or obese adolescents addressing this question [85], there were 99 (39%) cases of prediabetes and 3 (1.2%) cases of diabetes using fasting plasma glucose and OGTT as gold standards. Test performance was assessed using receiver operating characteristic (ROC) curves and calculations of area under the ROC curve (AUC). HbA1c (AUC 0.54 [95% CI 0.47–0.61]) displayed poor discrimination for identifying children with dysglycemia identified on OGTT. Taken together, these studies suggest that use of HbA1c alone may lead to misdiagnosis or missed diagnosis in children when compared with OGTT or fasting plasma glucose (FPG).

However, studies that compare HbA1c to existing methods of diagnosing diabetes in pediatric populations are conceptually handicapped by the fact that the existing methods—FPG and OGTT—are themselves not validated in the pediatric population. A truly validated definition of diabetes in pediatric populations requires insight into the relationship of the proposed definitions to relevant aspects of medium and long-term health [86, 87]. That is, while the number of pediatric individuals diagnosed by HbA1c, FPG, and OGTT clearly differ, it is not yet clear which of these measures will be more closely related to long-term complications, the only true gold standard for defining glucose abnormalities. Assuming that OGTT or FPG are better than HbA1c for determining risk of long-term complications is unfounded; in adults, even though HbA1c, FPG, and OGTT are often discrepant in individuals, all three markers are shown to correlate very well with risk of vascular complications.

In a recent study, we examined whether HbA1c or the OGTT is a better predictor of free-living glycemia as measured by continuous glucose monitoring (CGM) in 119 overweight and obese adolescents not on medications for glucose management. Participants had measurements of HbA1c, fasting plasma glucose, and 2 h glucose (2-h glucose) during OGTT and then wore a blinded CGM for 72 h. The results showed that obese adolescents with prediabetes by either OGTT or HbA1c criteria had significantly higher average glucose, glucose area under the curve (AUC), peak glucose, and duration with glucose >120 and >140 mg/dL than youth with normal HbA1c or OGTT. HbA1c had a stronger correlation with CGM average glucose, AUC, and minimum glucose, while OGTT 2-h glucose had stronger correlation with CGM standard deviation, peak glucose, and duration with glucose >140 and >200 mg/dL. However, there were no overall differences in the strength comparisons between 2-h glucose and HbA1c correlations to CGM outcomes. Therefore, this study suggests

that HbA1c and 2-h glucose performed equally well at predicting free-living glycemia on CGM, supporting the argument that both are valid tests for dysglycemia screening [88]. Furthermore, this study shows that comparing one non-validated test to another and dismissing one of them on the basis of noncorrelation may misinterpret reality.

Rather, we need to recognize that the diagnostic criteria for OGTT and fasting glucose were previously accepted based on extrapolation from adult populations for use in pediatrics. Thus, it does not make sense to reject new recommendations for the use of HbA1c for diagnosis, because the results do not correlate well with un-validated tests. Instead, we need to consider practicality and the scope of the obesity problem. The demographics of T2D are skewed towards the disadvantaged and those least likely to seek frequent medical care. Counseling against tools that can be employed quickly by high-volume primary and urgent care providers at the time of a clinic visit may be counter-productive. That is, while HbA1c may "miss" a small number of cases of diabetes identified by OGTT, no cases are identified when neither HbA1c nor an OGTT is done. We have previously shown that the implementation of HbA1c screening was associated with increased diabetes screening among adolescents seen in a network of primary centers caring for an ethnically and economically diverse population. At the same time, the incidence of confirmed T2D remained unchanged, indicating that the use of HbA1c for screening is as successful as previous approaches to screening [35]. The ADA acknowledges the limitation in using HbA1c in pediatric screening because of lack of data on long-term retinopathy and health outcomes on which the HbA1c criteria were based in adults [89]. Nevertheless the organization continues to recommend its use for diagnosing T2D in youth.

Diagnosis of Diabetes Type in Youth

The textbook description of an individual with YO-T2D is an overweight and/or obese adolescent in mid-puberty, with overrepresentation of minority ethnicity/racial groups and females [20, 90, 91]. In particular, obesity is the hallmark of YO-T2D in North American youth. However, with the escalating rates of obesity in the general population, children with autoimmune T1D are also increasingly likely to be overweight/obese [92], with obesity rates the same as the background population, making the clinical distinction between T2D and obese T1D difficult. Where obesity is prevalent in the population, the likelihood that an obese adolescent with new-onset diabetes has T1D will usually greatly exceed the likelihood that he or she has YO-T2D. The distinction between youth with T2D and obese youth with autoimmune T1D is further blurred because youth with T2D often present with ketosis, including DKA [78]. This challenge was illustrated in the TODAY study, in which 1206 youth clinically diagnosed with T2D by pediatric endocrinologists were screened for circulating GAD-65 and IA2 antibodies. Of these, 118 (9.8%) were antibody positive: 5.9% were positive for a single antibody and 3.9% were positive for both antibodies [93]. Phenotypically, the screened youth who had positive autoantibodies had lower fasting C-peptide concentrations, fewer cardiometabolic risk factors (lower blood pressure and triglycerides), higher HbA1c, lower BMI, less acanthosis nigricans, and less frequent family history of diabetes mellitus. This group included less females and mostly non-Hispanic Whites [93]. In other words, the antibody-positive youth were more like individuals with T1D. In other studies, the reported rates of positive pancreatic autoantibodies in youth clinically diagnosed with T2D range from 10 to 75% [90, 93]. Among youth clinically diagnosed with T2D, those who are antibody-negative are more insulin resistant and less insulin deficient than antibody-positive youth [94]. Moreover, antibody-negative youth are more likely to have elevated systolic blood pressure, triglycerides, and liver transaminases, and less likely to have ketonuria at initial presentation [95]. As in the TODAY study, fasting and stimulated C-peptide were significantly lower in antibody-positive youth, though overlap is substantial.

Several studies have tried to identify simple measures to differentiate between the various types of diabetes. In one US study, data from non-Hispanic Black and Hispanic patients were obtained retrospectively to examine differences between T1D and T2D patients at onset and to determine whether or not those differences could be utilized to create a simple, rapid, and inexpensive test to aid in the diagnosis of diabetes type in these populations [96]. Distinction was possible with good sensitivity and specificity using only three easily assessed variables: age, gender, and BMI z-score. In non-Hispanic Black individuals, gender was the strongest predictor of T2D, while in Hispanic patients, BMI *z*-score was the strongest predictor. In another study using weight *z*-score, age, and race, the scoring system had 92% sensitivity, 82% specificity, and a positive predictive value for T1D of 98.6%. The authors suggested that measurement of diabetes-associated autoantibodies was necessary in only 15% of patients. However, only 4% of the patients in this study were clinically diagnosed with T2D, of whom 30% had positive antibodies, implying that less than 2% of all the patients in the study had T2D. This would substantially increase the specificity and sensitivity of the scoring system and makes the generalizability of this result to a population with higher rates of T2D unclear [97]. As noted above, youth clinically diagnosed with T2D who have positive antibodies have higher rates of ketosis, higher HbA1c and glucose levels, lower insulin and c-peptide concentrations, lower BMI, and fewer cardiometabolic risk factors at diagnosis. However, there is substantial overlap between the two groups, making it hard to use these criteria for determination of diabetes type. Other measures have been suggested as helpful in discrimination between T1D and T2D, including adiponectin, leptin [98], and IGFBP1 [99], but no measures have been clearly identified as reliably diagnostic.

As the pediatric population becomes generally more obese and more likely to be minority, more children presenting with T1D will be, like their peers, more obese and more likely to be non-Hispanic Black or Hispanic. In this new setting, it is no longer feasible to rely on phenotypic characteristics to determine diabetes type and formulate a treatment plan. The demographic shift in ethnicity and phenotype of adolescents in general creates challenges for the clinician confronting an obese adolescent with recent onset of diabetes and requires a rigorous approach to diagnosis and treatment decisions.

There are some features of presentation and phenotype that may be useful in developing a presumptive determination of T1D vs. T2D. Of these, degree of pubertal development is the most useful; individuals with YO-T2D are nearly always pubertal [20]. However, pubertal status is less useful once individuals enter puberty; T1D accounts for nearly half of all adolescents with new-onset diabetes, depending on race/ethnicity. Similarly, T1D is nearly always symptomatic at presentation, but patients with YO-T2D can also present with severe ketoacidosis [78, 100, 101]. The presence of acanthosis nigricans, hypertension, microalbuminuria, dyslipidemia, and steatohepatitis make T2D more likely, but may also be seen in obese adolescents with T1D. Thus, while phenotypic features may make one or the other diabetes type more likely, they are not sufficiently discriminating to be entirely reliable.

According to current ADA definitions [10], T1D is characterized by insulin deficiency as a result of cellular-mediated autoimmune destruction of the β-cells of the pancreas and can be diagnosed by demonstration of pancreatic autoimmunity and loss of insulin secretion; T2D is defined as diabetes accompanied by obesity, evidence of insulin resistance, relative insulin deficiency, and the absence of pancreatic autoimmunity. Therefore, rigorous typing of diabetes in an obese adolescent requires examination for the presence of autoimmunity. Thus, clarification of antibody status is a critical first step in the correct typing of an obese adolescent presenting with diabetes and will have an important influence on initial treatment decisions. At the same time, clinicians should also keep in mind that there are a small number of patients with unequivocal insulin deficiency who lack evidence of autoimmunity [10] or who have evidence of newly identified autoantibodies [102].

However, antibody results may take days to weeks to return and more rapid distinction between T1D and T2D is often clinically desirable. Since

T1D and T2D are also distinguished by differences in insulin secretion, it has been proposed that measurement of insulin secretion would be useful in differentiating the two entities [103]. However, in the setting of acute metabolic decompensation, insulin and c-peptide secretion may be transiently (and markedly) decreased. Thus, there may be significant overlap in fasting c-peptide between T1D and T2D at the time of acute presentation. C-peptide may be more useful in the asymptomatic patient or the patient who has clinically recovered. In this setting, a fasting c-peptide less than 0.85 ng/mL was reported to have 83% sensitivity in distinguishing T1D from T2D in children [99]. However, these T1D and T2D children also differed substantially in age and ethnicity, so it is unclear whether the biochemical measures truly outperformed demographics. Therefore, measurement of c-peptide may provide additional insight into the degree of insulin deficiency present, but must be interpreted carefully due to acute changes in secretion in the ill patient with either type of diabetes, as well as the normal concentrations of c-peptide that may be present initially in the obese insulin-resistant adolescent with T1D. Ultimately, only the finding of unambiguous insulin deficiency in the metabolically stable patient is reliably diagnostic.

Thus, in the obese adolescent presenting with new-onset diabetes or in whom no previous diabetes type has been determined, measurement of pancreatic autoantibodies, preferably in a laboratory using DK standardized antibody assays, will provide important guidance for treatment decisions. Measures of insulin secretion may contribute to correct typing, but require careful interpretation based on the clinical setting. A presumptive diagnosis of T1D or T2D may be made based on presenting features and phenotype, but firm conclusions regarding diabetes type should be withheld pending results of biochemical testing.

Treatment Outcomes

The evidence base for treatment of T2D in youth is small and, with the exception of a small placebo-controlled trial of metformin [104], is limited to what can be extrapolated from the TODAY clinical trial. TODAY studied 699 racially and ethnically diverse US youth, aged 10–17 years and with a BMI ≥85th percentile, who were diagnosed with T2D based on ADA criteria ≤2 years prior to screening. They were randomized to one of three treatment arms: metformin monotherapy (M), metformin + intensive lifestyle intervention (M + L), and metformin + rosiglitazone (M + R). The primary outcome was loss of glycemic control, defined as HbA1c ≥8% for at least 6 months or failure to be weaned from temporary insulin therapy started for metabolic decompensation [20]. At study completion, nearly half (45.6%) of study participants lost glycemic control, after a median treatment duration of 11.8, 12.0, and 10.8 months in the M, M + L, and M + R groups, respectively [105]. M + R, with a 38.6% rate of loss of glycemic control, was more successful than M alone (51.7%, $p = 0.006$). The rate of loss of glycemic control in the M + L group was intermediate (46.6%), but was not significantly different from the other two. Important racial/ethnic and sex differences were seen. Most notably, rosiglitazone was significantly more effective in girls but not in boys and metformin alone was particularly ineffective in non-Hispanic Blacks, with a 66.2% rate of loss of glycemic control. There were increases in insulin sensitivity and DI in the M + R group relative to the other two groups in the first 6 months of the study [106]. Thereafter, all three groups showed parallel declines in insulin secretion and DI. These findings were not due to differences in medication adherence, which remained high in TODAY in all groups.

The results of TODAY suggest much more rapid β-cell deterioration in a large portion of those with YO-T2D compared to adults. Although not exactly a head-to-head comparison to TODAY, the A Diabetes Outcome Progression Trial (ADOPT) study compared monotherapy of metformin, rosiglitazone, and glyburide in a large cohort [4, 127] of North American and European adults [107]. At the end of the 5-year study, 21%, 15%, and 31% reached glycemic failure in the metformin, rosiglitazone, and glyburide groups, respectively. While the overall decline in insulin sensitivity in TODAY

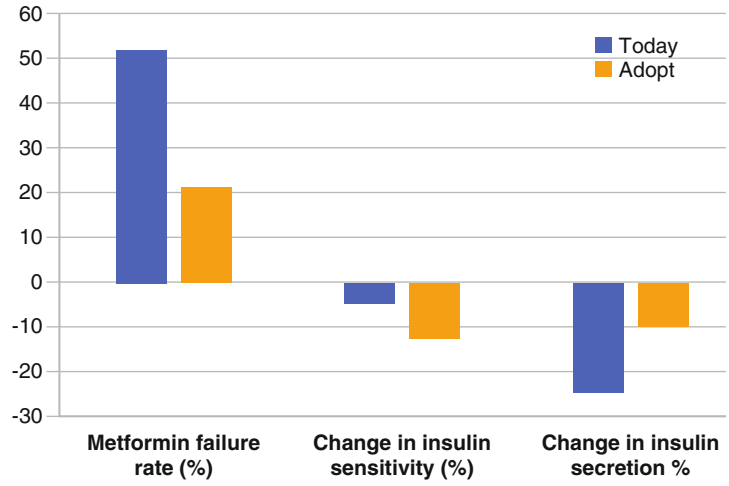

Fig. 24.2 Disease progression in youth with T2D compared to adults (Data from [105–107]

was slightly less than seen in ADOPT, the decline in β-cell function in TODAY exceeded that in ADOPT [108] (Fig. 24.2). While ADOPT lacked the ethnic and racial diversity of TODAY and used a different definition for loss of glycemic control (fasting plasma glucose ≥140 mg/dL), its cohort experienced significantly less glycemic failure despite having a much longer duration of diabetes at study entry and receiving only single drug therapy.

Post hoc analyses were done in TODAY to determine the best early predictors of loss of glycemic control [109]. TODAY participants who reached primary outcome prior to 48 months of treatment were compared with those who had not experienced glycemic failure by 48 months. Multivariate analyses determined that insulinogenic index, an estimate of insulin secretion, and an HbA1c cutoff of 6.3% were the only significant baseline predictors of glycemic failure. Thus, after a mean of ~3 months of metformin monotherapy, a HbA1c cutoff of 6.3%—significantly lower than the ADA recommended treatment target of <7.0%—predicts rapid β-cell deterioration. Moreover, while the cutoff was the same for girls as for the group as a whole, the cutoff for boys was considerably lower, at 5.6%. The positive likelihood ratio for the overall and sex and race/ethnicity cutoffs range from 2- to nearly 11-fold. These findings suggest that add-on therapy might be considered in YO-T2D at a much lower HbA1c than is recommended based on the adult literature. Yet, while the TODAY study provides robust data regarding treatment options, further studies are needed.

Approaches to Treatment

As noted, the evidence base for treatment of YO-T2D is limited. In addition to what is known from TODAY, pediatric T2D guidelines, which are largely based on expert opinion, have been published by the American Academy of Pediatrics (AAP) [110], the International Society for Pediatric and Adolescent Diabetes (ISPAD) [111], and the Canadian Diabetes Association [112]. New guidelines from the American Diabetes Association (ADA) are expected in 2017. The approach to treatment described here will be based on what is known from TODAY and supplemented with recommendations from published guidelines.

Treatment at Initial Diagnosis

YO-T2D is increasing in prevalence, particularly among certain racial and ethnic groups. Nevertheless, T1D is still more common than T2D among adolescents and significant overlap can occur in initial presentation: 10–15% of obese minority adolescents with new-onset diabetes will

have T1D and a significant proportion of youth with T2D will present with ketoacidosis. Therefore, careful consideration of the patient's risk for T2D and clinical presentation is necessary to formulate initial treatment plans.

For T2D patients who are acutely hyperglycemic (HbA1c ≥9–10%) or metabolically unstable (e.g. presenting with DKA or HHS), an intermediate or long-acting insulin should be administered once daily, at a dose approximating 20–40 units [111]. In many cases once daily insulin alone will successfully reestablish metabolic stability and improve glycemia without the addition of short-acting analogs. Short-acting analogs increase the need for monitoring and necessitate multiple daily injections, which ultimately interferes with adherence, and are unlikely to be needed to reach HbA1c targets in patients with T2D [113]. Thus, if possible, short-acting analogs may be avoided when there is a high suspicion for T2D. In the absence of renal compromise, metformin can be initiated once acidosis is resolved. If hyperglycemia is mild (HbA1c <9%) and suspicion for T2D is high based on family history, obesity, pubertal status, etc., metformin can often be employed without the addition of basal insulin.

The TODAY run-in phase provides important information on the initial response to diabetes treatment in youth with T2D. The goal of run-in was to provide standardized diabetes education, wean patients off basal insulin, and achieve an HbA1c <8.0% on metformin monotherapy. At screening, the 927 youth who entered run-in for TODAY were recently diagnosed with T2D (mean duration of 2 months) and had mean HbA1c of 6.9% (6.0% and 8.9%, 25th and 75th percentile, respectively); 38% were on insulin. At randomization, independent of initial insulin use and HbA1c, 90.9% of those who entered run-in were adequately controlled on metformin alone, with a mean HbA1c of 6.2% at the last run-in visit. These findings suggest that insulin can be rapidly and safely weaned (reducing by 30–50% of the daily dose per week over a period of 4–6 weeks) in the majority of youth with T2D at initial diagnosis [111].

Treatment Options After T2D Diagnosis Is Established

Lifestyle Intervention

Though management of diabetes with lifestyle alone is considered first-line in adults with mild hyperglycemia, lifestyle intervention in isolation is not well-studied in YO-T2D. In general, obese adolescents do not respond well to intensive lifestyle management with diet and exercise [114] and, at baseline, the TODAY study youth had more sedentary activity than obese NHANES participants. Because of lack of evidence for the effectiveness of lifestyle treatment alone and because of significant psychosocial barriers leading to poor follow-up rates in the face of high risk for rapid β-cell decline, initial treatment solely with diet and exercise is not recommended [110, 111]. Furthermore, the TODAY study found that intensive lifestyle intervention was not significantly better than metformin alone in maintaining glycemic control [105]. On the other hand, loss of as little as 7% of excess weight, no matter how attained, was associated with lower HbA1c, triglycerides, and LDL and with higher HDL and DI [115] in the TODAY trial. Therefore, despite the challenges of lifestyle intervention delivery, it should still be considered standard of care to provide youth the tools required to improve diet and physical activity.

Metformin

Metformin is the only approved oral agent for treatment of T2D in youth and is highly effective in achieving glycemic control early in the course of treatment [116, 117]. Furthermore, although 51.7% of youth in TODAY experienced glycemic failure on metformin alone, the other half were well controlled on metformin alone at the end of the trial. Metformin is also inexpensive and has an excellent safety profile. The most common adverse effect is gastrointestinal upset (abdominal pain, diarrhea, vomiting), but this can be limited by gradually titrating the dose up by 500 mg per week over a period of 3–4 weeks. Metformin is generally well tolerated in the pediatric population [116, 118, 119] and once-daily extended release preparations can mitigate gastrointestinal

effects and lessen adherence barriers. There is a risk for lactic acidosis in the face of renal compromise, so metformin should not be used in patients with renal failure. It should also be temporarily discontinued for procedures involving injection of radiologic contrast dye or anesthesia, but can be resumed after a few days once renal function is normal. In general, however, metformin is a safe, inexpensive, and effective treatment option in the majority of youth with T2D.

Insulin

Insulin is the standard add-on medication if diabetes is inadequately controlled (HbA1c ≥ 7.0%) on maximal tolerated doses of metformin. The efficacy of various insulin regimens has not been studied in YO-T2D; however, given the substantial psychosocial challenges faced by diabetic youth, a once-daily long-acting insulin analog is recommended to maximize adherence. Due to the substantial insulin resistance often present in YO-T2D, high doses of insulin may be required—often up to and in excess of 1–1.5 units per kg daily. Long-acting insulin is often started at a daily dose of 0.3 units/kg and titrated every 1–2 weeks based on home glucose monitoring. Side effects of insulin include weight gain and hypoglycemia, though severe hypoglycemia is very rare in youth with T2D [119]. Ongoing dietary counseling aimed at weight loss is critical when starting insulin therapy. Unfortunately, in TODAY, there was no significant improvement in HbA1c 1 year after starting insulin: HbA1c was 9.7 ± 1.7% at glycemic failure and 9.5 ± 2.0% 1 year later (Zeitler, ADA symposium, 2016). Insulin did result in some improvement in, but not correction of, dyslipidemia. These results suggest adherence barriers to insulin therapy in this population; alternative approaches to complement the effects of metformin need to be studied.

Other Agents

Sulfonylureas are associated with improvement of glycemic control in adults (1–2% decrease in HbA1c) and are often used as first-line agents or add-on to metformin in this population. However, the only pediatric trial evaluating sulfonylureas found it to be no more efficacious than metformin monotherapy, but with more weight gain and hypoglycemia [104]. Furthermore, there are concerns that sulfonylureas could accelerate the already rapid β-cell decline seen in YO-T2D [107].

There is increasing availability of new agents for treatment of T2D in adults, including thiazolidinediones (TZDs), incretin (GLP-1) analogs, DPP-4 inhibitors, and SGLT2 antagonists, as well as combination agents. These agents may be particularly useful for pediatric patients on metformin monotherapy for at least 3 months when the HbA1c rises above 6.3%, which appears to be the threshold for prediction of eventual β-cell failure and need for intensification of therapy. There are currently more than 15 clinical trials underway to study these newer agents in youth [53], but there are many challenges to completing these trials, including relatively low numbers of potential participants, psychosocial barriers to recruitment and retention, and stringent study entry criteria [108]. When and whether these trials will be completed and provide either drug approval or guidance on how to use these new agents is unclear.

As stated above, the addition of rosiglitazone to metformin appears to be more effective than metformin alone at preventing glycemic failure and was demonstrated to be safe in youth with T2D [105, 106, 119]. However, due to concerns about potential risks for heart failure and bone disease, rosiglitazone is rarely used in pediatrics. Pioglitazone, another TZD, is considered to be safer, although there is a possible associated risk for bladder cancer. At this time, there is, at a minimum, evidence that it may be considered as a second agent when the HbA1c is rising on metformin monotherapy, particularly in girls, who benefited more from rosiglitazone in TODAY [105]. An extensive discussion of the other agents is beyond the scope of this chapter, particularly given the lack of pediatric evidence. However, given the poor glycemic outcome of TODAY participants placed on insulin, treatment with newer agents should be considered after weighing the mechanism of action of each agent, cost and insurance coverage, potential adverse effects, mode and frequency of delivery, and impact on weight status.

Weight Loss/Bariatric Surgery

The ADA recommends weight loss for all diabetes patients with overweight/obesity. Beyond lifestyle intervention, it is advised to consider diabetes treatments that can be associated with weight loss (GLP-1 agonists, SGLT2 inhibitors), pharmacologic weight loss agents, and bariatric surgery in treatment of obesity. Like most diabetes agents, weight loss medications have not been well studied in pediatrics. Orlistat is approved for use in pediatrics, but is not well tolerated due to gastrointestinal side effects. In addition to the lack of pediatric evidence based and safety concerns, the most effective adult weight loss agents are limited in use due to cost. Phentermine is available in generic form, so is more accessible for the pediatric T2D population and is associated with ~8 kg weight loss; however, it is not approved for use in children or for long-term use in adults. Moreover, it is unclear how effective these weight loss agents will be in improving glycemic control in pediatrics.

Bariatric surgery is associated with improvement of β-cell function and diabetes control in obese adults with T2D. The ADA recommends bariatric surgery in adults if BMI ≥40 kg/m^2, regardless of glycemic control and with BMI 30–39.9 kg/m^2 if diabetes is inadequately controlled on medical therapy [10]. There is emerging evidence that bariatric surgery is also associated with significant weight loss and improvement of diabetes in youth with T2D. The largest pediatric longitudinal follow-up study, the Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study, prospectively enrolled 242 youth aged 13–19 years from five US centers who underwent roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy procedures [120]. These youth maintained a mean loss of 26% of initial body weight 3 years after the procedure, with similar weight loss in the RYBG and sleeve groups. Ninety-five percent of 29 youth with T2D had resolution of their diabetes. This is a higher remission rate than typically seen in adults (50–70%) [121, 122]. Moreover, evidence in adults and adolescents suggests that surgery performed early in the course of T2D is more likely to result in resolution of hyperglycemia. Risk for complications is high, particularly nutrient deficiencies, and 13% of youth in Teen-LABS required a repeat abdominal procedure [120]. However, given that youth with T2D are at high risk for irreversible β-cell damage, and that lifestyle intervention had no added benefit to metformin in the TODAY study, the benefits of surgery may outweigh its risks; see also Chap. 38 on Bariatric Surgery.

Short- and Long-Term Complications

Macrovascular Disease

Guidelines for cardiovascular risk reduction in high-risk pediatric patients, including those with T2D, were published in 2007 by the American Heart Association (AHA) and endorsed by the AAP [123]. It is important to note that cardiovascular events are exceedingly rare in pediatric T2D patients, so preventive guidelines cannot be based on hard outcomes. TODAY study participants showed worsening cardiovascular risk, including dyslipidemia, inflammation [124], and hypertension [125] as the study progressed. Moreover, noninvasive imaging of cardiovascular risk has shown evidence for endothelial dysfunction [126] and alteration in cardiac structure and function [127] in youth with T2D. Finally, long-term follow-up studies suggest that risk for cardiovascular mortality is higher for those with YO-T2D than T1D, despite shorter disease duration [128].

The AHA guidelines place T2D patients in the moderate risk category (Tier II) for cardiovascular disease, with tier-specific goals for treatment as follows: BMI ≤ 90 percentile for age/sex, BP ≤ 95 percentile for age/sex/height, low-density lipoprotein (LDL) cholesterol ≤130 mg/dL, and in adequate diabetes control (defined as fasting glucose ≤100 mg/dL and HbA1c <7%). Patients should be elevated to a high-risk category (Tier I) if there are two or more additional comorbidities, including elevated fasting LDL, smoking history, family history of early cardiovascular disease (male ≤55 years, female ≤65 years) in first degree relative, hypertension based on three measurements, obesity, or sedentary behavior; see also Chap. 25 on Dyslipidemia.

Treatment goals for Tier I include: BMI ≤ 85 percentile for age/sex, BP ≤ 90 percentile for age/sex/height, and LDL ≤100 mg/dL, with the same glycemic recommendations as for Tier II. Though lifestyle management is recommended as first-line management, TODAY has demonstrated that lifestyle intervention is challenging in youth with T2D, so pharmacological intervention should be considered early in youth ≥10 years of age. Hypertension should be managed with an ACE-inhibitor or angiotension receptor blocker—see Chap. 27 on Pathogenesis of Hypertension and Renal Disease in Obese Children—to a target of ≤90th percentile for age/sex/height or <130/80. Medical management for dyslipidemia is recommended for patients >10 years, which includes most youth with T2D. Statins are recommended for treatment of elevated LDL, with goals as described above. Finally, AHA guidelines recommend treatment of elevated fasting triglycerides >700 mg/dL with a fibrate or niacin; see Chap. 25.

Microvascular Disease

Retinopathy

Microvascular changes in the retina can lead to eye disease, including hemorrhages, microaneurysms, and abnormal vessel formation. In the TODAY study, the prevalence of retinopathy, as measured by dilated fundoscopy, was 13.7% after a mean diabetes duration of 2 years [129]. The SEARCH for Diabetes in Youth Study assessed retinopathy using retinal camera and found a prevalence of 42% in youth with T2D after a mean of 7.2 years after diagnosis [130]. Evidence from epidemiological studies, including SEARCH [128, 130], as well as TODAY [129], suggests that risk for retinopathy in youth with T2D is related to diabetes control. As stated above, it is recommended that all youth with T2D have regular dilated eye examinations.

Nephropathy

While overt renal disease due to T2D is relatively rare in pediatrics, nephropathy risk markers may be present in obese youth even prior to onset of diabetes [131, 132]; see Chap. 27 on Pathogenesis of Hypertension and Renal Disease in Obese Children. These include excess urinary albumin excretion (>30 mg albumin/g creatinine) or hyperfiltration (estimated glomerular filtration rate >120–150 mL/min/1.73 m^2) [133]. In the TODAY study microalbuminuria increased from 3 to 16.6% throughout the course of the study and correlated with HbA1c [125]. The ADA guidelines recommend treatment with an ACE inhibitor in patients with diabetes and hypertension if excess urinary albumin excretion is detected in at least 2 of 3 urine samples [134]. Medication dose should be titrated to achieve normal blood pressure.

Neuropathy

Neuropathy is defined as sensorimotor impairment or abnormal conduction in at least two peripheral nerves. It is typically identified using the Michigan Neuropathy Screening Instrument (MNSI). Prevalence rates for youth with T2D were estimated to be 21% after a mean diabetes duration of 7.6 years in the SEARCH cohort [135] and 26% after a mean diabetes duration of 1.3 years in a cohort of Australian youth [136]. In these studies, the prevalence was similar or higher in youth with T2D than those with T1D despite a shorter disease duration. In the Australian study, neuropathy was associated with glycemia [136] in youth with T2D, but not in those with T1D. In SEARCH there was no association between HbA1c and diabetic neuropathy; however, the T1D and T2D patients were combined for these analyses. There was some association between other cardiovascular risk factors and neuropathy in SEARCH.

The ISPAD guidelines for T2D in youth [111] recommend an initial foot examination (including inspection and assessment of pulses) followed by testing to evaluate protective (10-g monofilament) and vibratory (128 Hz tuning fork, pinprick sensation, ankle reflexes) functions. This examination should be repeated annually.

Sleep Disturbance

Disordered sleep, including disruption in normal circadian rhythms, shortened sleep duration, and obstructive sleep apnea (OSA) have all been

shown to be associated with weight gain, insulin resistance, and T2D (see Chap. 28 on Sleep-Disordered Breathing and Sleep Duration in Childhood Obesity); adult studies suggest that disordered sleep might be a causal factor in these relationships. Normal circadian rhythms change during adolescence and it is increasingly difficult for youth to adhere to their internal clocks due to environmental disruptors, such as school timing and exposure to artificial light at night from excess screen time. The lack of alignment between the adolescent circadian clock and environmental factors also has an impact on youth with T2D. Thus, it is important for sleep hygiene to be addressed during clinical visits. T2D is also associated with high risk for OSA, and data in adults suggest that improving OSA results in better HbA1c and insulin sensitivity. Pediatric data regarding beneficial glycemic effects of OSA treatment are limited and conflicting. Despite lack of evidence that treatment of OSA improves diabetes outcomes, there are other beneficial consequences of treatment of OSA, including improved school performance. Thus, sleep studies should be considered part of the routine assessment in any T2D patient with snoring or other signs/symptoms of increased risk for sleep apnea.

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) broadly ranges from fatty changes in the liver to hepatitis to fibrosis and cirrhosis. NAFLD is the most common cause of liver failure in adults and is increasingly common in youth [137]. Risk for NAFLD is increased by obesity, insulin resistance, male sex, and Hispanic ethnicity; see Chap. 26 on Fatty Liver Disease. T2D predisposes to progression from hepatic steatosis to steatohepatitis and fibrosis: in one multicenter cohort study, with high Hispanic representation, youth with T2D had a 3.0 times greater odds of having nonalcoholic steatohepatitis (NASH) [138]. Severity of NAFLD and fibrosis by histology was associated with T2D in youth undergoing bariatric surgery [139]. Diagnosis and severity of NAFLD can only be determined by biopsy and pharmacological interventions to improve NAFLD have not been highly successful [140, 141], leaving weight loss as the only known treatment. Screening with liver transaminases (expected ALT > AST predominance) is not sensitive and specific enough to detect disease and assess degree of severity, but is practical and should be performed annually along with other screening labs. If liver transaminases are persistently elevated, other causes of liver disease should be excluded.

Reproductive Function

Obesity and T2D are associated with reproductive dysfunction in adults. Men with T2D are at risk for hypogonadotropic hypogonadism [142] and, in women, there is a strong association with polycystic ovarian syndrome (PCOS) and risk for T2D [143]; see Chap. 20. At baseline in TODAY, i.e. after stabilization of glycemic control on metformin alone, there was a high prevalence (20%) of oligomenorrhea [117]. Irregular menses were associated with higher ALT, higher total testosterone, and lower estradiol, indicating that T2D and irregular menses are associated with altered sex steroid metabolism and increased risk for NAFLD. This association between NAFLD and reproductive dysfunction in girls is supported by a recent study of adolescents showing higher rates of NAFLD, as estimated by hepatic MRI, in girls with PCOS [144].

During the treatment phase of TODAY, there was a high frequency of pregnancy (10.2% of girls), suggesting that diabetes treatment may potentiate fertility in adolescent girls with T2D [145]. Pregnancy was associated with a disturbingly high rate of complications, including spontaneous abortion and stillbirths; among the 39 pregnancies carried to term, rates of prematurity (15.4%) and congenital anomalies (20.5%) were high. Interestingly, at the TODAY site at the University of Colorado, pregnancy rates declined significantly after a statewide program approved compensation for contraceptives for women; however, rates did not decline similarly at other sites, despite delivery of standardized pregnancy

education and encouragement for use of birth control at all sites. Of note, the Colorado program also significantly reduced teen pregnancy rates statewide [146]. This pregnancy rate reduction, along with the high risk for pregnancy complications in youth with T2D, strongly supports advocating for use of long-acting contraceptives in sexually active girls with T2D. Further research is needed about the overall impact of early-onset T2D on reproductive health.

Psychosocial Considerations

T2D is associated with an increased risk for depression in adults [147]. While both the SEARCH [148] and TODAY [149] studies found the rates of depressive symptoms to be comparable in youth with T2D and obese adolescents without diabetes, psychosocial stressors in youth with T2D, including low-socioeconomic status, low parental educational achievement, and single-parent households, are high [20]. Moreover, there was a high prevalence of self-reported disordered eating behaviors (25%) in SEARCH youth with T2D [150]; binge eating in TODAY was similarly high (26%) [151]. Clearly, further study of risks for depression and other psychological disorders in YO-T2D is needed. Because depression and eating disorders present barriers to diabetes care, ongoing surveillance for these disorders is recommended, with referral to mental health providers as needed.

Editor's Comments

1. You highlight the controversies regarding the rationale and methodology for screening for T2D in obese adolescents. Some thoughts:
   - First, in my opinion, screening should be designed to identify teenagers at high risk of progression to T2D as well as those with overt T2D. As you note, levels of HbA1c in the "prediabetic" range (5.7–6.4) represent a continuum; in high-risk populations (for example, obese ethnic minorities with a strong family history of T2D), HbA1c levels equal to or exceeding 6.0% are associated with rates of progression to T2D of nearly 5% *per year*. Given that the development of overt T2D increases exponentially the long-term risks of cardiovascular disease, renal disease, NASH, and liver cancer, the detection of levels of HbA1c in the "upper prediabetic" range necessitates intervention at an early stage. This may involve intensive lifestyle change and, in cases associated with persistent weight gain and/or lack of response in HbA1c, early institution of metformin therapy; see Chap. 35 on Pharmacotherapy. It should be noted that ADA guidelines[a] suggest that metformin be considered for treatment of adults with prediabetes but the drug has not been formally approved for this purpose in adolescents.
   - Second, you note the limitations of various screening procedures but emphasize, quite correctly in my opinion, the need for a realistic, simple, and practical approach to identifying obese adolescents with T2D (or a very high risk thereof). Fasting glucose levels are relatively insensitive and oral glucose tolerance tests are prohibitively expensive and highly impractical in the clinic setting, and you (and the ADA) recommend the use of HbA1c as a screening tool. The detection of HbA1c levels in the prediabetic range presents the challenge; a minority of such children will have (or will soon develop) T2D while others will remain prediabetic or normalize with time. We have argued[b] that T2D in children with "prediabetic" HbA1c can be identified at an early stage by home

glucose monitoring of fasting and 2 h post-prandial sugars. Home glucose levels approaching or exceeding the diabetic range can be confirmed with formal laboratory-based testing. In those with normal blood sugars, the availability of a home glucose monitor allows for future testing if weight gain persists or the child develops polyuria or polydipsia.

2. Many studies now provide evidence for self-reactive T cells and beta cell autoimmunity in some teenagers and adults with a phenotype and family history suggesting T2D.[c,d] Antibodies to glutamic acid decarboxylase (GAD65) are detected far more commonly in these patients than antibodies to other islet antigens such as insulin, IA-2, and zinc transporter 8. The pathogenesis of the autoimmunity is currently unclear; some postulate that inflammatory cytokines released by the adipose tissue of obese people may induce damage to beta cells and thereby expose cryptic beta cell antigens, which may trigger an autoimmune response. Relative to seronegative subjects with T2D, seropositive subjects with phenotypic T2D have lower C-peptide levels, lower insulin secretion, and less beta cell mass and are more likely to progress to insulin dependence within a relatively short time. Whether or not these seropositive patients have T1D or a variant of T2D, the care provider (and the patient) must be alert to the possibility of rapid deterioration of glycemic control while on metformin monotherapy.

References for Editor's Comments Section

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Pathogenesis and Management of Dyslipidemia in Obese Children

25

Brian W. McCrindle

Introduction and Summary

Lipid abnormalities are common in overweight and obese children and adolescents. The underlying pathogenesis is complex. It is most closely related to visceral adiposity, particularly ectopic liver fat, and driven by insulin resistance and high levels of circulating free fatty acids. This leads to hepatic overproduction of triglyceride-rich very-low-density lipoprotein (VLDL) particles. High levels of VLDL particles are reflected in a lipid profile as high triglycerides, which lead to changes in other lipid particles. Alterations in high-density lipoprotein (HDL) particles increase their clearance. There is an increase in the numbers of low-density lipoprotein particles (LDL) that are smaller and denser, making them more atherogenic. A high ratio of triglycerides:HDL-cholesterol together with a high non-HDL-cholesterol (total cholesterol minus HDL-cholesterol) level reliably identifies this underlying pattern from a standard lipid profile. This lipid pattern, often accompanied by clustering with other obesity-related cardiometabolic risk factors, greatly accelerates atherosclerosis, increasing the risk of premature cardiovascular disease. The evaluation of overweight and obese children and adolescents should include a fasting lipid profile and a detailed family history for risk factors and cardiovascular disease. Healthy lifestyle and weight management counseling are essential. Specific dietary recommendations focus on eliminating trans-fats, reducing refined carbohydrates and sugars, and increasing dietary fiber intake. The evidence supporting a role for fish oil supplementation is equivocal. Exercise and activity interventions, in addition to improving caloric balance, reducing adiposity, and increasing muscle mass, improve mitochondrial efficiency. This increases substrate clearance and improves insulin resistance. Few patients will meet criteria for starting lipid-lowering drug therapy unless there are important concomitant morbidities such as diabetes or hypertension or an underlying familial dyslipidemia. Identification and effective management of lipid abnormalities in this setting are important in order to prevent and reverse accelerated atherosclerosis.

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Pathophysiologic Aspects

Basic Lipid Metabolism

Lipoprotein Particles

In order for lipids to be transported in the hydrophilic environment of the circulation they must be packaged within particles that give them a

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hydrophilic surface. Lipoprotein particles consist of a hydrophobic core of triglycerides and cholesterol esters surrounded by a hydrophilic bilayer of phospholipids facing outward and free cholesterol facing inward. Embedded in the surface are various regulatory proteins responsible for receptor recognition, and metabolic functions. Lipoprotein particles are characterized by their internal density, which is lower if there is a greater proportion of triglycerides and higher if there is a greater proportion of cholesterol esters. They are also characterized by their size and by the types of proteins on their surface.

Transport and Metabolism of Exogenous Lipids

Dietary triglycerides (broken down to monoglycerides and free fatty acids [FFA]) and cholesterol (broken down to unesterified cholesterol and FFA) are absorbed from the intestinal lumen into the intestinal villae, where they are reassembled as triglycerides and cholesterol esters. These are then packaged as very large buoyant particles called chylomicrons, which enter the circulation via the lymphatic system. Chylomicrons are characterized primarily by the presence of apolipoproteins B48, CII, and E. As they circulate, the triglycerides are metabolized by peripheral lipoprotein lipase residing on endothelial cells. Triglycerides are removed and hydrolyzed to FFA and monoglycerol, with the FFA being taken up by muscle cells as an energy source and by adipocytes for storage. The particle shrinks in size and increases in density to become a chylomicron remnant particle, which is cleared by the liver through interaction with particle surface apolipoprotein E and hepatocyte low-density lipoprotein (LDL)-like receptors.

Transport and Metabolism of Endogenous Lipids

FFA taken up by the liver serve as substrates for triglyceride synthesis and stimulate production of apolipoprotein B. Endogenous synthesis of free cholesterol within hepatocytes from acetyl CoA is mediated by a rate-limiting enzyme, 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase. The triglycerides are incorporated with esterified cholesterol into lipoprotein particles called very-low-density lipoprotein (VLDL), which have surface apolipoproteins B100 and E. The triglycerides within circulating VLDL particles are metabolized by lipoprotein lipase and apolipoproteins C-II and C-III, causing the particle to become smaller and denser (higher proportion of cholesterol ester content). This generates an intermediate density lipoprotein (IDL). IDL can be cleared by the liver via hepatocyte LDL receptors by recognition of apolipoprotein E. Additionally, the triglyceride within IDL is further metabolized by lipoprotein lipase and hepatic lipase, causing the particle to become even smaller and denser, becoming a low-density lipoprotein (LDL) particle. LDL particles may deliver their cholesterol esters to macrophages and other tissues through a non-receptor mediated uptake, often after oxidation. LDL particles are cleared from the circulation by the liver through recognition of surface apolipoprotein B100 by the hepatocyte LDL receptor.

The pathway by which cholesterol is transported away from peripheral cells and tissues, such as macrophages and arterial wall foam cells, to the liver for uptake and excretion into bile is referred to as reverse cholesterol transport. Free cholesterol is removed from peripheral cells by the interaction of apolipoprotein A-I on the nascent HDL particle (a flattened disc-like structure) with the ATP-binding membrane cassette (ABC) transporter, ABCA1. The cholesterol in the nascent HDL is esterified by lecithin cholesterol acyl transferase (LCAT), with apolipoprotein A-I as a cofactor, becoming a more mature, larger, and more spherical HDL particle with cholesterol ester in its core. Less than half the time, this HDL particle can deliver its cholesterol ester to the liver through the interaction of apolipoprotein A-I with the HDL receptor (also called scavenger receptor type I). Similar to LDL particles, the cholesterol delivered to the liver may be excreted into bile either as cholesterol or by conversion of cholesterol into bile acids. Alternatively, HDL can transfer cholesterol esters to the apolipoprotein B-containing lipoproteins (VLDL, IDL, and LDL) in exchange for their triglyceride by the cholesterol ester transfer protein (CETP).

Pathogenesis of Obesity-Related Lipid Abnormalities: The Lipid Triad

The pathogenesis of the lipid abnormalities associated with obesity has been well described, although the relative contributions of various driving forces continue to be debated [1–5]. These lipid abnormalities, or *lipid triad*, are characterized by low levels of HDL-C, high triglycerides, and increased numbers of small dense LDL particles, which are more atherogenic. These abnormalities are also known as combined dyslipidemia [6]. The triad is accompanied by a host of other associated lipid abnormalities, which are listed in Table 25.1. The basic pathophysiology underlying the lipid triad is shown in Fig. 25.1.

Overproduction of VLDL

The features of the lipid triad are primarily explained by an increase in the number of VLDL particles, which have higher relative content of triglycerides [8]. Overproduction of VLDL is driven by the increased delivery of FFA to the liver, with subsequent increased synthesis of triglycerides as well as apolipoprotein B100. The excess FFA are derived from adipose tissue and from hydrolysis of triglycerides from VLDL which, under normal circumstances, are taken up by muscle as an energy source and by adipose tissue for storage. The insulin resistance associated with visceral adiposity, particularly ectopic fat deposition in the liver, appears to be a key factor [5]. Increased release of FFA from adipocytes occurs when visceral adipose triglyceride stores are increased and insulin resistance results in lack of inhibition of hormone-sensitive lipase. In extra-adipose tissues, the resistance to insulin impairs the activation of lipoprotein lipase, which favors the accumulation of VLDL particles. In addition, the metabolism of four specific foodstuffs—fructose, trans-fats, ethanol, and branched-chain amino acids—is not insulin regulated, and without mechanisms to manage excess substrate, there are further increases in FFA and triglycerides, exacerbating dyslipidemia [5]. A simple surrogate for insulin sensitivity, the *triglyceride glucose index (ln[fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2]),* has been shown to have an excellent correlation with results obtained from hyperinsulinemic-euglycemic clamp assessment in obese youth [9]. This measure may be a more specific marker of obesity-associated dyslipidemia.

Table 25.1 Lipid abnormalities associated with the cardiometabolic syndrome and obesity

Increased plasma free fatty acids
Postprandial lipemia
Increased plasma VLDL-C
Increased plasma remnant particles
Elevated non-HDL-C (calculated as total cholesterol minus HDL-C)
Elevated serum triglycerides
Increased numbers of small, dense LDL particles
Elevated apolipoprotein B
Reduced concentration of HDL-C
Elevated ratio of triglycerides to HDL-C
Presence of small, dense HDL particles
Decreased apolipoprotein A-1
Increased apolipoprotein C-III
Increased plasma free fatty acid levels
Postprandial lipemia

VLDL-C very-low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein, *apo* apolipoprotein

Low HDL and Increased Small, Dense LDL

A decrease in the number of HDL particles in obesity results from chemical transformation of the particle. Cholesterol ester transfer protein mediates an exchange of triglyceride in VLDL for cholesterol esters in HDL, resulting in a relative increase in HDL triglyceride. The triglyceride in HDL is then metabolized by the action of hepatic lipase, creating a smaller, denser particle, as well as free apolipoprotein A-I. This altered HDL particle is more readily cleared from plasma or excreted via the kidney, resulting in lower circulating HDL-C levels.

A similar process results in the production of small, dense LDL particles. Cholesterol ester transfer protein-mediated exchange of triglyceride from VLDL particles with cholesterol ester from LDL particles results in a triglyceride enriched LDL particle. As the triglycerides are metabolized by hepatic lipase, the particle becomes smaller and denser. The overproduction

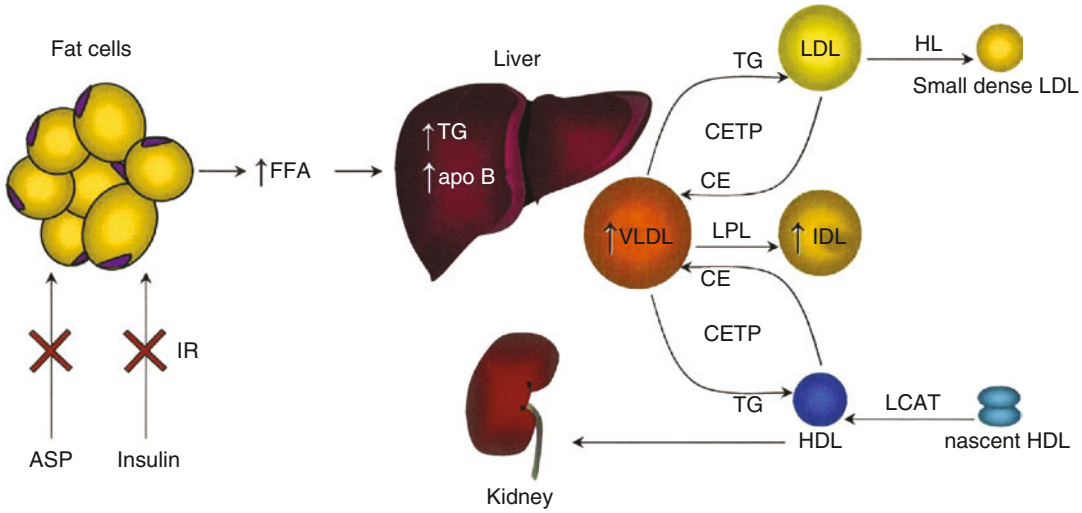

Fig. 25.1 Pathophysiology of the obesity-related lipid triad. Lack of sensitivity of the metabolically active adipocyte to the regulatory effects of insulin and acylation stimulating protein result in the increased release of circulating free fatty acids. These contribute excessive substrate for triglyceride production, stimulate production of apolipoprotein B in the liver, which are then incorporated into an increased production of triglyceride-enriched VLDL particles. Triglyceride from VLDL is exchanged with cholesterol esters from both LDL and HDL particles, a process mediated by cholesterol ester transfer protein. Hepatic lipase metabolizes the triglyceride content of both HDL and LDL, resulting in smaller, denser particles. For LDL, this results in a more atherogenic particle, and for HDL, this results in increased catabolism and clearance. *Apo* apolipoprotein, *ASP* acylation stimulating protein, *CE* cholesterol ester, *CETP* cholesterol ester transfer protein, *FFA* free fatty acids, *HDL* high-density lipoprotein, *HL* hepatic lipase, *IDL* intermediate-density lipoprotein, *IR* insulin resistance, *LCAT* lecithin cholesterol acyl transferase, *LDL* low-density lipoprotein, *TG* triglyceride, *VLDL* very-low-density lipoprotein (Used with permission of Elsevier from Mudd JO, Borlaug BA, Johnston PV, Kral BG, Rouf R, Blumenthal RS, Kwiterovich PO, Jr. Beyond low-density lipoprotein cholesterol: Defining the role of low-density lipoprotein heterogeneity in coronary artery disease. J Am Coll Cardiol. 2007;50:1735–1741)

of VLDL particles leads to increased numbers of LDL particles, which become small and dense. These particles are less readily cleared by LDL receptors, leading to a more prolonged circulation time and greater accumulation. Small, dense LDL particles are more atherogenic, in that they more easily enter and are retained within the arterial wall through greater binding to proteoglycans. They are also more susceptible to oxidation. These features induce foam cell formation and lead to endothelial dysfunction, which initiate and drive atherosclerosis.

Quantification of small, dense LDL particles requires specialized testing, specifically a nuclear magnetic resonance (NMR) lipid profile determination. However, this can be reliably estimated from a standard lipid profile with surrogate markers. In obese youth, both high non-HDL-C (≥120 mg/dL in white and ≥145 mg/dL in black youth) and high ratio of triglycerides to HDL-C (≥2.5 in white and ≥3 in black youth) have been shown to be associated with smaller LDL particle size and high numbers of small, dense LDL particles [10]. *Non-HDL-C* can be easily calculated from a lipid profile (total cholesterol minus HDL-C), is valid in a non-fasting state and can be measured at point of care. It is a measure of the cholesterol content of all atherogenic (apolipoprotein B containing) particles. Childhood levels have been shown to have a good correlation with adult levels, and it has now been recommended as a screening parameter for lipid abnormalities in childhood [11, 12]. In population studies, it is associated with cardiometabolic syndrome in youth [13]. Non-HDL-C is better than other lipid variables for predicting the presence of early atherosclerosis in both pathology studies and studies of ultrasound assessment of carotid intima media

thickness. It has emerged as a better independent predictor of cardiovascular disease events in adults than LDL-C [14].

High triglyceride to HDL-C ratio (TG/HDL), which reflects both high triglycerides and low HDL-C, is another lipid profile marker of increased numbers of small-dense LDL particles [10]. It is probably more valid measured in the fasting state. It is associated with insulin resistance, increased ectopic liver fat, and higher carotid intima media thickness in children [15]. A secondary analysis of data from the HEALTHY study (an intervention trial aimed to reduce type 2 diabetes) of 2384 grade 6 children showed that 2/3 of the variation in LDL particle number was explained by non-HDL-C, TG/HDL, and insulin resistance (HOMA-IR) [16].

FFA and Hyperglycemia

Incomplete oxidation of FFA can generate metabolites like diacylglycerol, ceramide, and reactive oxygen species that can increase hepatic gluconeogenesis, reduce insulin-dependent glucose uptake in skeletal muscle, and impair glucose-stimulated insulin secretion in pancreatic beta cells. In the aggregate, these effects contribute to hyperglycemia. Many of the effects of increased FFA are similar to the effects of decreased adiponectin, another feature of increased visceral adiposity. The effects of FFA and hypoadiponectinemia are potentiated by inflammatory cytokines produced in response to chronic inflammation in visceral adipose tissue; see Chap. 23.

Clinical Aspects

Assessment and Interpretation

When to Assess

Recommendations for the assessment of lipid abnormalities for children and adolescents differ depending on the context. For the *general population*, initial guidelines from an NIH Expert Panel published in 1992 advocated both a population-based and a high-risk individual-based strategy [17]. The population-based strategy did not recommend universal lipid assessment, but rather dietary goals to be applied to the general population. These aimed at shifting lipid levels for all children and adolescents. The *high-risk individual*-based strategy was a selective screening and tiered intervention algorithm aimed at identifying those children most at risk of having a clinically significant elevation of LDL. Decisions to screen were based on a family history of hypercholesterolemia and/or the presence of premature atherosclerotic cardiovascular disease events or morbidity in first-degree relatives. Children without available family history data could be screened if other risk factors were present, including obesity. Primary criticisms of these guidelines included (a) the lack of reliability of family history as an entry criterion for screening; (b) the limited focus on LDL; (c) the single lipid cut-points applied across age, sex, and ethnicity; and, eventually, (d) the failure to address the emerging epidemic of childhood obesity.

Some of these concerns led to modifications, including the addition of overweight and obesity as entry criteria for targeted screening, the confirmation of the safety but limited efficacy of fat and cholesterol dietary restrictions, and a clarification of the role of lipid-lowering drug therapy [18]. These modifications were adopted into 2008 guidelines from the American Academy of Pediatrics, with minor differences [19].

In 2011, guidelines were published from an Expert Panel convened by the National Heart, Lung and Blood Institute (http://www.nhlbi.nih.gov/guidelines/cvd_ped/) [11]. The panel was convened to develop best evidence-based guidelines for the detection, diagnosis, and management of cardiovascular risk factors and behaviors in children and adolescents [20]. The mandate was also to provide integrated guidelines, whereby the management of one risk factor might be influenced by the presence of other risk factors and conditions. In this way, recommendations for the management of lipid abnormalities (including abnormalities of triglycerides, HDL-C, and non-HDL-C) are more explicitly defined in relation to the presence and management of other risk factors and risk conditions, such as

obesity. While the Expert Panel provided definitions for a high-risk family history, risk factors, and risk conditions (Table 25.2), it is likely that this list will be refined and expanded (e.g., inclusion of childhood cancer survivors) with future revisions.

The Expert Panel guidelines departed from previous guidelines in that they recommended universal lipid screening (Table 25.3). This was largely based on studies that have shown that targeted screening based on high-risk family history misses a large proportion of patients with important elevations in LDL-C. For example, the Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) project screened 20,266 5th grade children, with assessment of family history and a fasting lipid profile [21]. A positive family history meriting targeted lipid screening was present for 71% of children, of which 8.3% were noted to have LDL-C ≥ 130 mg/dL; 1.2% had levels high enough to warrant lipid-

Table 25.2 High-risk family history, risk factors, and risk conditions that merit lipid screening and influence management

High-risk family history
• Parent, grandparent, aunt/uncle, or sibling with premature cardiovascular disease (age < 55 years in males; <65 years in females):
– Cardiovascular events: sudden cardiac death, myocardial infarction, onset of angina, stroke
– Objectively diagnosed cardiovascular disease
– Related procedures: coronary angioplasty or stent placement, coronary artery bypass grafting
• Parent with total cholesterol ≥240 mg/dL or known dyslipidemia
High-level risk factors
• Hypertension requiring drug therapy (blood pressure ≥ 99th percentile +5 mmHg)
• Current cigarette smoker
• BMI ≥97th percentile
High-risk conditions
• Kawasaki disease with current coronary artery aneurysms
• Post-orthotopic heart transplantation
• Chronic renal disease
• Diabetes mellitus
Moderate-level risk factors
• Hypertension not requiring drug therapy
• HDL-C < 40 mg/dL
• BMI ≥95th percentile but <97th percentile
Moderate-risk conditions
• Kawasaki disease with regressed coronary artery aneurysms
• Nephrotic syndrome
• HIV infection
• Chronic inflammatory disease (SLE, JRA)

BMI body mass index, *dL* deciliter (mg), *JRA* juvenile rheumatic arthritis (mg), *SLE* systemic lupus erythematosus

Table 25.3 Expert panel lipid screening and assessment recommendations

Age	Screening strategy	Screening/assessment method
Birth to 2 years	No lipid screening	
2–8 years	No routine lipid screening	
	Targeted lipid screening[a] (includes BMI ≥95th percentile)	Average of two fasting lipid profiles
9–11 years	Universal lipid screening	Non-fasting lipid assessment
		Measure total and HDL-C
		Calculate non-HDL-C
		If non-HDL-C ≥ 145 mg/dL or HDL-C < 40 mg/dL, obtain two fasting lipid profiles, average
		Fasting lipid assessment
		If LDL-C ≥ 130 mg/dL or
		Non-HDL-C ≥ 145 mg/dL or
		HDL-C < 40 mg/dL or triglycerides ≥100 mg/dL if <10 years or triglycerides ≥130 mg/dL if ≥10 years, repeat fasting assessment and average
12–16 years	No routine lipid screening	
	Targeted lipid screening[a] (includes BMI ≥85th percentile)	Average of two fasting lipid profiles

Table 25.3 (continued)

Age	Screening strategy	Screening/assessment method
17–21 years	Universal lipid screening	Non-fasting lipid assessment
		Measure total and HDL-C
		Calculate non-HDL-C
		If non-HDL-C ≥ 145 mg/dL (≥190 mg/dL if >19 year) or HDL-C < 40 mg/dL, obtain two fasting lipid profiles and average
		Fasting lipid assessment
		If LDL-C ≥ 130 mg/dL or
		Non-HDL-C ≥ 145 mg/dL (≥190 mg/dL if >19 year) or HDL-C < 40 mg/dL or triglycerides ≥150 mg/dL, repeat fasting assessment and average

[a]For children and adolescents with a high-risk family history, risk factors, or risk conditions as outlined in Table 25.2

Note: For repeat fasting assessment the interval between assessments should be 2 weeks to 3 months

lowering drug therapy. Elevated LDL-C was noted for 9.5% of those without a positive family history, with 1.7% recommended for medication. Thus, a majority met criteria for targeted screening, which had poor sensitivity and specificity for identifying both moderate and severe elevations in LDL-C. It has also been shown that universal screening can identify high-risk families [22].

The concept of universal screening of children with reverse cascade screening of parents has also been tested. A study of universal screening of lipids, including selected genetic testing for familial hypercholesterolemia, of 10,095 infants and toddlers at the time of immunizations, identified affected parents [23, 24]. However, the cost-effectiveness of universal screening has yet to be proven, which has prevented its wide adoption [25].

Targeted screening would also be expected to miss an important proportion of children with other forms of dyslipidemia. The Expert Panel guidelines included adiposity as a risk factor justifying targeted screening; lipid screening was recommended for children ages 2–8 years with a BMI ≥95th percentile, and for adolescents ages 12–16 years with a BMI ≥85th percentile. While not included in the guidelines, there may be a role for waist circumference as an additional measure of adiposity indicating a higher likelihood of dyslipidemia [26, 27].

What to Assess

The Expert Panel recommends targeted screening of overweight and obese children and adolescents with two fasting lipid profiles. A fasting lipid profile includes assessment in plasma of total cholesterol, triglycerides, and HDL-C, with calculation of LDL-C using the *Friedewald formula* (LDL-C = total cholesterol – HDL-C – [triglycerides/5]; measurements in mg/dL) [28]. For children with triglyceride levels ≥400 mg/dL, the Friedewald calculation of LDL-C is invalid. While direct methods of LDL-C measurement are more accurate than the Friedewald calculation, they remain primarily a specialized tool [29].

The requirement for fasting (8–12 h) assessment has been called into question. A consensus statement from Europe concluded that the differences between fasting and non-fasting (1–6 h after a meal) lipid assessment were not clinically significant [30]. Non-fasting lipid profiles were recommended for routine assessment. Similar findings have been reported for young children, although a significant impact on glucose (small), insulin, and HOMA-IR was noted for time since last meal [31]. They noted that impact of fasting for HDL-C and triglycerides differed by weight status. Thus, for lipid assessment for overweight and obese youth, fasting assessment may be prudent, since triglyceride:HDL-C ratio, non-HDL-C, and triglyceride glucose index are markers of combined dyslipidemia and increased numbers of small, dense LDL particles [9, 10].

Standard lipid profile assessment measures the cholesterol content attributable to a class of lipoprotein particles, but do not assess the number or characteristics of these particles. However, non-HDL-C and triglyceride/HDL-C have been

shown to identify overweight and obese youth with high numbers of small, dense LDL particles as measured on NMR lipid assessment [10]. Further, a higher LDL particle number relative to LDL cholesterol level has been shown to be common in obese middle school children [16]. The addition of measurement of *apolipoprotein B* has been advocated as a measure of the number of atherogenic particles and a more accurate assessment of LDL-C, as well as an additional, indirect indicator of increased numbers of small, dense LDL particles [7, 32]. Likewise, assessment of *apolipoprotein AI* levels may be an additional indirect indicator of the number and size of HDL particles.

A number of specialized methods have been developed to more directly determine lipoprotein particle size and concentration, particularly NMR lipid assessment, but they are not widely available or routinely used at present [33–35]. Distributions of values, demographic correlates, and relationship to measures of adiposity have been shown in children in the Bogalusa Heart Study, with a suggestion that they may provide a better understanding of the relationship between early lipid abnormalities and cardiovascular risk [36, 37]. They have been shown in adults to provide a more accurate assessment of risk of cardiovascular disease and may identify patients with "normal" levels of LDL-C who may benefit from LDL-lowering therapy [38]. In children, variations in subclasses of VLDL have been noted in relation to measures of adiposity, with significant racial differences [39].

In summary, a standard fasting lipid profile and glucose assessment may give a sufficiently accurate evaluation of obesity-related lipid abnormalities. It should include calculation of non-HDL-C, triglyceride:HDL-C ratio, and triglyceride glucose index. NMR lipid profile assessment and determination of apolipoprotein levels might be reserved for more specialized testing, but are probably not necessary for routing assessment.

Definition of Abnormal

Normal lipid values are based on representative population-based standardized assessments of fasting lipid profiles. Definitions of abnormality for children and adolescents are based on the magnitude of deviation from the central value of the distribution, usually based on percentile cut-points. Table 25.4 gives a classification scheme based roughly on LDL-C, non-HDL-C [40] and triglyceride values above the 75th percentile (borderline) and 95th percentile (abnormal), or HDL-C levels below the 10th percentile.

Table 25.4 Classification of *fasting* plasma lipid concentrations (mg/dL[a]) for children and adolescents

Laboratory measure	Acceptable	Borderline	Abnormal
Total cholesterol	<170	170–199	≥200
LDL-C	<110	110–129	≥130
HDL-C	>45	40–45	<40
Triglycerides			
<10 years of age	<75	75–99	≥100
10–19 years of age	<90	90–129	≥130
Non-HDL-C[b]	<120	120–144	≥145

[a]For conversion to mmol/L, divide cholesterol measures by 38.6, divide triglyceride measure by 88.6
[b]From the Bogalusa Heart Study [40]

The normal values derive from the Lipid Research Clinics (LRC) Program Prevalence Study, which included a cross-sectional assessment of predominately white children and adolescents, and are the cut-points used in the original and current NIH Expert Panel recommendations [41–44]. This study determined age and gender-related maturational associations with lipid values. These cut-points have been used as the basis for classifying dyslipidemia in both the Expert Panel and AAP lipid guidelines for children and adolescents. They do not, however, take into account maturational changes with age, or differences with respect to sex and race.

The National Health and Nutrition Examination Survey (NHANES) is a contemporary series of cross-sectional assessments based on a sampling strategy within the general population and, thus, has greater validity than the Lipid Research Clinics Program Prevalence Study. NHANES

data have been used to determine the distribution of lipid values and associations with age, sex and race, and trends over time. Age and sex-specific normal values are linked to the cut-points for young adults used for the Adult Treatment Panel (ATP) III recommendations, which are calibrated to risk of cardiovascular disease in adults [45, 46].

For males ages 12–20 years, borderline high and high cut-points correspond to the 86th and 97th percentiles, respectively, for total cholesterol, the 86th and 98th percentiles for LDL-C, and the 89th and 95th percentiles for triglycerides, with low HDL-C defined as below the 26th percentile. For females ages 12–20 years, borderline high and high cut-points correspond to the 78th and 94th percentiles, respectively, for total cholesterol, the 83th and 95th percentiles for LDL-C, and the 89th and 95th percentiles for triglycerides, with low HDL-C defined as below the 26th percentile. Growth curves are provided with these cut-points modeled over the age spectrum. Comparison of the lipid classification schemes from the LRC and NHANES as applied to several population-based cohort study datasets has shown that the age and sex specific cut-points from NHANES are more predictive of low HDL-C levels in adults but less predictive of high total cholesterol, LDL-C and triglyceride levels [47]. It might be argued that for clinical purposes, the simpler cut-points from the LRC be preferred over the more complex cut-points from NHANES, especially given that exact specification of future risk of atherosclerotic cardiovascular disease remains unclear.

The roles of race and sex in relation to lipid values have been addressed in several studies. After puberty, young white males have been shown to have significant adverse changes in total cholesterol, LDL-C, VLDL-C, and HDL-C levels, with less significant changes for white and black females and black males [48]. Race differences in triglycerides and VLDL-C between blacks and whites have been noted, with higher VLDL-C and triglyceride levels in whites and slightly higher HDL-C in blacks [39, 49]. White males have lower HDL-C levels than black males and white females. Although differences in lipid values are evident relevant to race and sex, the magnitude of these differences is felt to be sufficiently small such that their specification regarding cut-points would add complexity without significantly enhancing relevance.

Normal values for triglyceride:HDL-C ratio have not been reported from large population based datasets. Burns and colleagues reported that in a cohort of 141 overweight adolescents, a ratio ≥ 3 was associated with a higher concentration of small, dense LDL particles and smaller LDL particle size [10]. Further, a cut-point of 3 in white and 2.5 in black youth had the best discrimination. [Note: calculation of this ratio using mmol/L units is not equivalent, due to different conversion factors for triglycerides and HDL-C.]

Lipid Abnormalities and Atherosclerosis (See Also Chap. 30)

The relationship of lipid abnormalities identified in youth with the subsequent development of atherosclerotic cardiovascular disease in adulthood is an important issue; direct evidence, which is emerging, would provide the necessary imperative to identify and treat lipid abnormalities in youth. A growing body of indirect evidence is available, derived from autopsy studies and from studies of noninvasive markers of early atherosclerosis.

The Bogalusa Heart Study performed serial cross-sectional assessments in a biracial community, and has reported normal lipid values and important correlates, including associations with the degree of atherosclerotic arterial involvement both in pathologic studies and studies using noninvasive vascular markers [50–53]. This study and other similar studies were also instrumental in confirming tracking of lipid abnormalities from childhood and adolescence into adulthood, particularly when measures of adiposity are taken into account [54–56]. Autopsy studies from this cohort have shown strong correlations between lipid measures and early atherosclerosis of the aorta and coronary arteries, with an exponential increase associated with greater number of risk factors, such as would occur with cardiometabolic syndrome [53, 57].

The Pathobiological Determinant of Atherosclerosis in Youth (PDAY) Study determined risk factors at the time of autopsy as well as the degree of vascular involvement, and showed similar correlations between lipid variables, early atherosclerosis and adiposity.

While autopsy studies have provided important evidence, noninvasive markers of early atherosclerosis have proven invaluable in determining cross-sectional associations and long-term prediction. A risk score from the PDAY study has been shown to predict the presence of coronary artery and abdominal aortic calcium, a marker of atherosclerosis, 25 years later in middle age [58]. Carotid intima-media thickness (CIMT) was assessed in 486 adults ages 25–37 years who were serially assessed during youth in the Bogalusa Heart Study [52]. Increased CIMT was independently related to childhood measures of higher LDL-C and BMI, adulthood measures of higher LDL-C and systolic blood pressure and lower HDL-C, and long-term cumulative burden of LDL-C and HDL-C. The relationships with LDL-C and CIMT appeared to be slightly nonlinear, with some acceleration in the upper quartile of LDL-C values. Metabolic syndrome definitions and scores measured in youth have been shown to predict type 2 diabetes and high CIMT in adulthood in the Cardiovascular Risk in Young Finns cohort study [59, 60]. Higher CIMT has been more specifically associated with low HDL-C [61]. Arterial stiffness, another measure of early atherosclerosis, has been shown to be associated with increased triglyceride:HDL-C ratio [62] and small HDL particle size [63] in obese youth. From these studies, it is apparent that maintaining low cardiovascular risk factors beginning in youth may be necessary to prevent adult cardiovascular disease [64]. These observations provide an important imperative for prevention, detection, and treatment of lipid abnormalities and associated metabolic comorbidities in overweight and obese youth. These noninvasive measures will prove to be compelling outcome measures for intervention studies targeting dyslipidemia in obese youth.

Lipid Abnormalities as Components of Definitions of the Metabolic Syndrome (See Also Chap. 29)

The metabolic syndrome remains a controversial concept when applied to children and adolescents, and it is unclear what additional information is derived from its application to a population experiencing changes in growth and development [65]. The dichotomous categorization of what, in reality, is a continuous marker of risk may oversimplify a complex pathophysiologic process that remains incompletely understood [5]. Some have argued that there is currently insufficient evidence to define the metabolic syndrome in children and adolescents [66, 67]. The relationship of the metabolic syndrome to measures of adiposity appears to be nonlinear, with the risk of metabolic syndrome increasing dramatically when measures of anthropometry exceed the 85–95th percentile [68]. A study using NHANES data showed prevalence of metabolic syndrome in 12–19-year-old adolescents to be 0.1% for those with BMI <85th percentile, 6.8% for those with BMI at the 85th to <95th percentiles, and 28.7% for those with BMI >95th percentile [69].

Yet, in terms of lipid abnormalities, the use of the concept of metabolic syndrome may raise the imperative to evaluate and treat high-risk patients more aggressively. Therapies can be aimed at altering the underlying pathophysiologic millieu generating the metabolic syndrome, which is the main goal of lifestyle interventions aimed at reducing adiposity [5]. Alternatively, therapies can be aimed at the individual risk factor components, including lipid abnormalities, but in an integrated manner [11].

Despite controversy regarding the conceptualization of the metabolic syndrome in youth, many definitions have been proposed, leading to differing estimates of prevalence [70–72]. Most of the definitions are based on extrapolations of definitions developed for adults, and differ in the com-

Table 25.5 Fasting lipid abnormalities contributing to definitions of metabolic syndrome in children

	HDL-C	Triglycerides
Cook (2003) [69]	≤40 mg/dL	≥110 mg/dL
De Ferranti (2004) [74]	<50 mg/dL in girls	
	<45 mg/dL in boys	≥100 mg/dL
Weiss (2004) [75]	<5th percentile	>95th percentile
IDF (2007) [76]		
6 to <10 years	No cut-point	No cut-point
10–16 years[a]	≤40 mg/dL	≥150 mg/dL
≥17 years[a]	≤50 mg/dL in girls	≥150 mg/dL
	≤40 mg/dL in boys	≥150 mg/dL

[a]Children and adolescents aged 10 years and older who are taking lipid-lowering drugs are to be considered as having met the lipid abnormality criteria
dL deciliter, *HDL-C* high-density lipoprotein cholesterol, *IDF* International Diabetes Federation, *mg* milligrams

ponents included and their cut-points for defining abnormalities (Table 25.5) [69, 71, 73–76].

Definitions include values from a fasting lipid profile, predominately HDL-C and triglyceride levels; patients taking lipid-lowering drugs are considered to have met the lipid abnormality criteria. The definition proposed by the International Diabetes Federation seems to be gaining popularity, mainly because it represents a compromise between single cut-points across age and gender groups and strict use of percentile cut-points.

Lipid abnormalities remain one of the most prevalent components in the setting of metabolic syndrome. From NHANES data, triglyceride levels >110 mg/dL were noted in 23.4% of the general population of 12–19-year-old adolescents, with a prevalence of 17.6% for those with BMI <85th percentile, 33.5% for those at the 85th to <95th percentile, and 51.8% for those with BMI >95th percentile [69]. Likewise, HDL-C levels ≤40 mg/dL were noted in 23.3%, with a prevalence of 17.7% for those with BMI <85th percentile, 32.3% for those at the 85th to <95th percentile, and 50.0% for those with BMI >95th percentile. In a case-control study of children and adolescents, fasting triglyceride levels were strongly associated with higher degrees of adiposity; however, no further differences were noted between moderately versus severely obese subjects (Fig. 25.2) [75]. A gradient of lower HDL-C was also noted, with a less marked gradient for higher LDL-C. There was a nonlinear association between lipid values and insulin resistance. Of note, the 95th percentile of the LDL-C distribution for each adiposity category did not exceed 110 mg/dL; thus, it would be unlikely for even a severely obese child or adolescent to meet criteria for starting a lipid-lowering drug based on LDL-C criteria alone.

Consideration has been given as to the inclusion of other lipid abnormalities in the definition of metabolic syndrome. Non-HDL-C and triglyceride:HDL-C ratio are easily calculated from a standard fasting lipid profile [77]. Non-HDL-C has been shown to be a marker for diabetes risk in adolescents, a relationship that is strengthened in the presence of obesity [78]. Further study using NHANES data suggests that non-HDL-C is significantly related to the number of components of existing definitions of the metabolic syndrome present in adolescents [79]. Non-

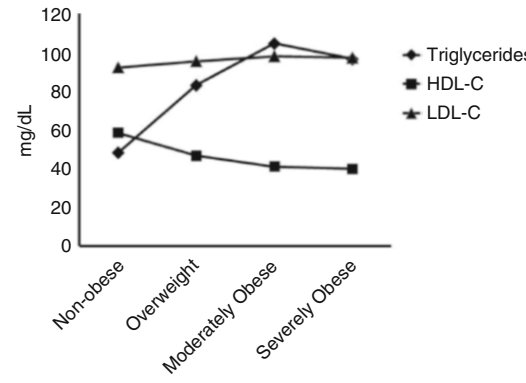

Fig. 25.2 Mean fasting lipid value related to level of adiposity. Nonobese = BMI <85th percentile; overweight = BMI 85th to 97th percentile; moderately obese—BMI *Z* score 2.0–2.5; severely obese = BMI *Z* score > 2.5. *dL* deciliter, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *mg* milligrams

HDL-C assessed during childhood has been shown to be as predictive as other lipid parameters of CIMT in young adults [77]. Population-based values from the Bogalusa Heart Study are available [40].

Relation to Abdominal Adiposity and Fatty Liver

While the relation to anthropometry (e.g., BMI) is well studied, lipid abnormalities are more closely related to adiposity, or more specific measures of both the quantity and distribution of body fat [80]. In particular, ectopic liver fat has been shown to be a better correlate of altered insulin dynamics, which drive the combined dyslipidemia of obesity [5]. A systematic review has shown in youth that measures of abdominal obesity or central body fat distribution were more consistently associated with high blood pressure, less so for dyslipidemia [81]. In a meta-analysis, waist-to-height ratio has been shown to be a more convenient measure of adiposity associated with increased cardiometabolic risk [82]. This has led to conceptualization and support of the "hypertriglyceridemic waist phenotype" as a marker of atherogenic lipid abnormalities associated with obesity, defined as a waist circumference ≥ 90th percentile for age and gender together with triglycerides ≥100 mg/dL [83]. Hobkirk and colleagues showed in 75 obese children and adolescents that fasting triglycerides and waist circumference accounted for 27% of the variation in a continuous metabolic triad score (fasting insulin, apolipoprotein B, and LDL particle density) [84]. Reduction in fasting triglycerides with weight loss was associated with a lowering of the metabolic triad score. Together with the triglyceride glucose index [9], these measures that link central adiposity, insulin resistance, and triglycerides may lead to a more precise conceptualization and definition of metabolic syndrome in youth, particularly with regard to dyslipidemia.

Contribution of Obesity-Related Lipid Abnormalities to Other Dyslipidemias and Risk Conditions

The dyslipidemia associated with obesity may in some cases be superimposed upon the metabolic abnormalities in other primary lipid disorders. For example, obese patients with primary hypercholesterolemia secondary to LDL-receptor mutation may have concomitant reductions in HDL-C and elevations in plasma triglycerides [85, 86]. In other conditions (Table 25.6), obesity may exacerbate or unmask an underlying primary predisposition for lipid abnormalities, particularly those associated with overproduction of VLDL and *primary hypertriglyceridemias* [87].

Familial combined hyperlipidemia is a genetically heterogeneous condition; the inheritance pattern is usually autosomal dominant [88–92]. There is considerable variation of phenotypic expression both within and between affected family members [93]. Lipid features include elevations in total cholesterol (more specifically associated with increased LDL-C or non-HDL-C), triglycerides (concomitantly associated with decreased HDL-C), or both. It is also associated with an increased risk of premature cardiovascular disease, has recently been shown to be manifest as increased carotid intima-media thickness in children, and increases vulnera-

Table 25.6 Etiology of hypertriglyceridemia

Genetic disorders
Lipoprotein lipase deficiency
Apolipoprotein C-II deficiency
Familial hypertriglyceridemia (hyperprebetalipoproteinemia)
Familial dysbetalipoproteinemia
Familial combined hyperlipidemia
Metabolic disorders
Diabetes mellitus
Obesity and insulin resistance
Fatty liver disease
Hypothyroidism[a]
Nephrotic syndrome[a]
Drugs and medications
Alcohol
Estrogens
Androgens
Corticosteroids
β-Blockers, thiazides
Isotretinoin
Valproic acid
Antiretroviral protease inhibitors
Atypical (second generation) antipsychotics

[a]Less common; hypercholesterolemia dominant abnormality

bility to the metabolic syndrome [94]. The phenotype has many similarities or overlap with the lipid abnormalities associated with the metabolic syndrome, and differentiating the two conditions from each other can be challenging, particularly since they often coexist within the same patient [90]. This is particularly true for children and adolescents, where the metabolic abnormalities associated with obesity may be necessary for the clinical condition to manifest [95]. Indeed, the primary underlying pathophysiology is an overproduction of VLDL, a feature it shares with obesity-related dyslipidemia. Clinical features that may distinguish familial combined hyperlipidemia from obesity-related dyslipidemia are the presence of higher fasting levels of LDL-C, apolipoprotein B, and non-HDL-C than would be seen in the metabolic syndrome, together with a positive family history of variable lipid abnormalities and premature cardiovascular disease.

Familial dysbetalipoproteinemia is an autosomal recessive condition manifest as elevated total cholesterol, non-HDL-C, and triglycerides, with decreased HDL-C [96, 97]. The cause of familial dysbetalipoproteinemia is homozygosity for ApoE2, which occurs in about 1 in 170 people. Apolipoprotein E can exist as three isoforms, designated ApoE2, ApoE3, and ApoE4. Homozygosity for the E2 isoform results in decreased hepatic clearance of VLDL and intermediate lipoprotein particles, as well as an overproduction of VLDL. It is associated with an increased risk of premature cardiovascular disease. The lipid abnormalities are usually not manifest during childhood, but can be unmasked in the presence of obesity and the metabolic syndrome. While the molecular biology is different, the phenotype and management is very similar to that of familial combined hyperlipidemia [98].

High-Risk Conditions Associated with Lipid Abnormalities

Lipid abnormalities associated with overweight and obesity can contribute important cardiovascular risk in the setting of high-risk clinical conditions other than primary lipid disorders [99].

High-risk conditions are those that may be associated with coronary artery disease before 30 years of age; these include type 1 diabetes (mixed dyslipidemia), chronic renal disease (mixed dyslipidemia), heart transplantation recipients (lipid abnormalities associated with chronic inflammation and immunosuppressive medications), and patients who have had Kawasaki disease with persistence of coronary artery aneurysms (low HDL-C associated with subclinical inflammation).

Moderate risk conditions are those associated with accelerated atherosclerosis and cardiovascular disease; these include type 2 diabetes (mixed dyslipidemia), chronic inflammatory diseases such as systemic lupus erythematosus and juvenile rheumatoid arthritis (lipid abnormalities associated with chronic inflammation and medications), and patients who have had Kawasaki disease with regression of coronary artery aneurysms (low HDL-C).

At risk conditions are those associated with accelerated atherosclerosis supported by epidemiologic evidence; these include post-cancer-treatment survivors, patients with congenital heart disease, and patients who have had Kawasaki disease without detected coronary artery involvement.

Evaluation of children and adolescents with any of these conditions requires a fasting lipid profile and attention to the level of adiposity. Changes in clinical status and/or drug therapy may necessitate repeat lipid screening.

It should be noted that the presence of obesity, hypertension, smoking, and/or a family history of early cardiovascular disease increases the risk level for any underlying condition and places a child with no underlying condition "at risk." The magnitude of the overall risk will influence decisions regarding aggressiveness of treatment for the lipid abnormalities, and the target lipid levels to be achieved.

Intervention

Lifestyle Management

Healthy behavior change remains the cornerstone of therapy for obesity-related lipid abnormalities. Therapy is aimed at reducing adiposity and

improving the metabolic milieu, but treatment may also be targeted directly towards the lipid abnormalities.

Dietary Management

Dietary management is aimed at fat and cholesterol restriction, reduction in intake of simple carbohydrates, and increases in intake of dietary fiber and omega-3 fatty acids. Consultation and counseling with a registered dietician is recommended. Recommendations for the Cardiovascular Health Integrated Lifestyle Diet-2 (CHILD-2) from the Expert Panel guidelines are noted in Table 25.7 [11].

The safety of the fat- and cholesterol-restricted diet in the general pediatric population has been shown in some large-scale clinical trials. The Dietary Intervention Study in Children (DISC) was a randomized trial of an intensive fat and cholesterol-restricted dietary intervention in prepubertal children with increased LDL-C who were below the thresholds at which drug therapy would be considered [100]. After 3 years, there was no impact of the dietary intervention on growth, development, and nutritional indices. However, the degree of LDL-C reduction was modest (mean—3.2 mg/dL). The effect was maintained for up to 7 years of follow-up [101].

Table 25.7 Dietary recommendations for targeting lipid abnormalities[a]

Reducing LDL-C
– Restrict proportion of total calories to:
25–30% from fat
≤ 7% from saturated fat
– Restrict cholesterol intake to <200 mg/day
– Preferred use of monounsaturated fat
– Avoidance of trans fats
– Consideration of use of fat sources enriched with plant sterol/stanol esters
– Increased consumption of dietary fiber
Reducing non-HDL-C, triglyceride levels
– In addition to dietary guidance as per reducing LDL-C:
Decrease sugar intake- no sugar sweetened drinks, replace simple with complex carbohydrates
Increase dietary fish intake as a source of omega-3 fatty acids

[a]Referral to a registered dietician for family medical nutrition therapy is recommended to support these dietary targets

HDL-C high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *mg* milligram

The Special Turku Coronary Risk Factor Intervention Project (STRIP) randomized 7-month-old infants to an intervention aimed at restricting dietary fat and cholesterol and increasing the proportion of mono- and polyunsaturated fat. At age 5 years, boys had a 9% lower LDL-C level, with no significant difference noted in girls [102]. There was no impact on growth, development, or nutritional indices. A follow-up study at age 7 years confirmed persistence of the relative reductions in total cholesterol and LDL-C levels in boys, together with larger LDL particle size, effects that were not observed in girls [103]. Ongoing follow-up of these participants into early adulthood showed improved insulin sensitivity [104], and a decreased prevalence of metabolic syndrome between ages 15 and 20 years, varying from 6 to 7.5% in the intervention group versus 10% to 14% in the control group [105]. A greater number of ideal cardiovascular health metrics, as noted in the intervention group, was shown to be associated with reduced aortic intima-media thickness and improved elasticity [106]. It would, therefore, appear that very early dietary interventions may have lifetime benefits in terms of cardiometabolic abnormalities and vascular health.

Lipogenic Macronutrients

There have been a number of studies that have focused on specific nutrients as drivers of metabolic syndrome and dyslipidemia. Bremer and colleagues identified four foodstuffs that are primarily metabolized by the liver, are not insulin regulated, and in excess contribute to lipogenesis and ectopic fat deposition: fructose, branched chain amino acids (valine, leucine, and isoleucine), trans-fat, and ethanol [5]. Higher total sugar intake has been linked to greater adiposity, lower insulin sensitivity, and reduced insulin response in overweight Latino youth [107]. Higher fructose consumption has been linked to decreased LDL particle size and lower HDL-C in overweight children [108]. A longitudinal study

in adolescent girls showed that those with <10% total energy intake from sugars had increasing HDL-C levels regardless of level of adiposity [109]. A study in obese children and adolescents showed that elevations in circulating branched-chain amino acids were independently associated with increasing insulin resistance during follow-up [110]. Gender differences may be evident, in that fasting blood levels of branched-chain amino acids in obese adolescents have been shown to be associated with increased insulin resistance in boys and higher triglyceride:HDL-C ratio in girls [111]. Trans fat consumption leads to hepatic ectopic fat accumulation, worsening insulin resistance, and dyslipidemia [112]. While there has been a trend towards decreased consumption of solid fats and added sugars among youth, intake continues to be above recommended levels [113]. Concomitantly, there has been a trend towards improved serum lipid concentrations, although the prevalence of abnormalities remains increased [114, 115].

Effects of Dietary Alterations

There have been several small studies of the effect of specific dietary alterations or supplements on dyslipidemia in youth. Studies of dietary substitution with soy-based protein showed that it may increase HDL-C and lower VLDL-C levels and triglycerides, and may lower LDL-C levels [116, 117]. Probiotic supplementation was shown in a trial of overweight youth to decrease total cholesterol, LDL-C, and triglycerides [118]. Dietary enrichment with rapeseed or canola oil has been shown to lower triglyceride and VLDL-C levels [119]. A small trial of flaxseed supplementation showed adverse lipid changes, including lowering of HDL-C and increases in triglycerides [120]. Intake of antioxidant vitamins has not been shown to be of benefit in adults, but in children and adolescents with familial hyperlipidemia, has been shown to be associated with improvements in endothelial function, an early precursor of atherogenesis, and lipoprotein subclasses [121, 122]. A clinical trial of docosohexanoic acid in children and adolescent with familial hyperlipidemia showed increases in total cholesterol, LDL-C, and HDL-C, and an improvement in endothelial function [123]. There is some clinical trial evidence to support the use of plant sterol/stanol-enriched fat sources and dietary fiber enrichment. Plant sterols/stanols have been shown to result in modest reductions in LDL-C but no improvement in endothelial function [124–128], while dietary fiber supplementation has been shown to have a variable effect in lowering triglyceride levels [129, 130].

Increased fish consumption and fish oil (omega-3 fatty acids) supplementation has been recommended for lowering triglyceride levels [131]. In the setting of hepatic steatosis, a systematic review concluded that omega-3 fatty acid supplementation improved steatosis grade without a significant effect on metabolic syndrome components [132]. Two trials and a clinical practice review of fish oil in hypertriglyceridemic adolescents showed a nonsignificant reduction in triglycerides and no effect on LDL particle number or size [133–135]. The use of other nutritional supplements has not been well studied or, in the case of garlic extract supplements, have been shown to be of no benefit [136].

Physical Activity and Sedentary Pursuits

Increasing daily physical activity levels is an essential goal in healthy lifestyle behavior change. Exercise increases substrate clearance by increasing hepatic mitochondrial activity, reducing lipogenesis and insulin resistance, and increasing mitochondrial biogenesis and efficiency in liver and muscle [5, 137]. A study using magnetic resonance spectroscopy showed overweight children have reduced skeletal muscle mitochondrial oxidative phosphorylation that is associated with increased insulin resistance [138]. Exercise has also been shown to prevent reductions in adiponectin with improvements in adiposity in obese youth [139]. Several studies have reported favorable changes in lipid abnormalities in response to physical activity in children. Acute exercise before a high fat meal improves the post-prandial triglyceride response in overweight adolescents [140]. A 12 week aerobic exercise intervention for obese children

showed reductions in adiposity and improvements in lipid values [141]. A randomized trial evaluating physical training in obese adolescents showed that high-intensity training was more effective than no training in reducing triglycerides, total cholesterol to HDL-C ratio and diastolic blood pressure [142]. Subjects with the greatest lipid abnormalities at baseline experienced the most marked effects of high-intensity training, including a beneficial effect on LDL particle size. However, the high-intensity program did not improve adiposity compared to the moderate-intensity program. Another clinical study demonstrated that higher intensity physical activity is more strongly associated with reductions in LDL-C in children than is the total energy spent on physical activity [143]. Exercise training in prepubertal children has been shown to reduce LDL-C and increase HDL-C independent of changes in exercise capacity or adiposity [144]. In an evaluation of the use of a resistance exercise program in male adolescents, reductions in LDL-C and increases in HDL-C were noted in the absence of changes in body composition [145].

Some clinical trials, particularly those with a predominant exercise training component, have shown improvements in noninvasive vascular markers despite the lack of significant changes in indices of adiposity other than improvements in visceral adiposity and increases in muscle mass [146, 147]. A review suggested that aerobic physical activity, particularly higher intensity exercise, reduces visceral adiposity, with attendant improvements in metabolic indices [148]. Evidence was less compelling for an independent effect of resistance training. Therefore, an ideal exercise prescription as part of the management of lipid abnormalities in obese youth may be one that includes 30–60 min/day of higher intensity physical activity combined with resistance exercise.

In concert with the promotion of physical activity there should be a reduction in the amount of time spent in sedentary pursuits; see also Chap. 18. Limitations on the amount of time spent watching television, playing video and computer games and text-messaging should be established. Media-based sedentary pursuits should be limited to $\leq$2 h/day [11].

Bariatric Surgery

In highly selected circumstances, bariatric surgery may be considered in adolescents with morbid obesity and comorbidities who have failed to achieve sufficient reductions in adiposity from lifestyle changes; see Chap. 38. A recent paper presents a multi-center review of 242 patients with a mean age of 17 years and BMI of 53 kg/m^2 who underwent bariatric surgery with either a Roux-en-Y gastric bypass or sleeve gastrectomy [149]. After 3 years, mean weight loss was 27%, with remission in 95% of patients who had type 2 diabetes, 76% of those with prediabetes, and 66% of those with dyslipidemia. However, hypoferritinemia was noted in 57%, and 13% required additional intra-abdominal procedures. While effective in reducing cardiometabolic risk, including dyslipidemia, in the short-term, the long-term benefits and risks remain unknown.

Drug Therapy

Drug therapy for lipid abnormalities in the setting of childhood obesity should be reserved for: (a) those with severe abnormalities that persist after attempts at reduction in adiposity and adoption of healthy lifestyle behavior change; or (b) those with additional risk factors and risk conditions. Recommendations for decision-making regarding drug therapy independent of obesity are available, including how to use these medications in children and adolescents [11, 18]. The goal of drug therapy is reduce lipid abnormalities ideally into the normal range, but minimally into the borderline high range (Table 25.4).

Short-term clinical trials and longer-term observational studies provide support for the use of several classes of medications in children and adolescents with primary lipid disorders (Table 25.8) [150–174]. There have, however, been no clinical trials of lipid-lowering therapy in obese children and adolescents with combined dyslipidemia.

Bile acid sequestrants bind bile acids in the intestinal lumen and prevent their enterohepatic reuptake, thus removing them from the choles-

terol pool. Synthesis of replacement bile salts leads to depletion of intracellular cholesterol in hepatocytes; this in turn leads to upregulation of LDL receptors in order to increase cellular uptake of cholesterol, which increases the clearance of circulating LDL particles. These agents result in a modest decrease in LDL-C, but increase triglyceride levels. In addition, they are associated with gastrointestinal symptoms and poor palatability, leading to poor compliance. They are now used for patients with mild LDL-C abnormalities or in combination with a statin for those with more severe elevations of LDL-C, particularly familial hypercholesterolemia or familial combined dyslipidemia. They do not have an important role in the treatment of obesity-related dyslipidemia.

Cholesterol absorption inhibitors (e.g., Ezetimibe) inhibit intestinal absorption of cholesterol and plant sterols, which leads to upregulation of hepatic LDL receptors and increased LDL clearance similar to bile acid sequestrants. These agents cause a modest decrease in LDL-C but have limited or no effect on triglycerides and HDL-C levels. They are predominately used in combination with a statin for patients with severe LDL-C elevations who do not meet lipid targets with a statin alone. Their use as monotherapy in young children has been proposed prior to statin therapy at an older age.

Statins or 3-hydroxyl-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors are the primary therapy proposed for treatment of dyslipidemias associated with LDL-C elevations, and have a role in the treatment of obesity-related dyslipidemia and LDL particle clearance. Statins inhibit HMG-CoA reductase, a rate-limiting enzyme in pathway of endogenous cholesterol synthesis. This leads to intracellular cholesterol depletion, resulting in upregulation of LDL receptors and increased LDL particle clearance. These agents are very effective in lowering LDL-C and LDL particle numbers, with some increase in HDL-C levels. In addition, the statins have potentially beneficial pleotropic effects. Adverse effects are uncommon; they include myopathy; rhabdomyolysis, and increases in serum hepatic transaminases. Reports of an increased incidence of new onset diabetes in adults have not been noted in youth. They have been shown to have no adverse effect on growth and development, and beneficial effects on vascular markers of early atherosclerosis [175, 176]. There have been several meta-analyses of pediatric trials of statins in familial hypercholesterolemia, which have shown no significant increase in the incidence of adverse effects [177]. However, given that obese youth are at risk for incident type 2 diabetes and nonalchoholic steatohepatitis, safety needs to be confirmed in this specific population before widespread use is recommended. *It should also be noted that statins are potentially teratogenic, and repeated reproductive counseling regarding prevention of pregnancy is essential in females of child-bearing potential.*

While little is known regarding the benefits and risks of statin therapy of combined dyslipidemia in youth, trials of statin therapy in adults with combined dyslipidemia have shown improvements in LDL particle size and decreases in number [178]. A new and more potent statin, pitavastatin, has been shown in adults with diabetes to have a more favorable risk:benefit profile [179–181]. There have been two pediatric trials of pitavastatin in patients with familial hypercholesterolemia that confirm similar safety to other statins [170, 171]. Novel agents that inhibit LDL receptor degradation (PCSK9 inhibitors) or interfere with apolipoprotein B transcription (mipomersen) have not yet completed study in children and will unlikely be applicable to treatment of combined dyslipidemia.

Fibric acid derivatives, or fibrates, seem ideally suited for management of obesity-related lipid abnormalities. As agonists for nuclear peroxisome proliferator-activated receptor (PPAR)-alpha, they upregulate lipoprotein lipase and downregulate apolipoprotein CIII, which increase the degradation of VLDL-C and triglycerides. They also may decrease hepatic synthesis of VLDL-C by stimulating oxidation of free fatty acids and reducing their contribution to triglyceride synthesis. Fibrates increase expression of the genes encoding for apolipoproteins A-I and A-II, impacting HDL metabolism. As a result, they

Table 25.8 Clinical trials of drug therapy of lipid abnormalities in children and adolescents

Study	Medication	Subjects/gender Condition	Daily dose	Effect on lipid profile TChol (%)	LDL-C (%)	HDL-C (%)	TG (%)
Bile acid sequestrants							
Tonstad [150] RCT 1 year	Cholestyramine	96/both HFH	8 g	−12	−17	+8	NA
McCrindle [151] RCT cross-over 2 × 8 weeks	Cholestyramine	40/both HFH	8 g	−7 to −11	−10 to −15	+2 to +4	+6 to +9
Tonstad [152] RCT 8 weeks Open label 44–52 weeks	Colestipol	27/both HFH	2–12 g	−17	−20	−7	−13
McCrindle [153] RCT cross-over 2 × 18 weeks	Colestipol	36/both HFH FCH	10 g	−7	−10	+2	+12
Stein [154] RCT 8 weeks Open label 18 weeks	Colesevelam	191/both HFH	1.875 g 3.75 g	−3 −7	−6 −13	+5 +8	+6 +5
Cholesterol absorption inhibitors							
Yeste [155] Open label 12 months	Ezetimibe	6/both PH 11/both HFH	10 mg 10 mg	−31 −26	−42 −30	NC −16	NC NC
Clauss [156] Open label 3.5 months	Ezetimibe	26/both HFH 10/both FCH	10 mg 10 mg	−22 −13	−26 −19	NC NC	NC NC
Kusters [157] RCT 12 weeks	Ezetimibe	118/both (107 HFH) Ages 6–10 years	10 mg	−21	−27	+1	−15
HMG CoA reductase inhibitors (statins)							
vander Graf [158] Open label 2 years	Fluvastatin	85/ both HFH	80 mg	−27	−34	+5	−5
Lambert [159] RCT 8 weeks	Lovastatin	69 males HFH	10 mg 20 mg 30 mg 40 mg	−17 −19 −21 −29	−21 −24 −27 −36	+9 +2 +11 +3	−18 +9 +3 −9
Stein [160] RCT 48 weeks	Lovastatin	132 males HFH	10 mg 20 mg 40 mg	−13 −19 −21	−17 −24 −27	+4 +4 +5	+4 +8 +6
Clauss [161] RCT 24 weeks	Lovastatin	54 females HFH	40 mg	−22	−27	+3	−23
Knipscheer [162] RCT 12 weeks	Pravastatin	72/ both HFH	5 mg 10 mg 20 mg	−18 −17 −25	−23 −24 −33	+4 +6 +11	+2 +7 +3
Wiegman [163] RCT 2 years	Pravastatin	214/ both HFH	20–40 mg	−19	−24	+6	−17
Rodenburg [164] Open label 2.1–7.4 years	Pravastatin	186 both HFH	20 or 40 mg	−23	−29	+3	−2
de Jongh [165] RCT 48 weeks	Simvastatin	173/ both HFH	10–40 mg	−31	−41	+3	−9
de Jongh [166] RCT 28 weeks	Simvastatin	50/ both HFH	40 mg	−30	−40	+5	−17
McCrindle [167] RCT 26 weeks + Open label 26 weeks	Atorvastatin	187/both HFH/Severe	10–20 mg	−30	−40	+6	−13

Table 25.8 (continued)

Study	Medication	Subjects/gender Condition	Daily dose	Effect on lipid profile TChol (%)	LDL-C (%)	HDL-C (%)	TG (%)
Avis [168] RCT 12 weeks + Open label 40 weeks	Rosuvastatin	177/both HFH	5 mg 10 mg 20 mg	−30 −34 −30	−38 −45 −50	+4 +10 +9	−13 −15 −16
Braamskamp [169] Open label 2 years	Rosuvastatin	197/both HFH Age 6–17 years	5–20 mg	−32	−43	+12	−5
Harada-Shiba [170] RCT 52 weeks	Pitavastatin	14/males HFH	1 mg 2 mg	NC NC	−27 −34	NC NC	NC NC
Braamskamp [171] RCT 12 weeks + Open label 52 weeks	Pitavastatin	106/both HFH/Severe	1 mg 2 mg 4 mg	−18 −24 −31	−24 −30 −39	+6 −2 −3	−8 −6 <1
Other agents							
Colletti [172] Open label 1–19 months	Niacin	21 both Severe	500–2200 mg	−13	−17	+4	+13
Wheeler [173] RCT 8 weeks	Bezafibrate	14 both HFH	10–20 mg/kg	−22	NC	+15	−23
McCrindle [153] RCT cross-over 2 × 18 weeks	Pravastatin and Colestipol	36/both HFH FCH	Pravastatin, 10 mg (with Colestipol, 5 g)	−13	−17	+4	+8
Van der Graaf [174] RCT 6 and 27 weeks; Open label to 53 weeks	Simvastatin and Ezetimide	248/both HFH	Simvastatin 10–40 mg with Ezetimide 10 mg	−38	−49	+7	−17

d day, *g* grams, *mg* milligrams, *NA* not available, *NC* not calculated, *TC* total cholesterol, *wks* weeks, *HFH* heterozygous familial hypercholesterolemia, *FCH* familial combined hyperlipidemia, *FH* familial hyperlipidemia, *RCT* randomized clinical trial, *Severe* severe hyperlipidemia

lower non-HDL-C and triglyceride levels, with increases in HDL-C levels and particle size, and increases in LDL particle size. Adverse effects are rare; they include myositis (particularly when administered in combination with a statin, more commonly with gemfibrozil versus fenofibrate) [182], anemia, and gastrointestinal complaints. Despite their theoretic potential, there are minimal pediatric data regarding their use [183]. A review of 47 children and adolescents with metabolic syndrome who were treated with gemfibrozil showed a 57% reduction in triglycerides, with a 20% increase in HDL-C; 2 subjects reported muscle pain [184].

Nicotinic acid formulations also seem ideally suited for treatment of obesity-related lipid abnormalities, as they inhibit release of free fatty acids from adipose tissue, and reduce VLDL-C and LDL-C production and HDL-C degradation. They effectively lower non-HDL-C, LDL-C, and triglycerides, and raise HDL-C levels. Their main limitation is prevalent and symptomatic adverse effects, primarily flushing; there are also concerns about hepatic toxicity and poor glycemic control, which would likely contraindicate their use in obese youth. They are reserved for combination with a statin, and there are almost no pediatric data regarding their use.

Decision-making regarding drug therapy is complex, and dependent not only on the severity of lipid abnormalities, but the presence and severity of associated risk factors and risk conditions, or which obesity is one (Table 25.2). Drug therapy is not usually considered for obese children and adolescents with combined dyslipidemia until an adequate attempt has been made at healthy lifestyle behavior change. In general, drug therapy is not considered in children

younger than 10 years of age, although children aged 6 and 9 years may be selectively treated if lipid abnormalities are very severe and there is a strong family history of premature cardiovascular disease, such as with familial hypercholesterolemia. Recommendations for patient selection in the setting of obesity are given in Table 25.9, and guidelines for management of statin therapy for pediatric patients exist [11]. In the setting of obesity, it may be reasonable to use non-HDL-C cut-points in place of LDL-C cut-points in the LDL algorithm described in the Expert Panel guidelines. This is because high non-HDL-C together with low HDL-C and high triglycerides is a good surrogate for the presence of atherogenic high numbers of small, dense LDL particles.

There are concerns that recommendations for drug therapy of lipid abnormalities in the setting of childhood obesity would lead to an epidemic of medication (particularly statin) use. A population-based study using NHANES data estimated that, using Expert Panel guidelines, only 0.85% of adolescents would be potentially eligible for treatment of increased LDL-C [11, 185]. When the results were stratified by BMI category, 0.6% of those with BMI <95th percentile, none with BMI ≥95th but <97th percentile, and 3.1% of those with BMI ≥97th percentile would be recommended for statin therapy. For obese participants with LDL-C between 130 and 159 mg/dL, current smoking was the additional factor indicating statin therapy in the majority.

Lipid abnormalities in overweight youth are not being addressed effectively within the context of the health care system [186]. Administrative data from 2004 for pediatric patients suggests that the prevalence of statin use currently is extremely low [187]. The predominant statin in use was atorvastatin, with a prevalence of use for those aged 12 to 19 years equal to 0.03%, or 3 per 10,000. With the prevalence of heterozygous familial hypercholesterolemia at 1 in 200–400, it would appear that only a small proportion of eligible children are currently being treated with drug therapy, despite a clear recommendation. It would seem unlikely that recommendations for drug therapy in the setting of obesity would lead to an epidemic of medication use.

Table 25.9 Recommendations regarding drug therapy for hypercholesterolemia in obese children and adolescents

1. Measure and average values from two fasting lipid profiles
2. Statin therapy may be initiated under the following circumstances (if HDL-C < 40 mg/dL or triglycerides >200 mg/dL may use non-HDL-C cut-points):
Consider statin if BMI ≥ 97th percentile (considered a high-risk factor) and: LDL-C ≥ 160 mg/dL (non-HDL-C ≥ 175 mg/dL), *or* LDL-C 130–159 mg/dL (non-HDL-C 145–174 mg/dL) *and* the patient has 1 high-level RF/RC or ≥2 moderate-level RF/RC (see Table 25.2) or clinical CVD
Consider statin if BMI ≥ 95th and < 97th percentile (considered a moderate risk factor) and: LDL-C ≥ 190 mg/dL (non-HDL-C ≥ 205 mg/dL), *or* LDL-C 160–189 mg/dL (non-HDL-C 175–204 mg/dL) *and* the patient has a high-risk family history or 1 high- or moderate-level RF/RC (see Table 25.2), *or* LDL-C 130–159 mg/dL (non-HDL-C 145–174 mg/dL) and the patient has 2 high-level or 1 high +1 moderate level RF/RC (see Table 25.2) or clinical CVD
Consider statin if BMI < 95th percentile and: LDL-C ≥ 190 mg/dL (non-HDL-C ≥ 205 mg/dL), *or* LDL-C 160–189 g/dL (non-HDL-C 175–204 mg/dL) *and* the patient has a high-risk family history or 1 high- or 2 or more moderate-level RF/RC (see Table 25.2), *or* LDL-C 130–159 mg/dL (non-HDL-C 145–174 mg/dL) and the patient has 2 high-level or 1 high- +2 or more moderate-level RF/RC (see Table 25.2) or clinical CVD
3. The choice of statin is a matter of preference. Start with the lowest dose, monitor for adverse effects, and titrate the dose upward if therapeutic targets are not achieved
Therapeutic target:
Minimal: LDL-C < 130 mg/dL (non-HDL-C < 145 mg/dL) **Ideal**: LDL-C < 110 mg/dL (non-HDL-C < 125 mg/dL) **Diabetic**: LDL-C < 100 mg/dL (non-HDL-C < 115 mg/dL)

CVD cardiovascular disease, *dL* deciliter, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *mg* milligram, *RF/RC* risk factor/risk condition

The role of insulin sensitizers in the management of hyperlipidemia in obese children has not been extensively evaluated. Metformin has been assessed in clinical trials, and has shown equivo-

cal results in terms of correction of lipid abnormalities [188–190].

Summary

Combined dyslipidemia is a major component of the metabolic syndrome related to overweight and obesity in youth, is highly atherogenic, and is characterized by high triglyceride levels, low HDL-C levels, and increased numbers of small, dense LDL particles. These abnormalities are primarily driven by elevation in plasma free fatty acids derived from metabolically active visceral adipose tissue, particularly ectopic hepatic fat, resulting in increased hepatic triglyceride synthesis and overproduction of VLDL particles. Assessment of lipid abnormalities relies on a fasting lipid profile. Reduction in adiposity through healthy lifestyle behavior change is the cornerstone of therapy, although dietary and physical activity interventions may have direct benefits independent of weight loss. Drug therapy may be required for those with severe lipid abnormalities and associated risk factors and risk conditions. Evidence-based research in many areas is lacking; the intersection of clinical care recommendations with the health care system has assumed increasing importance.

Editor's Comments and Questions

Triglyceride levels exceeding 1000 mg/dL can cause *pancreatitis*; chylomicrons in excess are postulated to impair blood flow in pancreatic capillary beds, leading to ischemic changes, and hydrolysis of TG by pancreatic lipase results in necrosis and inflammation. In addition to fibrates, concentrated preparations of omega-3 fatty acids ethyl esters, which contain primarily eicosapentaenoic (EPA) and docosahexaenoic (DHA), are approved by the FDA for treatment of severe hypertriglyceridemia (>500 mg/dL) in adults.[a] At a dose of 3–4 g/day can reduce TG levels by 26–47%; this effect is mediated by reductions in hepatic lipogenesis, increases in fatty acid oxidation, and degradation of apoB-100. Such benefits have not yet been clearly demonstrated in children.

High doses of omega-3 fatty acids can also cause variable increases in LDL-C (10–46%) and HDL-C. Increases in LDL-C levels are most common in patients with the highest TG levels; concomitant use of a statin may be required to reduce cholesterol levels. Other possible adverse effects of pharmacologic doses of omega-3 fatty acids include dyspepsia, decreased platelet aggregation, increases in serum ALT levels, and a transient rise in blood glucose.

In adults, a high level of *lipoprotein(a) [Lp(a)]* is associated with increased risks for atherosclerosis, heart disease, and stroke. Lp(a) may also serve as a marker of stroke risk in children, but its relationship to future atherosclerosis and coronary heart disease is currently unclear.[b–g] Levels of Lp(a) are primarily under genetic control and vary by ethnicity, and attempts to reduce Lp(a) levels with lifestyle intervention or pharmacotherapy have had limited and variable success; some data suggest that niacin may be beneficial. Some investigators suggest screening Lp(a) levels in children with ischemic or hemorrhagic stroke or with a parental history of early cardiovascular disease that is not explained by classical risk factors.[b]

1. *What is your view of the value of measuring Lp(a) levels in children with hyperlipidemia?*
2. *Should the level of Lp(a) influence the decision to use, or the choice of, pharmacotherapy for hyperlipidemia in children?*
3. *Does pharmacologic reduction of Lp(a) in children or adolescents reduce carotid intimal medial thickness or future risk of cardiovascular disease?*

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Author's Responses

1. There are very few pediatric data regarding Lp(a) in youth, particularly obese youth. As a result, current Expert Panel guidelines do not recommend routine assessment.[a] However, in children with familial hypercholesterolemia, the presence of elevated Lp(a) has been associated with an increased likelihood of premature cardiovascular disease in the parents.[b] As a result, guidelines specific to this population do recommend its assessment.[c] It is also part of the thrombophilia assessment of pediatric patients after stroke. In my clinic, few patients are referred for assessment and management of elevated Lp(a) at this time, and I do not routinely assess for it. When these patients do come up, their management demonstrates a lot of controversy and uncertainty on discussion boards.
2. Elevated Lp(a) does not enter into the Expert Panel guidelines as a risk factor that influences decisions about drug therapy for elevated LDL-C, since so much is unknown. In familial hypercholesterolemia, it may indicate a more high-risk phenotype through family history, but family history already influences decision-making in that population.
3. This hypothesis has not been tested, nor is it currently testable. Currently, specific treatments for elevated Lp(a) are not widely available. Niacin has been suggested but is not well-tolerated or safe in pediatric populations, and studies in adults have not shown benefit when LDL-C is well-controlled. The efficacy of Lp(a) lowering needs to be shown first in adults. Statins seems to have little effect, although new agents targeting LDL receptor cycling (PCSK9 inhibitors) and apolipoprotein B100 antisense oligonucleotide (mipomersen) may lower levels by 20–30%. Specific RNA targeting therapies may reduce Lp(a) by 80%.[d] The need for, feasibility, and utility of lowering Lp(a) in pediatric populations remains unknown. In the

meantime, the mainstay of management is to ensure that all other risk factors and behaviors are assessed and managed, in order to maintain overall low risk.

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Fatty Liver Disease

26

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Introduction

Also named hepatic steatosis, fatty liver disease is characterized by the accumulation of fat in liver cells. Table 26.1 summarizes the causes of fatty liver in adolescents and children. These include chronic alcohol consumption, C viral hepatitis, type-2 diabetes, obesity, and some metabolic aberrations [1]. Nonalcoholic fatty liver disease (NAFLD), associated with obesity and the metabolic syndrome, is the most prevalent form of fatty liver [2, 3].

Nonalcoholic fatty liver disease is now considered a *continuum* of hepatic disorders, ranging from simple fat accumulation in >5% of hepatocytes to advanced forms of liver involvement, with varying degrees of inflammation, ballooning, and fibrosis that may progress to advanced liver diseases and to cirrhosis [4].

The prevalence of NAFLD in the general adult population is estimated to be 20–46% in Western countries and 5–18% in Asia, with differences according to the diagnostic method, age, sex, and ethnicity. The prevalence is lower (3–12%) in the general pediatric population but reaches rates as high as 70% in obese children [5].

To date, NAFLD represents the most common cause of chronic liver disease in children and adolescents. In the United States, NAFLD is becoming an increasingly frequent indication for orthotopic liver transplantation (OLTx), considering that approximately 10% of OLTx are now performed for NASH cirrhosis [6].

Clinical series of pediatric NAFLD have uniformly demonstrated that it is more common in boys than girls and there is a higher prevalence in Hispanic and Asian children than in white and black children. Gender-based differences in the development of fatty liver are related to the influence of sex steroids on body fat distribution and hepatic lipogenesis. Racial/ethnic differences may be related to genetic, environmental, or sociocultural factors as well as differences in body composition.

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Table 26.1 Possible causes of fatty liver in children and adolescents

Nutrition	Obesity Severe weight loss due to starvation and jejunoileal or gastric bypass Total parenteral nutrition Malnutrition
Drugs	Amiodarone; glucocorticoids; tamoxifen; methotrexate; valproic acid; aspirin; antiretroviral therapy
Dysmetabolism	Dyslipidemia, lipoatrophy; insulin resistance; metabolic syndrome; type-2 diabetes, polycystic ovary syndrome
Genetic	Lipodystrophy syndromes; cystic fibrosis; hereditary fructose intolerance; galactosemia; α_1-antitrypsin deficiency; Wilson disease, etc.
Others	Inflammatory bowel disease; hepatitis C and B infection; human immunodeficiency virus infection; celiac disease Alcohol Other hepatotoxins

Risk Factors

Obesity and Metabolic Syndrome (MetS)

Obesity and metabolic syndrome is the major risk factor for NAFLD. The prevalence of NAFLD is higher in overweight or obese children (50–80%) as compared with normal weight children (2–7%). It seems clear that abdominal fat or central obesity plays an important role in pathogenesis of NAFLD and correlates more strongly with diagnosis than BMI alone [7].

Some pediatric studies, evaluating obese adolescents, demonstrated a positive correlation between increased abdominal fat and the incidence of NAFLD, independent of insulin resistance and dyslipidemia. Moreover, significant correlations between waist circumference, total fat mass, and intra-abdominal adipose tissue and the incidence of NAFLD were also reported. Therefore, waist circumference may represent an interesting and reliable screening tool for pediatric NAFLD.

Visceral adipose tissue is the primary source of triglyceride accumulation in the liver, the major site of fat storage in NAFLD. Visceral adipose tissue also produces pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 as well as leptin and adiponectin, all of which are implicated in the clinical manifestation of NAFLD and its progression to NASH and cirrhosis [8]. Abdominal visceral adipose tissue has higher rates of lipolysis and greater release of adipokines than subcutaneous fat.

As the adipose bed expands, the adipocytes suffer from a micro-hypoxic environment due to insufficiency of its vascular network. This results i.n cell injury and death and consequent upregulation of the pro-inflammatory cascade. The adipokines promote specific patterns of lipid storage and metabolic stress, which activate the oxidative stress cascade and trigger an inflammatory response [9].

Insulin Resistance (IR)

Insulin resistance is the most common metabolic abnormality associated with NAFLD and the most useful indicator of disease severity and progression in adults and children [10]. The severity of IR is strongly associated with the amount of accumulation of fat in the liver, independent of global and intra-abdominal adiposity. In NAFLD, hepatic IR can be detected prior to the development of peripheral IR, suggesting that the former may facilitate development of the latter. Hepatic steatosis induces hepatic insulin resistance by promoting serine rather than tyrosine phosphorylation of insulin receptor substrates; this limits the ability of insulin to suppress hepatic glucose production. On the other hand, the compensatory rise in circulating insulin levels promotes hepatic triglyceride synthesis through induction of the transcription factor SREBP-1c [3].

Genetic Factors

Although environmental factors such as sedentary lifestyle, hypercaloric diet, and visceral adiposity play central roles in the pathogenesis of NAFLD, several recent studies have demonstrated the

importance of genetic susceptibility in disease onset and natural history. Many epidemiological, familial, and twin studies find strong hereditability for NAFLD, as demonstrated also by the limited number of confounding factors in children compared with adults (duration of disease, smoking, metabolic comorbidities, and medications) [11, 12].

PNPLA3, also known as adiponutrin, is a member of the patatin-like phospholipase family. The rs738409 C > G single nucleotide polymorphism (SNP), which encodes an Ile148Met variant protein, is described as a genetic determinant of hepatic steatosis. Several studies have established a strong link between this PNPLA3 variant and the development of NAFLD; it is associated with advanced fibrosis among patients with a variety of liver diseases and is an independent risk factor for hepatocellular carcinoma (HCC) among patients with nonalcoholic steatohepatitis (NASH) [13]. Moreover, the polymorphism rs738409 predicts severity of necroinflammatory changes independent of metabolic factors [14].

Recently, additional single nucleotide polymorphisms (SNPs) of genes implicated in NASH pathogenesis have been shown to influence liver damage and fibrosis progression. These include genetic variants regulating insulin receptor activity, ectoenzyme nucleotide pyrophosphate phosphodiesterase 1 (ENPP1), and insulin receptor substrate-1 (IRS-1), underscoring the causal role of IR in the progression of liver damage in NAFLD. Other genes implicated in disease pathogenesis include the manganese superoxide dismutase (SOD2), which regulates SOD2 mitochondrial import and antioxidant activity, and Kruppel-like factor 6 (KLF6), which is involved in the regulation of metabolism in hepatocytes and fibrogenesis in hepatic stellate cells [15].

Finally, an interleukin-6 polymorphism (174G/C) and tumor necrosis factor (TNF)-α were identified as probable variables involved in inflammation and hepatic insulin resistance [16].

Pathogenesis

The pathogenesis of NAFLD is complex and still partially obscure [17]. Several authors have suggested a model consisting of two or more hits [18]. Liver fat accumulation, which is the suggested "first hit," is thought to increase vulnerability to possible "second hits," which are responsible for progression to NASH [19]. All models of pathogenesis include fat accumulation, insulin resistance, adipocytokines, oxidative stress, and the innate immune response.

The so-called gut–liver axis is another feature that may be crucial to the pathogenesis of NAFLD and chronic liver disease. Recent studies reported that poor diet and slow intestinal transit, which is frequent in obese patients, may induce small intestinal bacterial overgrowth (SIBO), increasing the release of endotoxins (mainly gut-derived lipopolysaccharides), and TNF-α. These inflammatory mediators easily cross the intestinal barrier that is more permeable in patients with NAFLD, increasing the severity of hepatic steatosis and promoting the progression of liver damage.

In addition, recent studies have shown that high-fat/high-fructose diets may modify gut microbiota, inducing a dysbiosis and the release of both pathogen- and damage-associated molecular pattern molecules (PAMPs or DAMPs). These molecules cross the more permeable intestinal epithelium and act as triggers of liver damage, inducing necroinflammation and fibrosis. In NAFLD patients, disruption of tight junctions (TJ) may explain the contribution of intestinal products (such as lipopolysaccharides) to the progression of liver disease. These discoveries are relevant because of the possible therapeutic implications of prebiotics/probiotics and dietetic supplements [20].

Clinical Features

NAFLD is generally an asymptomatic disease. In the majority of cases, the diagnostic work-up is initiated after the discovery of elevated transaminase levels in routinely laboratory tests (Table 26.2) or following the detection of hepatic steatosis in an echographic evaluation performed for other clinical reasons. Occasionally, NAFLD patients present with hepatomegaly or vague right upper quadrant discomfort but more commonly have fatigue (42–59% of cases). About 80% of

Table 26.2 Laboratory tests in children with suspected nonalcoholic fatty liver disease (NAFLD)

Baseline routine tests	Blood counts, electrolytes, urea, uric acid, INR, ALT, AST, GGT, TSH, FT4
Lipid profile	Cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, lipoproteins
Glucoinsulinemic pattern	Fasting glucose and insulin, OGTT, glycosylated hemoglobin
Exclusion other hepatopathies	Iron and ferritin Serum lactate Ceruloplasmin levels, 24-h urinary copper α1-Antitrypsin levels Antibodies transglutaminase IgA and total IgA Urinary steroid metabolites ANA, ASMA, LKM1, LC-1 Viral serology
Second-level metabolic screening, if indicated	Amino and organic acids Acylcarnitine profile Plasma free fatty acids

children with NAFLD are overweight (body mass index (BMI) ≥85th percentile) or obese (BMI ≥95th percentile), with abdominal distribution of adipose tissue (visceral fat). Frequently, NAFLD is associated with the stigmata and biochemical features of insulin resistance and the metabolic syndrome, including acanthosis nigricans, hypertension, dyslipidemia, cardiomegaly, sleep apnea, and elevated waist circumference. Acanthosis nigricans, a characteristic pigmentation of the flexion areas, is noted in 30–50% of cases [11, 21]. Actually, NAFLD is considered to be the hepatic manifestation of metabolic syndrome, even if hepatic steatosis is not included in the diagnostic criteria in either adults or children.

Signs and symptoms of chronic hepatic disease—such as jaundice, ascites, and esophageal varices— are extremely rare in children.

Diagnosis

As previously stated, NAFLD is often asymptomatic. Therefore, some physicians perform targeted measurements of ALT or ultrasound screening of obese children based on expert committee recommendations. Recently, the Hepatology Committee of European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has published guidelines for the diagnostic work-up of pediatric NAFLD [22].

Measurements of serum ALT, AST and GGT are the most common laboratory tests used *to* screen for NAFLD. However, there are no data to determine the sensitivity and specificity of any given transaminase level(s) for detection of fatty liver. Furthermore, it is now well documented that children can have NAFLD and even NASH without hypertransaminasemia [23]. Therefore, it is mandatory to exclude other forms of liver disease associated with elevated ALT and AST levels and/or steatosis, including viral and autoimmune hepatitis, drug or toxic liver injury including alcohol abuse, Wilson's disease, and alpha1-antitrypsin deficiency. The differential diagnosis of pediatric NAFLD is shown in Table 26.3.

Other metabolic abnormalities commonly observed in children with NAFLD include hyperinsulinemia, impaired glucose tolerance, dyslipidemia, and hyperuricemia. *Thus, an increase in ALT in an obese child with the metabolic syndrome most likely represents fatty liver disease.*

Several *imaging techniques* have been used to detect and quantify deposits of fat within the liver. However, in children, no noninvasive method has been validated against liver histology. Furthermore, no existing imaging technology is able to discriminate between hepatic steatosis and NASH.

Hepatic ultrasound is the imaging tool most frequently employed to detect fatty liver, as it is widely available, inexpensive, and noninvasive. In adults, ultrasound has a sensitivity of 60–94% and a specificity of 73–93% for the diagnosis of liver fat [24]. However, ultrasound is unable to detect fat infiltration when steatosis involves <30% of hepatocytes and cannot assess disease severity or the presence or absence of NASH. Moreover, the diagnostic sensitivity of ultrasonography decreases when fat liver content is <30% and when BMI exceeds 40 kg/m^2.

Table 26.3 Differential diagnosis of pediatric NAFLD

Metabolic disorders	α-1 antitrypsin deficiency Cholesterol ester storage disease Glycogen storage disease Wilson's disease Tyrosinemia Galactosemia Fructosemia Homocystinuria Organic acidosis Abeta/hypobetalipoproteinemia Defects of bile acid synthesis Hemochromatosis Schwachman syndrome Niemann–Pick disease type C Congenital disorders of glycosylation
	Cystic fibrosis
Infection	Chronic C hepatitis (HCV)
Autoimmune disorders	Autoimmune hepatitis Celiac disease Inflammatory bowel disease Type-1 diabetes mellitus
Drugs	Amiodarone Glucocorticoids Valproic acid
Nutritional	Obesity Metabolic syndrome Starvation Protein–calorie malnutrition Total parenteral nutrition
Endocrinological disorders	Polycystic ovary syndrome Thyroid disorders Type-1 diabetes Hypothalamo-pituitary disorders or surgery
Genetic disorders	Alström syndrome Bardet–Biedl syndrome Lipodystrophy Turner syndrome Dorfman–Chanarin syndrome
Others	Obstructive sleep apnea Alcohol abuse Drug intoxication (ecstasy, cocaine)

Hepatic magnetic resonance (MRI) has a number of advantages including operator independence and reproducibility and includes the possibility of acquiring in-phase (water) and opposed-phase (fat) images in one breath hold. Like ultrasound, MRI cannot distinguish NASH from simple steatosis or detect the presence of fibrosis.

Computed tomography (CT) is more sensitive than ultrasonography for detection of fatty liver, but given its radiation exposure and high costs, CT is rarely used in the diagnostic work-up of NAFLD in children [25].

The recent development of *transient elastography (FibroScan)*, a technique based on the evaluation of tissue elasticity through ultrasound, is a promising noninvasive tool for the detection of advanced fibrosis caused by chronic hepatitis and NASH. However, abdominal obesity may reduce its utility in patients with NASH. The detection accuracy of the method increases with worsening grades of fibrosis [26]. Large studies are required

to define normal values and the accuracy of transient elastography in children.

Liver biopsy remains the only reliable way to precisely diagnose NASH and establish the severity of liver injury and presence of fibrosis. NAFLD is characterized histologically by accumulation of macrovesicular fat in hepatocytes in a patient in whom other causes of liver disease are excluded. The main limitation of liver biopsy is its invasivity, with potential life-threatening complications. Moreover, it is subject to sampling errors that could lead to a misdiagnosis.

The major histological findings in NAFLD/NASH are steatosis, ballooning, inflammation, and fibrosis, though other liver lesions may also be present (Fig. 26.1a–d). However, diagnosis of pediatric NASH can be difficult because histological features commonly seen in adults are less common in children with definite NASH. The National Institutes of Health NASH Clinical Research Network (NASH CRN) established the heterogeneity of pediatric NASH [27, 28], identifying three distinct histological types: *type-1 NASH*, characterized by steatosis with ballooning degeneration and/or perisinusoidal fibrosis, without portal involvement; *type-2 NASH*, characterized by steatosis with portal inflammation and/or fibrosis, in the absence of ballooning degeneration or perisinusoidal involvement; and a *NASH overlap type*, in which characteristics from both types are present [29]. Most pediatric subjects have type-2 NASH, which is more likely to be associated with advanced fibrosis [28].

Some scoring systems for the pathological diagnosis of NASH have been proposed. One of the more commonly used is the *NAFLD activity score (NAS)*, which is the unweighted sum of steatosis, lobular inflammation, and hepatocellular

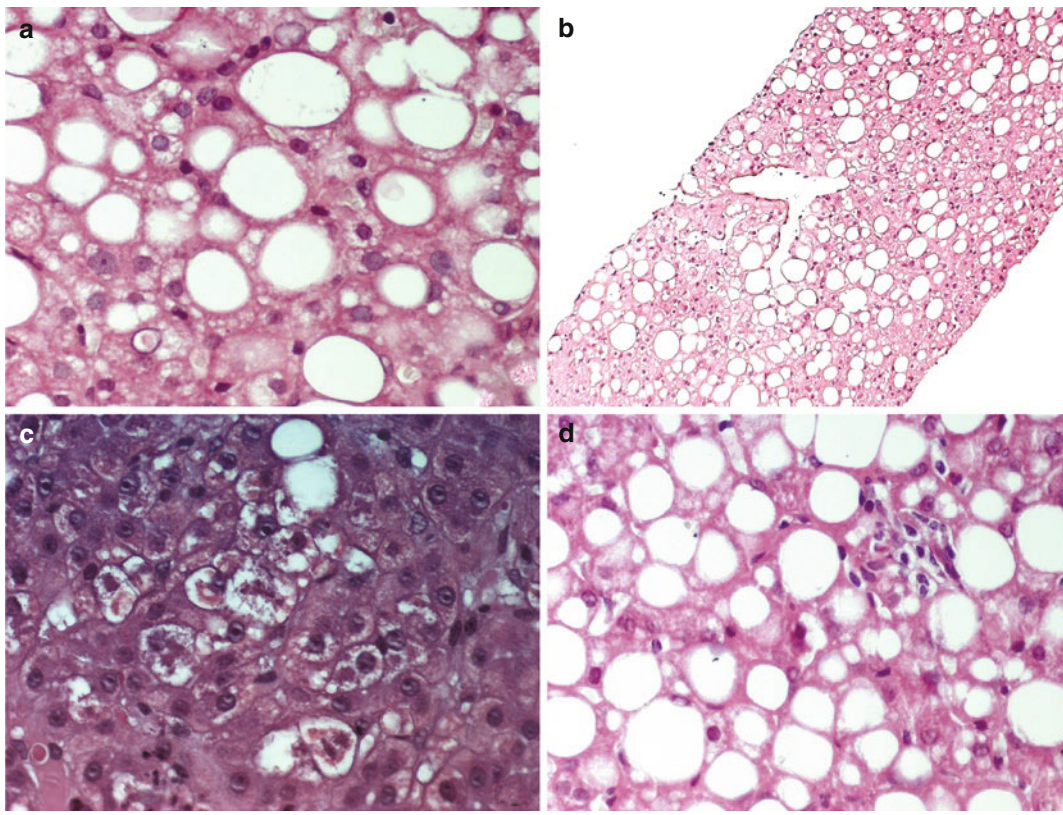

Fig. 26.1 (**a**)–(**d**) Major histological features of pediatric NAFLD/NASH. Steatosis is evident in (**a**) (×40 magnification) and (**b**) (×10 magnification); ballooning and lipogranulomas are present in (**c**) and (**d**), respectively (×40 magnification)

ballooning scores. A NAS of 5 or more correlates with the diagnosis of NASH, whereas a NAS less than 3 is defined as "not NASH" [28].

Natural History

The natural history of pediatric NAFLD remains unknown because of the scarcity of longitudinal prospective studies. The available data, however, suggest that children with NAFLD may be at increased risk for both hepatic and extrahepatic morbidity and mortality [30].

Recent interesting data indicate that hepatic fibrosis represents the most important prognostic marker of progression of liver disease [31]; thus, the prognosis of children with NAFLD is likely related to the severity of baseline liver histology as defined primarily by the fibrosis score [31]. Nevertheless, data on the progression of liver damage in pediatric NAFLD/NASH are scant. Some clinical series have reported cases of cirrhotic NASH in children or in young adults who received a diagnosis of NAFLD in childhood.

Even if the long-term prognosis of NAFLD in children remains uncertain, NAFLD should be considered a potentially progressive form of liver disease in children as well as adults, with a significant risk of cirrhosis and end-stage liver disease even in young adults.

Treatment

The goals of treatment of pediatric NAFLD are to block the progression of liver damage and reverse the histological features of NAFLD/NASH in order to reduce long-term hepatic and extrahepatic complications. In the last few decades, several advances have been made in our understanding of NAFLD pathogenesis, spawning novel therapeutic strategies. Unfortunately, guidelines for the management of pediatric NAFLD are still lacking, and none of the tested drugs have proved totally satisfactory in the treatment of NAFLD/NASH in children [32]. The cornerstone of treatment is represented by change in daily habits and adoption of a healthy lifestyle, but this is very difficult to achieve and maintain in clinical practice.

Non-pharmacological Approaches

Gradual weight loss, as a result of a program combining balanced diet and regular physical exercise, represents the first-line therapeutic approach for treating NAFLD. Several studies describe improvement of laboratory (transaminase concentrations), echographic, and histological features of NAFLD following weight loss, both in adults and children. Weight loss also had metabolic benefits in NAFLD, ameliorating insulin resistance by reducing hepatic delivery of fatty acids and increasing peripheral glucose utilization. Additionally, a positive anti-inflammatory effect has been reported, through inhibition of oxidative stress and reduction in pro-inflammatory adipocytokines [4]. There is currently no strong evidence base regarding dietary composition or intensity or duration of physical activity for pediatric patients with NAFLD. Based on limited data, therapeutic strategies include a balanced diet containing low-fat meats and fish, vegetables, legumes, and fruits and a reduction in sugar-sweetened beverages, saturated fat, starches, and salt [33].

In both animal and human studies, high-fructose intake is strongly associated with metabolic dysregulation and hepatic dysfunction [34]. Consequently low glycemic index diets have been proposed for the dietary therapy of patients with NAFLD, with promising results in a pilot study in children [35]. A significant reduction of daily fructose intake may be associated with metabolic and hepatic improvement, even in the absence of weight loss or dietary energy restrictions.

Reduced dietary intake of saturated fatty acids and increased intake of polyunsaturated fatty acids (omega-3), which reestablish a physiological omega-6/omega-3 ratio (1:4), can also improve insulin resistance and inflammatory status. This supports the restrictions on saturated fat as well as fructose and simple sugars in NAFLD/NASH.

The main problem linked to lifestyle modifications as a treatment of pediatric NAFLD is the difficulty in maintaining compliance of children and their families with the proposed programs, with disappointing results. Reports cite success rates as low as 10% after 2 years of intervention [36].

Pharmacological Approaches

Based on new discoveries related to the pathogenesis of NAFLD and metabolic syndrome, possible pharmacological interventions have been tested in an attempt to reverse liver damage and its complications. The final and ideal goal of a pharmacological approach is to restore normal liver histology, inducing a complete regression of liver lesions. Unfortunately, none of the drugs thus far tested have proven to be totally satisfactory; therefore, novel possible targets or pharmacological associations are now being evaluated.

Insulin-Sensitizing Agents

Given that insulin resistance is a key contributor in the development of NAFLD and NASH, much attention has been placed on insulin sensitizers. Metformin, a biguanide, is the principal insulin sensitizer evaluated in children. Metformin activates the 5′ adenosine monophosphate (AMP)-activated protein kinase (AMPK) pathway, which increases lipid and glucose catabolism. Recently, the large clinical TONIC trial, which enrolled 173 patients, found that metformin (500 mg twice daily) caused only minor reductions in serum transaminase levels and had no significant effect on liver histology [3–9].

Antioxidants

Antioxidants have therapeutic potential because fatty acid oxidation generates reactive oxygen species, which cause direct cellular damage and activate pro-inflammatory cytokines. The number of antioxidants with potential beneficial hepatic effects is increasing, but only a few have been studied systematically. The main antioxidant tested in children has been vitamin E (alpha-tocopherol), a fat-soluble vitamin. Initial small studies showing some efficacy of vitamin E in reducing transaminase levels were not confirmed in the TONIC trial, in which vitamin E was no better than placebo in attaining the primary end point, that is a sustained decrease of ALT levels. Likewise there was only a limited effect on hepatocellular ballooning and NAFLD activity score [37].

Dietary Supplements

Long-chain omega-3 polyunsaturated fatty acids (omega-3, PUFA) are important regulators of hepatic gene transcription, with anti-inflammatory, insulin-sensitizing, and anti-steatotic effects [38, 39]. Interesting results have emerged in randomized controlled trials of omega-3 PUFA in children and adults. Nobili and colleagues [40, 41] showed that oral administration of docosahexaenoic acid (DHA) to children with NAFLD induced at 6 and 24 months an improvement in serum ALT, triacylglycerol levels, insulin sensitivity index, and hepatic steatosis. There were no significant differences between groups treated with 250 mg and 500 mg/day, and there were no major complications of therapy.

Recently, *probiotics* have been proposed as a possible option for treatment of NAFLD. As noted previously, poor diet and slowed intestinal transit, frequent in obese patients, may induce small intestinal bacterial overgrowth (SIBO) and thereby increase the release of endotoxins [mainly gut-derived lipopolysaccharides (LPS)] and tumor necrosis factor (TNF)-α. These inflammatory mediators easily cross the intestinal barrier, which is more permeable in patients with NAFLD, and promote the progression of

NAFLD to NASH with a profibrogenic phenotype [20, 42]. VSL#3, a mixture of eight probiotic strains (*Streptococcus salivarius* subsp. *thermophilus*, *Bifidobacterium* [*B. breve*, *B. infantis*, *B. longum*], *Lactobacillus acidophilus*, *L. plantarum*, *L. casei*, and *L. delbrueckii* subsp. *Bulgaricus*), has been tested in animal models and human studies that include children. These studies show a beneficial effect on the intestinal barrier, reducing inflammation and permeability as well as liver damage, as measured by hepatic steatosis and aminotransferase levels [43, 44]. These results, in association with optimal safety and tolerability, make probiotics a promising therapeutic tool in pediatric NAFLD. However, to confirm these results, further larger randomized studies are still needed.

Novel Developing Therapeutic Strategies

Several novel approaches have been explored only in NAFLD animal models or in adults, with possible future evaluation in children. Farnesoid X receptors (FXR) are expressed in bowel and liver cells, and their activation by ligands may reduce hepatic inflammation through various mechanisms, acting on glucose and lipid homeostasis and controlling bacterial flora growth. Therefore, *FXR agonists* might have a role in the pharmacological therapy of NAFLD/NASH. Future studies are expected, initially in adults, in order to test their efficacy and safety profile [45]. *Incretin mimetics* (exenatide and liraglutide) used for treatment of type-2 diabetes may hold promise for the treatment of NASH, since they decrease hepatic inflammation and lipogenesis and improve hepatic glucose metabolism [11]. Toll-like receptor (TLR) stimulation results in activation of the transcriptional factor NF-KB, crucial for the inflammatory response. Therefore, *TLR antagonists* may represent a novel tool in NAFLD therapy as anti-inflammatory agents, but further investigation is necessary.

Surgical Procedures

In obese adults, *bariatric surgery* has beneficial effects on metabolic comorbidities including NAFLD/NASH, with resolution in about 75% of treated patients. Based on these encouraging results and its acceptable safety profile, bariatric surgery has been proposed in selected cases for the treatment of severe complicated obesity in adolescents [46]. Recently, the Hepatology Committee of European Society of Pediatric Gastroenterology, Hepatology And Nutrition (ESPGHAN) issued a position statement regarding indications for bariatric surgery in severe obese adolescents [47]. In this paper, the experts recommended consideration of bariatric surgery for patients with BMI >40 kg/m^2 and severe comorbidities (including NASH with advanced fibrosis) or with BMI >50 kg/m^2 and mild comorbidities. Temporary nonsurgical devices, such as mini-invasive intragastric balloons, represent another possible approach. In 2015, a pilot study of the effects of intragastric balloons in obese adolescents with NAFLD demonstrated a positive effect on BMI and aminotransferase levels [48].

Conclusions

During the last two decades, NAFLD has been transformed from an unknown disease in the pediatric setting to the most common cause of chronic liver disease in children and adolescents in industrialized countries. Although the natural history of NAFLD in young children must be further defined in longitudinal studies, it is clear that NAFLD/NASH should be considered a potentially progressive condition that may evolve to advanced forms of liver disease. Cases of cirrhosis have been described even in children, and end-stage liver disease requiring liver transplantation has been reported in young adults. Research efforts must focus on the development of better tools for screening, diagnosis, and treatment of pediatric NAFLD in order to prevent the development of hepatic and extrahepatic complications that interfere with quality of life.

Editor's Comments and Question

The prevalence of fatty liver disease is higher in teenage males than females, in part because estrogen protects against visceral fat deposition and reduces hepatic lipogenesis. Ovariectomy or knockout of the estrogen receptor[a] in mice increases liver fat deposition, as does deletion of aromatase,[b] which converts androgens to estrogens. Likewise, NAFLD is more common in women with Turner syndrome and those treated with the estrogen receptor antagonist tamoxifen. Conversely, excess androgens promote hepatic lipogenesis in females[c] and, together with visceral adiposity and insulin resistance, may explain the higher rates of fatty liver disease in teenagers with polycystic ovary syndrome.[d]

The development of fatty liver disease reflects the interplay of environmental and genetic determinants. Among the genes implicated in the pathogenesis of fatty liver disease, PNPLA3 appears to play a central role. The rs738409 C > G single nucleotide polymorphism of PNPLA3, which encodes an Ile148Met variant protein, is expressed at high rates in Hispanics and low rates in African-Americans and predisposes to hepatic steatosis, cirrhosis, and hepatocellular carcinoma. It is currently unclear how the mutant protein facilitates liver fat storage and fibrosis, though studies in mice suggest that the variant reduces hepatic acylglycerol hydrolysis and may increase hepatic lipogenesis.[e]

Interestingly expression of wild-type PNPLA3 is induced by carbohydrate feeding and insulin.[e] Do you think that progression of liver disease in obese subjects with the PNPLA3 mutation might be driven by glucose- and/or insulin-induced overexpression of the mutant protein?

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Authors' Response

The patatin-like phospholipase containing domain 3 gene (*PNPLA3*) is the most important gene involved in the development of hepatic steatosis, interacting with environmental NAFLD risk factors. Among environmental factors involved in this interesting interaction, some nutrients appear. Some animal studies have shown that expression levels of hepatic *PNPLA3* mRNA are low during fasting and increase ≈90-fold in response to carbohydrate feeding. This effect occurs as a secondary effect of insulin-mediated upregulation of sterol regulatory element-binding protein 1 (SREBP-1). Even if it is still unclear how the PNPLA3 I148M polymorphism induces the progression of liver damage, *GG* subjects

could be more susceptible to the effects of dietary sugar because transcriptional upregulation of *PNPLA3* would still result in a protein with severely reduced function and therefore reduced hydrolysis of hepatic triglycerides.

Considering the complex interplay between genetic determinants, metabolic status, and environmental factors, it is suitable that hyperinsulinemia induced by obesogenic lifestyle in susceptible individuals may drive liver damage in GG subjects, but further studies are needed in order to clarify this aspect.

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27 Pathogenesis of Hypertension and Renal Disease in Obese Children

Tracy E. Hunley, Vance L. Albaugh, and Valentina Kon

Introduction

Obesity, hypertension, and renal injury are linked by complex inter-relationships. Obesity-associated metabolic abnormalities promote both systemic hypertension and renal injury while hypertension results from and contributes to progressive renal damage. Obesity with or without hypertension also predisposes to chronic kidney disease and accelerates its progression. This chapter will discuss the pathogenesis of obesity-associated hypertension and renal disease and reflect on their implications for therapy.

Epidemiology

Overweight and obesity are associated with much comorbidity including type 2 diabetes, dyslipidemia, atherosclerosis, nonalcoholic steatohepatitis, and obstructive sleep apnea. However, the most common comorbidity of childhood adiposity is elevated blood pressure (BP) which parallels increased trends in overweight and obesity (Fig. 27.1). Hypertension in turn is a leading contributor to the global disease burden promoting coronary and cerebrovascular disease and kidney damage. There is now strong evidence that elevated BP in childhood is a reliable predictor for development of hypertension in adulthood [1]. The Bogalusa Heart Study emphasizes that rather than being additive, cardiovascular risk factors that develop during childhood have synergistic effects on the severity of cardiovascular disease (CVD) [2–4]. Critically, overweight and obese children who have hypertension are more likely to have both excess weight and elevated BP persist into adulthood and are more likely to develop cardiovascular and renal disease and to have shorter life span than with those with either risk factor alone.

Life-threatening complications of hypertension rarely manifest during childhood. However, several intermediate endpoints of hypertensive end-organ damage are increasingly recognized in obese children including left ventricular hypertrophy, carotid artery intima-media thickness (CIMT), endothelial dysfunction, proteinuria, and renal scarring [5]. Remarkably, hypertension-related changes in cardiac structure have been documented in children as young as 24 months [6]. Recently, the Young Taiwanese Cohort study reported that overweight/obese Asian children

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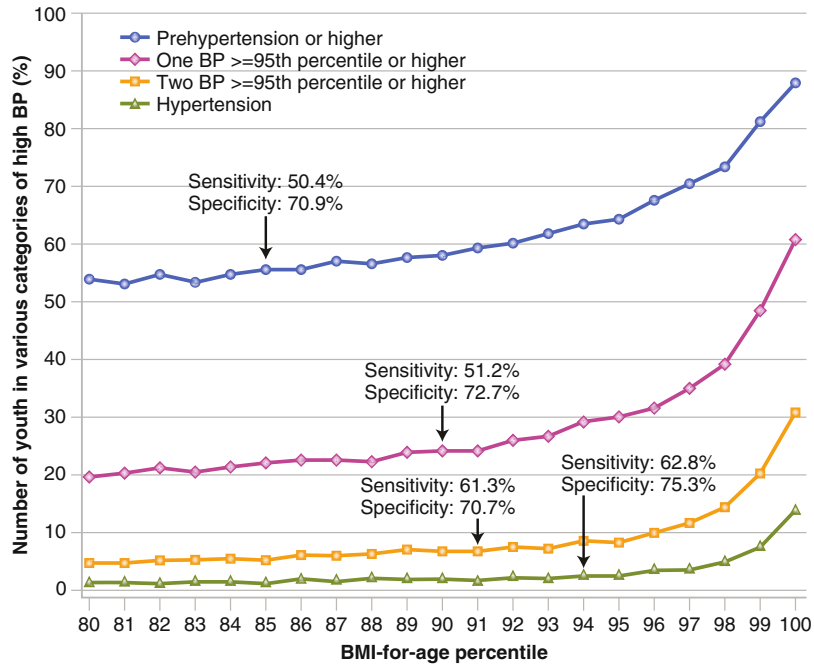


Fig. 27.1 Prevalence of high blood pressure in youth (6–17 years) by BMI-for-age percentile. Sensitivity and specificity are given as the optimum thresholds (Used with permission of John Wiley and Sons from Koebnick C, Black MH, Wu J, Martinez MP, Smith N, Kuizon B, Cuan D, Young DR, Lawrence JM and Jacobsen SJ. High blood pressure in overweight and obese youth: implications for screening. J Clin Hypertens (Greenwich). 2013;15:793–805)

are at increased risk of prehypertension/hypertension and increased CIMT after a mean follow-up of only 8.5 years [7]. These findings fit with projections that childhood hypertension will significantly impact future burden of cardiovascular and renal diseases in adulthood and hasten development of these complications in the pediatric population. This scenario is especially worrisome because diagnosis of hypertension typically lags about 10 years behind development of obesity.

The prevalence of hypertension in children and adolescence has been estimated to be 3–5% [8–11]. Population-based cross-sectional studies show a strong association between hypertension prevalence and excess weight. A large retrospective study of >100,000 children age 3–17 documented the parallel changes between baseline BMI, or change in BMI, with change in BP percentiles among all age-gender groups followed for a median of only 3.1 years [12]. Extremely obese youth were ten times, moderately obese four times, and overweight twice as likely to be hypertensive that normal-weight youth. It should be underscored that these numbers likely underestimate the true incidence of elevated blood pressures in the pediatric population because of the difficulties in obtaining pressure readings in children and the natural changes in blood pressure levels occurring during normal maturational development.

In adults, the diagnosis of hypertension depends on documentation of blood pressure readings above absolute cut-points on at least two occasions: prehypertension is classified as systolic BP 120–139 and diastolic BP 80–89 and hypertension is classified as systolic BP ≥140 and diastolic BP ≥90. In children, diagnosis is more complicated. The current guidelines define prehypertension as BP between the 90–95th age-, sex-, and height-determined percentiles and hypertension as BP between the 95–100th age-, sex-, and height-determined percentiles with elevated values documented on ≥3 separate occasions. The National Health and Nutrition Examination Survey (NHANES) found that 10% of 8–17-year-olds have high and borderline-high BP values [13]. Although this very large study included more than 1700 children and adolescents, the measurements were obtained using up to three readings on a single visit and thus do not meet the criterion for diagnosis of pediatric hypertension. The more cumbersome process

required to establish hypertension in children was also proposed as an explanation for the low frequency of correct hypertension diagnosis made in a large cohort of children and adolescents followed in primary care practices in Ohio [14]. That study of more than 14,000 children found that of the 507 with blood pressure values documented to be in the hypertensive range only 26% had a diagnosis of hypertension entered in the medical record. Notably, obesity was one of the factors that increased the odds of recording the diagnosis, an observation that likely reflects the growing recognition of the link between obesity and hypertension in childhood.

In the past, the diagnosis of hypertension in childhood prompted a search for an underlying cause. It is now appreciated that the majority of pediatric hypertension is not secondary to a detectable medical condition but "essential," with no directly identifiable cause, especially in older children and adolescents in whom it is responsible for 85–95% of diagnoses. There is little doubt that the overarching reason for the increasing incidence of essential hypertension in childhood is the epidemic increase in weight and adiposity. Analysis of NHANES data from 1988–1994 to 1999–2008 revealed the odds of elevated BP increased by 27% [15]. Obesity was independently associated with prehypertension and hypertension in both boys and girls across all age groups [6, 8, 16, 17]. Figure 27.1 depicts results of a large cross-sectional study of >230,000 children (age 6–17) that suggests that the threshold for prehypertension is at 85th BMI-for age percentile while hypertension is at the 94th BMI-for age percentile [16]. It is estimated that for each decile increase in BMI, systolic blood pressure increases by 10mmgHg while diastolic blood pressure increases by 3 mmHg [18, 19].

Excess weight during adolescence appears especially harmful. A study of 7746 adolescents reported that the attributable fraction (AF) for increased BMI is highest among boys 12–13 years (AF = 39%) and girls 15–16 years (AF = 39%), values which are much higher than 5% and 9% estimated in 5–6-year-old boys and girls, respectively. A recent analysis of 13 studies of overweight adolescents found a 0.34 correlation between BMI and systolic BP and 0.21 correlation between BMI and diastolic BP [4]. These findings indicate that overweight adolescents are more likely to have isolated systolic BP or elevation in both systolic and diastolic BP than an isolated increase in diastolic pressure.

While it is clear that overweight and obesity increase the risk of hypertension, not all overweight/obese children develop elevated BP, and the phenotypic characteristics which separate obese children with and without hypertension remain obscure. A variety of factors have been shown to increase the likelihood of hypertension in overweight children including male gender, older age, pubescence, dyslipidemia, family history of hypertension, diabetes, and cardiovascular disease, diets high in fat and salt, sedentary behavior, insufficient physical activity, low birth weight and ethnicity (Fig. 27.2) [20, 21]. As in adults, the prevalence of overweight and elevated blood pressure is higher in Native Americans, African Americans, Hispanics, and Asians than in white children. Recently Indian and Turkish children have also been reported to be at particular risk for obesity-related hypertension. A British study observed that obese Indian adolescents were almost nine times more likely to develop hypertension than obese white adolescents [22]. Hypertension was not significantly higher in nonobese Indian adolescents, suggesting that the effect of ethnicity in this population is weight-dependent. Among modifiable factors, video game playing and television watching increase hypertension risk in overweight children [23]. Indeed, video game playing was the only behavior independently linked to elevated BP in overweight adolescents [23]. By contrast, cardiorespiratory fitness (measured by ability to supply oxygen to skeletal muscles), although not high levels of physical activity per se, appears protective against developing obesity-induced hypertension [24].

While increased adiposity in childhood and adolescence is associated with morbidity and mortality in adulthood, it is currently not clear if childhood obesity per se has direct impact on cardiovascular complications or if childhood obesity that begets obesity in adulthood is the

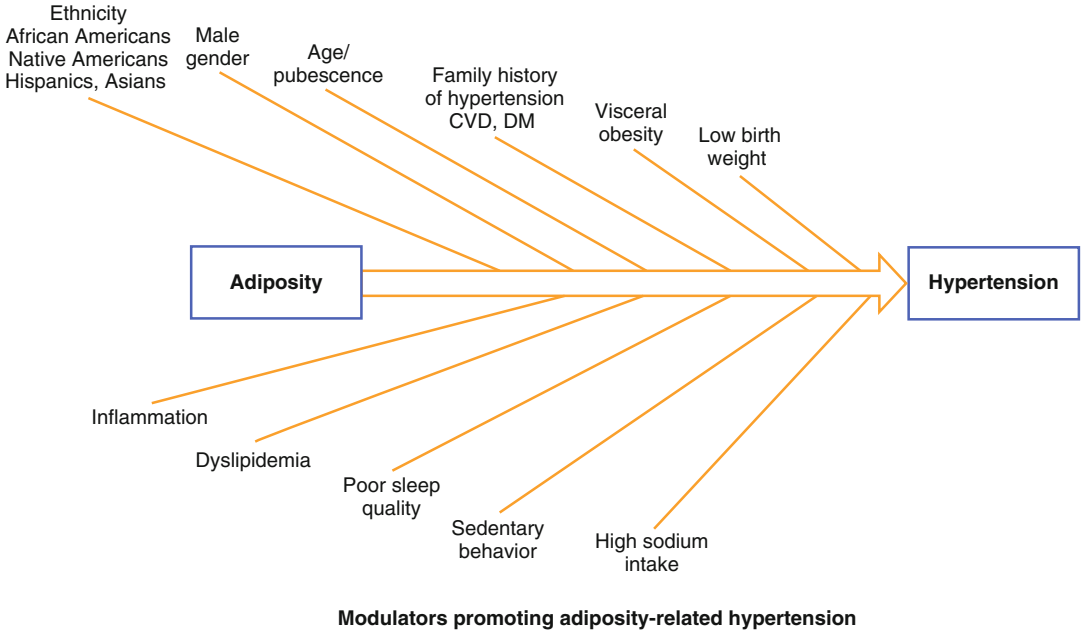


Fig. 27.2 Modulators promoting adiposity-related hypertension

pathway for developing the adult obesity-related morbidity and mortality. In adults, risk estimates from the Framingham Heart Study indicate that 78% of hypertension in men and 65% in women is directly attributable to excess body mass [25]. The influence of obesity depends on the duration of overweight with greater impact of longer time of excess adiposity. In children, mean age 10.2 years followed for 4.5 years, BMI >85th% was associated with fourfold increase in elevated blood pressure across all age groups [26]. It is interesting that the dose-response between excess weight and elevation in blood pressure occurs not only with weight accrual but also with weight reduction. Thus, reduction in adiposity prior to adulthood is associated with less hypertension in adulthood, while control of hypertension before adulthood leads to less elevated BP and subclinical atherosclerosis in adulthood [7, 27]. This means that lifestyle modifications that increase lean body mass and reduce abdominal obesity correlate with improvement in markers of cardiovascular injury in hypertensive children [28] and provide an opportunity to prevent or intervene prior to reaching adulthood.

Blood Pressure Homeostasis

Blood pressure is the force exerted by blood against a unit area of vessel wall and is defined as

$$BP = CO \times TPR = (HR \times SV) \times TPR$$

where BP is blood pressure, CO is cardiac output, HR is heart rate, SV is stroke volume, and TPR is total peripheral resistance. CO and TPR depend on the extracellular fluid volume, which is determined primarily by the renal excretion of sodium and water.

Adiposity affects all of these parameters. Obese and overweight individuals have increased resting CO by virtue of increased heart rate, which reflects heightened sympathetic tone and reduced vagal tone. Perturbed autonomic regulation has been implicated in obesity-related blunting in heart rate variability that is linked to cardiovascular disease, including hypertension. Obesity also increases

stroke volume; this results from expansion in the circulatory volume necessary to perfuse the increased adipose tissue mass and fat-free mass that accompanies weight gain. The increased stroke volume also reflects increased ventricular filling pressure and blood volume that follows an increase in tubular sodium reabsorption. As in all hypertensive states, obesity-associated hypertension is associated with impaired pressure natriuresis, a mechanism that normally allows the kidney to regulate systemic BP. Thus, obese individuals have an inappropriately limited natriuretic response to a saline load which necessitates that obese individuals require a higher blood pressure than those of normal weight to excrete given sodium load.

The homeostatic mechanisms that maintain the balance between cardiac output and peripheral vascular resistance are disrupted in obesity. Compared with normal weight or obese individuals who are normotensive, peripheral vascular resistance is increased in hypertensive obese individuals despite increased CO. This abnormal vascular response is especially apparent in obese/overweight individuals whose fat is centrally distributed. Indeed, even in the absence of overt obesity, there is an independent association between visceral adiposity and increased CO and/or increased (or insufficiently reduced) vascular resistance. This suggests that the metabolically active visceral fat contributes directly or indirectly to body requirements for blood flow supply. The underlying mechanisms include enhanced vasoconstriction, endothelial dysfunction with impaired vasodilation, and vascular wall remodeling associated with deposition of lipids, advanced glycation end products, and extracellular matrix components that impair normal adjustments in vasomotor tone (Fig. 27.3).

Early stages of overweight and obesity are characterized by an exaggerated vasoconstrictive response. However, as obesity becomes severe, there ensues a progressive impairment in the vascular response. Such findings suggest that the initially heightened vasomotor response is followed by vascular remodeling that limits the hemodynamic response. Markers of endothelial dysfunction and vessel remodeling, including impaired brachial artery flow-mediated dilation and increased carotid artery intima-media thickness, previously established in adults, have now been well documented in obese children.

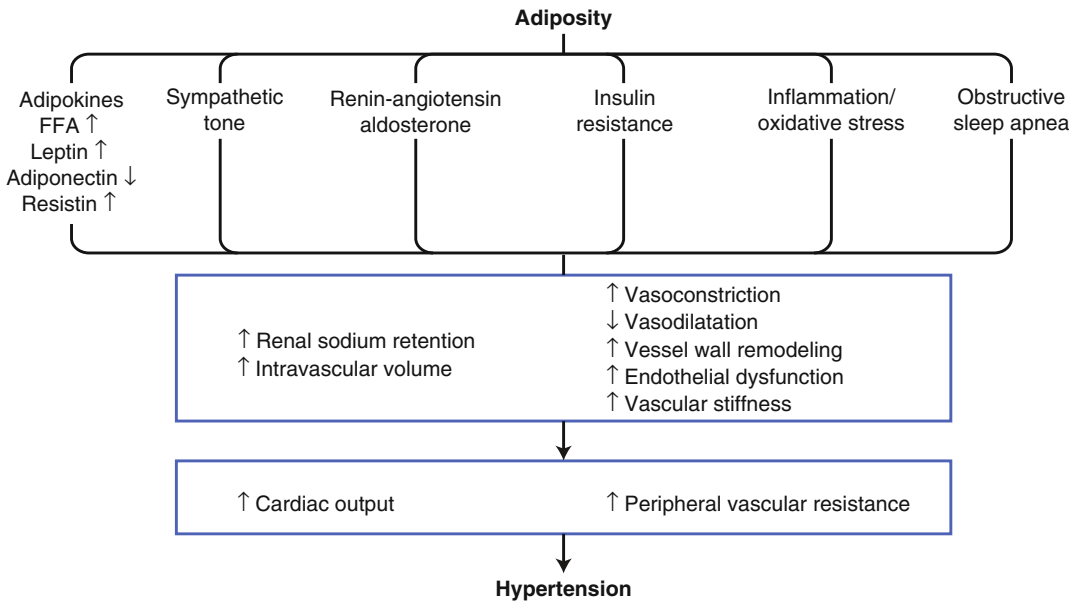


Fig. 27.3 Pathophysiologic mechanism contributing to obesity-related hypertension

Pathogenesis of Hypertension in Obesity

Sympathetic Nervous System Activity (SNS)

There is strong support for an important pathophysiological role of an overactive SNS in obesity-associated hypertension. Studies in experimental animals show that a high calorie diet that causes obesity leads to hypertension. This effect is not seen in obese animals with pharmacologic blockade of α- and β-receptors or in those with bilateral renal denervation that achieve similar weight gain. Obese humans have heightened SNS activity and elevated levels of plasma and urinary catecholamines [29]. The degree of SNS activation is especially dependent on body fat distribution, with central obesity causing greater activation than subcutaneous obesity. The positive correlation between waist circumference and muscle sympathetic nerve activity has been documented in both obese hypertensive adults and children. Compared to normotensive obese children, hypertensive obese children have significantly higher heart rate, increased blood pressure variability, and higher excretion of urinary epinephrine and norepinephrine [30].

The deposition of visceral fat appears to be modulated by sex hormones, particularly androgens. In a cohort of 324 adolescents, visceral fat mass correlated with elevated BP and increased sympathetic activity in adolescent boys, but not girls [31]. Functional polymorphisms of androgen receptors, BP, and sympathetic activity found that high activity androgen receptors are associated with higher BP [32]. In this study, boys, but not girls, with a high activity receptor form had more visceral fat and greater SNS activity. The SNS-to-adiposity connection is further solidified by observations that weight loss leads to reduction in muscle sympathetic nerve activity [33]. In adolescent boys with primary hypertension reduction in waist circumference correlated with changes in BP levels and amplitude as well as the peaks and troughs in HR [28].

The mechanism underlying overweight/obese SNS activation includes not only overeating but also contribution from concurrent risk factors related to the renin-angiotensin-aldosterone system, hyperinsulinemia, adipokines, obstructive sleep apnea, and heightened immune responses (see below). It is interesting that overeating-induced stimulation of the autonomic nervous system has been suggested to be an adaptive physiologic response to stabilize body weight by increasing thermogenesis [34]. However, persistent overeating causes chronic autonomic activation that triggers cardiovascular and renal responses that over the long-term promote sustained elevation of blood pressure by direct vasoconstriction and cardiovascular remodeling and increased heart rate, stroke volume, and cardiac output. Obesity-induced changes in cardiac response not only reflect increases in sympathetic activity but rather decreased parasympathetic tone. By contrast, increased sympathetic activity in the kidneys drives obesity-driven hypertension by promoting intrarenal vasoconstriction and by increasing renal tubule sodium reabsorption that expands the extracellular fluid volume.

Obese children appear especially susceptible to the adverse consequences of sympathetic overdrive [28]. Although there are no studies in children, open label trials have documented efficacy of renal denervation in adults with resistant hypertension, many of whom were obese [35]. However, a recent blinded, sham-controlled study that included overweight adults (SYMPLICITY HTN-3) failed to show a major effect of renal denervation on blood pressure after 6 months [36].

As noted, not all obese individuals develop hypertension and not all obese hypertensives show increased SNS activity. For example, Pima Indians have increased propensity for obesity but do not have heightened sympathetic tone and do not develop hypertension to the same degree as other racial groups. These observations suggest that BP is modulated by ethnic/genetic factors that may counteract the effects of adiposity on sympathetic drive; such factors may promote the differential reactivity of vascular beds. Thus, obese but normotensive individuals have elevated sympathetic nerve activity in skeletal muscle but normal vasodilatative response to α-adrenergic

receptor blockade [37]. Similar counterbalancing effects may be provided by other vasodilators including nitric oxide and natriuretic peptides or local regulators of sympathetic nerve activity, such as insulin, leptin, or adiponectin.

Recently, the CNS proopiomelanocortin pathway, which regulates appetite and energy expenditure, has been linked to obesity-induced activation of sympathetic tone and hypertension. Proopiomelanocortin-expressing neurons stimulate the release of a-melanocyte-stimulating hormone, an agonist for melanocortin 3/4 receptors (MC3/4Rs) [38]. Deficiencies in either of these components cause severe obesity. Chronic activation of MC4R increases BP, although a functionality intact proopiomelanocortin-MC4R system is necessary for obesity to increase sympathetic tone and produce hypertension. Together these observations indicate that while obesity is regularly accompanied by enhanced SNS, the heightened sympathetic tone is tempered by several layers of compensatory mechanisms and local factors that determine the final/sustained vascular tone. Currently, it is unclear whether obesity itself or increased SNS is the primary disturbance. For example, the recent Tecumeh Blood Pressure study found that children with faster heart rate at the age of 7 went on to have higher blood pressure and greater subscapular skinfold thickness at age 20, supporting the idea that SNS activation is actually the primary disturbance underlying obesity-linked hypertension.

Renin Angiotensin Aldosterone System (RAAS)

In addition to overactive SNS activity, the renin-angiotensin-aldosterone system (RAAS) appears causal in obesity-related hypertension. A recent study of obese adolescents found a positive correlation between levels of renin and aldosterone and 24-h blood ambulatory pressure, with the more severely obese teens having the highest renin activity [39]. Activated RAAS contributes to hypertension by increasing sympathetic tone and promoting insulin resistance and hyperinsulinemia. Activation of RAAS in adipose tissue itself contributes to hypertension. White adipose tissue, particularly visceral as opposed to subcutaneous adipose, has all the molecular machinery for local angiotensin (AII) generation and AII-stimulated signal transduction. Overexpression of angiotensinogen in adipose tissue dramatically increases BP in mice through mechanisms that include an autocrine positive feedback loop that serves to amplify synthesis of its components as well as upregulated expression of its receptors. Activated RAAS also encourages obesity by stimulating appetite and by acting as a trophic factor for adipocytes, increasing adipocyte mass and preadipocyte differentiation and thereby fueling a vicious cycle. The critical role for adipocyte RAAS in obesity-associated hypertension is demonstrated by studies showing that selective ablation of adipose tissue angiotensinogen does not lessen weight gain associated with high fat diet feeding but prevents development of elevated blood pressure [40].

Just as increasing adiposity is accompanied by increased RAAS activity, reduction in weight is followed by decrease in RAAS activity. For example, dietary restriction that produced a 5% reduction in weight in adults led to a 7 mmHg reduction in ambulatory systolic blood pressure that was accompanied by a 27% decline in angiotensinogen, 43% decline in renin, 12% reduction in adipose tissue ACE activity, and 20% reduction in the angiotensinogen expression in adipose tissue [41]. Mice deficient in components of the RAAS are leaner and gain less weight when fed a high fat diet than mice with an intact RAAS. Obese animals undergoing antagonism of AII actions have less sodium retention, reduced volume expansion, and lower systemic blood pressure [42]. Obese Zucker rats appear more sensitive to blood pressure lowering effects of RAAS blockade than lean rats [43]. In humans, RAAS antagonism is effective in lowering blood pressure in obese individuals. Several large clinical studies have shown that RAAS blockade improves insulin sensitivity, prevents or delays the onset of diabetes, and reduces CV events [42]. Interestingly, although there are no large-scale direct comparisons of their effectiveness in obese versus lean individuals,

antagonism of mineralocorticoid receptors appears to be an important therapy to lower blood pressure in obesity hypertension. Experimental and clinical studies show mineralocorticoid receptor antagonisms such as eplerenone decrease blood pressure in obese individuals with resistant hypertension on angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) treatment [44]. The findings support the growing recognition that factors other than AII may activate mineralocorticoid receptors and/or that obesity enhances sensitivity of the aldosterone-mediated mineralocorticoid activation.

Race appears to have an impact on the relationship between RAAS and adiposity. A study comparing the effects of adiposity on RAAS in black and white children revealed that increasing adiposity is accompanied by suppressed levels of plasma renin activity in black children; in contrast, BMI and renin were unrelated in white children, whose elevated aldosterone was thought related to non-angiotensin II stimuli [45]. Since suppressed renin reflects volume expansion, it is possible that blacks retain more sodium than whites. In view of the higher prevalence of both obesity and hypertension in blacks, including children and adolescents [46], a synergistic adiposity effect that may compound African American susceptibility to hypertension through increased salt sensitivity.

Adipose Tissue-Related Metabolic Factors

Adiposity

As noted previously, not all obese individuals become hypertensive. There is now strong evidence that fat distribution, specifically visceral adiposity, is a key determinant of hypertension. Even normal weight individuals who demonstrate insulin resistance and hypertension have increased intra-abdominal fat mass. Waist circumference and waist-to-height ratios are good predictors of hypertension in children, especially obese children, suggesting a pathophysiologic role of visceral fat per se.

Visceral fat, as opposed to subcutaneous or intramuscular fat, has strong associations with many pathophysiologic features. Accumulation of large poorly differentiated preadipocytes in visceral fat augments production of bioactive molecules including angiotensinogen, plasminogen activator inhibitor, endothelin, and reactive oxygen species that can vasoconstrict and remodel blood vessels. Visceral fat is often infiltrated by macrophages that constitute an important source of pro-inflammatory mediators including TNF-α, IL-6, monocyte chemoattractant protein 1 (MCP-1), and inducible nitric oxide synthase (iNOS). Fatty acids released by adipocytes stimulate TNF-α release by macrophages which, in turn, can enhance production of IL-6 by fat cells, further amplifying the inflammatory response. Indeed, mice deficient in IL-6 have a blunted hypertensive response to stress [47]. Many of the bioactive substances produced by macrophages also inhibit preadipocyte differentiation, further expanding a population of large, dysfunctional, insulin-resistant adipocytes that may fuel the vicious cycle between obesity and hypertension.

Adipokines

Fat, particularly visceral adipose tissue, is an active endocrine organ that secretes bioactive substances collectively known as adipokines, some of which have been implicated in development of hypertension. *Leptin* is an adipocyte gene product that regulates food intake, energy expenditure, and intracellular lipid homeostasis. Circulating levels of leptin closely parallel fat stores, increasing with overfeeding and decreasing with fasting or caloric deprivation. Despite severe obesity, known mutations in leptin or its receptor are not accompanied by hypertension. On the other hand, leptin replacement in deficient mice increases blood pressure despite reduction in body weight. Moreover, increased leptin levels in obesity are associated with increased blood pressure. Indeed, about half of the correlation between blood pressure and body weight has been attributed to the variance of leptin levels. A recent prospective population-based study found higher leptin levels not only associated with

prevalent hypertension but also predicted 5-year incident hypertension [48].

The mechanisms by which higher leptin levels cause hypertension involve the sympathetic nervous system, RAAS, inflammatory cytokines, and modifying factors such as duration of hyperleptinemia and the site of leptin action, e.g., systemic or central [49]. High fat diet feeding increases circulating levels of leptin and increases BP in obese rodents and rabbits through pathways that include activation of leptin receptors in the dorsomedial hypothalamus linked to stimulation of sympathetic outflow to lumbar and renal regions [50]. The systemic hypertension and renal sympathetic nerve activity can be blocked by central infusion of a leptin antagonist [51]. The persistent sympathetic activation reflects selective leptin resistance, whereby the anorexic effect of leptin is attenuated but its action to increase sympathetic tone and blood pressure remain intact through activation of the hypothalamic NF-kB pathway and modulation in expression of leptin receptors. Adolescents have leptin resistance along with greater adiposity and inflammation that were recently linked to higher sodium consumption [52]. The selective resistance involves differential intracellular signaling pathways and brain-specific sites of action for cardiovascular versus metabolic effects of leptin. Recent observations suggest that high fat diet driven activation of sympathetic tone and hypertension involves an enhanced angiotensin-elicited hypertensive response through leptin-mediated upregulation of RAS components and inflammatory cytokines in the lamina terminalis and paraventricular nucleus of the brain [53].

Central leptin antagonism prevented hypertension sensitization in this high fat diet model, providing evidence that CNS leptin-RAS interactions are causally linked in obesity-associated hypertension. The net effect of leptin-mediated activation in sympathetic tone encompasses all pathways described above including increased heart rate, vasoconstriction and enhanced renal reabsorption of sodium and water. Normally, acute administration of leptin promotes diuresis. However, chronic increases in circulating leptin blunt the normal leptin-induced increase in urinary sodium and water excretion; this effect appears to be independent of systemic or renal hemodynamics and likely reflects a direct tubular effect. The antidiuretic effect reflects enhanced renal sympathetic tone and decreased local NO that attenuate the effects of leptin on the renal tubules.

In addition to the strong evidence linking leptin to obesity-associated hypertension, recent data also suggest participation of another adipose tissue-generated cytokine, *resistin.* In rodents, white adipose tissue is the main source of resistin while in human adipose tissue resistin expression is low and it is the macrophages of adipose tissue that are the main source of this adipokine. Similar to leptin, resistin is sympatho-excitatory and its levels correlate with hypertension. It is possible that the effects of leptin and resistin act in synergy to amplify and sustain adipokine role in hypertension.

Adiponectin is the most abundant plasma protein produced by adipose tissue. In contrast to other adipocytokines which are elevated in obesity, an inverse relationship characterizes the relationship between adiponectin and hypertension in many animal models and human disease. Hypoadiponectinemia was an independent risk factor for hypertension in cross-sectional and prospective studies in lean and obese hypertensive adults and adolescents, even after adjustments for BMI, age, glucose and cholesterol levels [54]. In obese as well as normal-weight children, adiponectin level was inversely correlated to hypertension [55]. It is notable that antihypertensive treatment (ACE inhibition with ramipril or angiotensin receptor antagonism with valsartan) elevates circulating adiponectin level and insulin sensitivity in parallel with their effects on blood pressure. A subset of obese individuals with adiponectin concentrations similar to those of normal weight subjects did not have metabolic abnormalities including hypertension [56]. Experimentally, adiponectin replenishment ameliorated obesity-related hypertension in the KKAy mouse model, while hypertension in salt-fed adiponectin-deficient mice was reversed by adiponectin treatment [57]. Hypoadiponectinemia likely contributes to

hypertension by way of endothelial dysfunction that is independent of insulin resistance, BMI, or lipid status; adiponectin upregulates endothelial NO synthase expression and reduces production of reactive oxygen species (ROS), resulting in heightened NO production and bioavailability in endothelial cells.

In addition to adipokines, acute elevation in plasma non-esterified fatty acids (NEFA) increases blood pressure in experimental animals and humans [58]. Chronic elevation of NEFA observed in those with central obesity correlates with elevated blood pressure. Baseline elevation of NEFA is a highly significant independent risk factor for developing hypertension in nondiabetic, non-hypertensive men. The pathophysiological mechanisms involve stimulation of α-adrenergic tone which causes vasoconstriction, reduces baroreflex sensitivity, and enhances tubular sodium reabsorption. NEFA also stimulate expression of angiotensinogen in preadipocytes and aldosterone in adrenal cells; these can increase blood pressure through vasoconstriction, vascular remodeling, and sodium reabsorption. NEFA reduce endothelial nitric oxide synthase and thus nitric oxide (NO)-mediated vasodilatation as well as insulin-induced vasodilatation, which is NO-dependent. Finally, NEFA increase oxidative stress in vivo and in vitro, another mechanism postulated for development of hypertension.

Obstructive Sleep Apnea (OSA)

OSA is an independent risk factor for the presence as well as future development of hypertension. Up to 50% of hypertensive adults have obesity-linked OSA, the severity of which parallels an elevation in blood pressure that is especially resistant to antihypertensive treatment. A 10% excess of body weight increases by sixfold the risk of developing OSA. Even in the absence of obesity, OSA predicts hypertension, while treatment of OSA can reduce blood pressure. This benefit is particularly significant in those with resistant hypertension. While there is little doubt about the association between OSA and hypertension, the precise contribution of OSA to hypertension remains unsettled, especially in children [59]. This reflects the multifactorial pathogenesis of each process, the lack of consensus for diagnostic criteria in children, and the uncertainty as to what portion of which component of OSA (sleep fragmentation, duration, and intermittent hypoxia) can promote the development of hypertension. Nevertheless, children with OSA have blood pressure dysregulation that includes elevated diurnal and nocturnal systolic and diastolic pressure, greater mean BP variability during wakefulness and sleep, a higher night-to-day systolic BP, and marked reductions in the physiological nocturnal dip in blood pressure [60]. Children with OSA also exhibit increases in morning BP surges, BP load, and 24-h ambulatory BPs that are associated with ventricular remodeling. Interestingly, even individuals with primary snoring, which is considered a mild form of OSA, have increased daytime blood pressure with reduced arterial dispensability. It is therefore likely that the link between OSA and hypertension demonstrated in adults begins early in childhood, particularly in obese children.

The pathogenesis of increased blood pressure and hypertension with OSA includes recurrent episodes of apnea and intermittent hypoxia/carbon dioxide retention and negative intrathoracic pressures which depress myocardial contractility, elevate heart rate, and activate the sympathetic nervous system and RAAS which in turn increase sodium retention and promote metabolic dysfunction such as insulin resistance and hyperinsulinemia. OSA has been linked to enhanced inflammation and oxidative stress which likely disrupt nitric oxide bioactivity and lead to endothelial dysfunction and elevated blood pressure. OSA may also contribute to development of hypertension through circadian misalignment that disrupts the autonomic balance and diurnal rhythm of cardiac output. In adults, treatment directed at lessening OSA with CPAP appears particularly effective when combined with pharmacologic antihypertensives, especially in the

subgroup with resistant hypertension. Because therapeutic adherence is particularly challenging in children, there is currently little information as to the efficacy of positive airway pressure to reduce hypertension in this population.

Hyperinsulinemia/Insulin Resistance

Hypertension is regularly associated with increased plasma levels of insulin. However, hyperinsulinemia per se does not cause hypertension. Chronic insulin administration in animals or humans does not lead to hypertension, and patients with insulinomas do not have elevated blood pressure. Instead the hyperinsulinemia associated with insulin resistance plays a central role in pathways that promote hypertension. For example, insulin acts centrally to augment sympathetic tone; intracerebrovascular administration of insulin increases central sympathetic nerve activity that involves disinhibition of neuropeptide Y neurons in the arcuate nucleus of the hypothalamus [61]. Moreover, hyperinsulinemia induces hyperplasia and hypertrophy of adipocytes that promote oxidative stress and inflammation by increasing production of adipokines, free fatty acids, and inflammatory cytokines. Hepatic and peripheral insulin resistance also activate synthesis of several RAAS components, upregulating AT1 receptors by stabilizing the AT1 receptor mRNA. These pathophysiologic pathways are well established in adults. In children, the relationship between insulin resistance and hypertension are not yet completely characterized although insulin resistance has recently emerged as an independent risk factor for increased blood pressure in children and adolescents [62]. Even in the absence of obesity, the association of insulin resistance strengthens with onset of pubescence and adiposity. Together with other metabolic, hormonal, and hemodynamic disturbances, insulin resistance fosters vasoconstriction and vascular remodeling that leads to vascular stiffness, increased renal sodium reabsorption, and volume expansion.

Inflammation/Immunity

In the last several years there has been an increasing appreciation that in addition to perturbations in vessels, kidneys, and nervous system, cells within the innate and adaptive immune system have important roles in both obesity and hypertension. Macrophages and T cells accumulate and contribute to vascular and kidney damage in experimental models and human hypertension. For example, immunosuppressive drugs, thymectomy, or anti-thymocyte serum can prevent or blunt development of hypertension in several animal models [63]. In humans, treatment with the immunosupressor, mycophenolate mofetil, reduced blood pressure in patients with psoriasis or rheumatoid arthritis and hypertension [64].

These data suggest that immune suppression can lower blood pressure in certain hypertensive states. The key participation of T cells was demonstrated in studies of lymphopenic mice, which had a blunted hypertensive response following infusion of angiotensin II, norepinephrine, or salt challenge [65]. Adoptive transfer of effector T cells, but not B cells, restored the blood pressure response to these hypertensive stimuli. Interestingly, infusion of angiotensin II increases circulating markers of effector memory T cells, which accumulate in the perivascular adipose tissue of the aorta. The cellular infiltration stimulates production of cytokines that can affect vascular and renal functions, including interleukin-6,-17, TNF-α, and interferon-γ. The immune activation is not mediated directly in T cells; rather it is driven by action in the central nervous system. The current concept of immune regulation of hypertension includes participation of T cells and monocytes that involves activation of the NADPH oxidase, which increases production of ROS [63]. In the brain, ROS stimulate sympathetic outflow that has pro-hypertensive effects (see above). In the kidney, immune cell infiltration and the associated cytokine release and oxidative stress promote sodium retention. Oxidative stress also encourages oxidation of fatty acids, e.g., isoketals, which rapidly react with protein lysines. The modified proteins

cause T cell proliferation and cytokine production that sustain and amplify elevation in blood pressure. In adults, inflammatory markers, especially, C-reactive protein (CRP) and IL-6 have been used to stratify risk and treatment initiation for cardiovascular complications, including obesity-related hypertension. In children, inflammatory markers have been shown to be positively associated with weight [66]; however, after controlling for adiposity and dyslipidemia the relationship between hypertension and CRP level is controversial. Long-term data linking inflammation and outcome are currently lacking but may be useful in the future.

Renal Disease in Obesity

Clinical Spectrum of Obesity-Related Glomerulopathy (ORG)

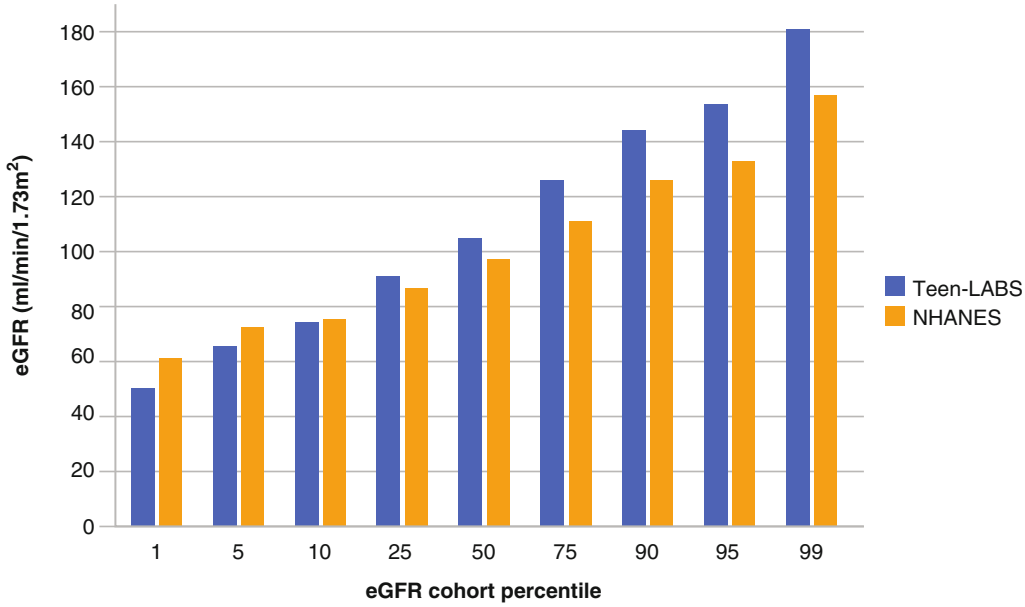
High-grade proteinuria in obese adults that remitted with weight loss and returned with weight gain was first described in 1974 [67]. The renal histology was comparable to idiopathic focal segmental glomerulosclerosis (FSGS). The term obesity-related glomerulopathy (ORG) is now used to describe this secondary form of FSGS, the incidence of which has increased 14-fold in the last 30 years [68, 69]. Underscoring the gravity of ORG is the recognition that progression to end-stage renal disease occurs in half of patients by 10 years [69].

ORG is increasingly recognized in the pediatric population. Although a report documented ORG in an 8-year-old child with BMI 58.1 kg/m^2, in most series it is detected in the second decade of life [69–73]. In a contemporary pediatric cohort of severe obesity presenting for surgical treatment (mean age 17 years and median BMI 50.5 kg/m^2), decreased GFR was detected already in 24%, with 3% <60 mL/min/1.73 m^2 (Fig. 27.4) [74]. The presumption is that progressive decline in kidney function would ensue with ongoing duration of obesity. Indeed, obesity at age 17 years has been shown to increase dramatically the risk for end-stage renal disease over 40 years follow-up (hazard ratio 6.89, 95% CI: 5.52–8.59) compared to subjects with normal weight when young [75]. Moreover, obesity potentiates progression of other renal diseases including IgA nephropathy, unilateral renal agenesis, and transplant nephropathy [71, 76, 77].

The clinical characteristics of ORG in pediatric patients are similar to those in adults. The condition is milder than idiopathic FSGS; daily protein excretion is lower (1.8–4.5 g/day), serum albumin is normal or only minimally depressed, and edema is absent or mild. About half of pediatric patients with ORG are hypertensive or hyperlipidemic. Many have been shown to respond to inhibition of the renin–angiotensin system with marked reduction in proteinuria, though as in adults, this intervention may not prevent progressive glomerulosclerosis [70, 78]. Interestingly, one report describes an adolescent who had amelioration of proteinuria with weight loss but nevertheless had histologic progression of glomerulosclerosis over ensuing years [72]. This suggests that ORG may in some cases cause progressive glomerular scarring despite reductions in body fat mass.

In clinical practice, proteinuria is a well-accepted indicator of renal injury and comprises a spectrum from microalbuminuria (30–300 mg/g creatinine; not detectable by routine urinalysis) to overt proteinuria (>300 mg/g creatinine, detectable by dipstick). As in other glomerulopathies, obesity-associated microalbuminuria appears to be an early indicator of renal damage [79]. The prevalence of microalbuminuria in obesity is increased and parallels the BMI. Even among normoglycemic first-degree relatives of type-II diabetics, central obesity has been found to be an independent risk factor for microalbuminuria [80]. Likewise, in 10,000 young adults, those with BMI > 35 had significant increases in albuminuria compared to lower BMI groups [81].

Albuminuria correlates with substantial renal structural alteration even with normal renal function (see below) [79]. In a pediatric cohort with severe obesity (median BMI 50.5), microalbuminuria was present in 14% and overt proteinuria in 3% [74]. The impact of the duration of obesity is seen in a study of extremely obese adults (mean BMI 52 and mean age 42 years) in whom micro-



	1st	5th	10th	25th	50th	75th	90th	95th	99th
Teen-LABS Larsson GFR	50.1	65.5	75.3	90.8	104.9	125.7	144.2	153.6	180.7
NHANES Larsson GFR	60.7	71.8	76.3	87.0	97.2	111.1	125.7	133.0	157.0

Fig. 27.4 Percentile distribution of eGFR in the severely obese Teen-LABS cohort and general population adolescents in NHANES data. Within the lower percentiles of eGFR, obese adolescents have lower GFR levels. By contrast, within the highest percentiles of eGFR, relative hyperfiltration characterizes obese adolescents compared to adolescents in the general population (Used with permission of John Wiley and Sons from Xiao N, Jenkins TM, Nehus E, Inge TH, Michalsky MP, Harmon CM, Helmrath MA, Brandt ML, Courcoulas A, Moxey-Mims M, Mitsnefes MM and Teen LC. Kidney function in severely obese adolescents undergoing bariatric surgery. Obesity (Silver Spring). 2014;22:2319–25)

albuminuria was much more common, seen in 41% and overt proteinuria in 4%. Thus, children and adolescents with BMI > 95th percentile should be assessed for microalbuminuria and glomerular filtration rate by serum creatinine. Thereafter, urine microalbumin should be followed periodically. Currently there are limited data to guide therapeutic interventions, although reports of efficacy by inhibition of the renin–angiotensin system in advanced obesity-related glomerulopathy suggest a potential benefit. As with any renal injury, the presence of hypertension accelerates glomerular injury. Control of hypertension is essential to limit progression of renal disease. There is accumulating evidence that, similar to adults, bariatric surgery may reduce albuminuria and lessen decline or even improve kidney function (see below) [82].

Renal Hemodynamics

There are significant changes in renal hemodynamics in patients with obesity. Adults with mean BMI 43.8 kg/m^2 had glomerular filtration rate (GFR) 51% higher than that of normal weight controls. Extremely obese pediatric patients demonstrate a high rate of glomerular hyperfiltration as well compared to general population adolescents (Fig. 27.4). Besides increased GFR, renal plasma flow (RPF) is also elevated, though not to the same degree, changes that underlie a higher filtration fraction (defined as GFR/RPF) a hemodynamic adjustment that parallels the degree of BMI and adipose mass [77, 83]. Glomerular filtration is determined by the pre- and post-glomerular arteriolar tone, both of which are altered by obesity. Molecular sieving

experiments in obese individuals suggest that afferent arteriolar vasodilatation together with efferent arteriolar vasoconstriction contribute to the increase in filtration fraction [83].

Experimentally, obese rats have heightened renal vascular resistance in response to infusions of Ang II. As the Ang II type-I receptor density is highest in the efferent arteriole, these data suggest that obesity promotes renal efferent arteriolar vasoconstriction [84]. Furthermore, inhibition of Ang II action in obese subjects increases renal plasma flow, again pointing to efferent arteriolar vasoconstriction as a prominent renal response to obesity [85]. Increased filtration fraction has been linked to glomerular injury and scarring through mechanisms that include elevated glomerular pressure and stimulation of local growth factors. Importantly, obesity-induced increase in GFR is not immutable; hyperfiltration can normalize following gastroplasty [86].

Tubuloglomerular feedback (TGF) describes the coupling of each nephron's distal tubule flow to glomerular filtration. Nephron anatomy dictates that the distal tubule signals to its originating glomerulus and contributes to the formation of the macula densa, which encompasses specialized tubular cells abutting the afferent and efferent arterioles. The stimulus to adjust GFR includes the rate of distal tubular flow and the composition of tubular fluid. The signal is perceived in the macula densa and transmitted to the vascular structures of the nephron, particularly the afferent arteriole, which adjusts the rate of filtration. An inverse relationship between tubular flow and filtration is thus established, such that an increase in tubular flow decreases glomerular filtration and vice versa. In simplest terms, increased luminal NaCl leads to a decrease in glomerular filtration through afferent arteriolar vasoconstriction.

As discussed in the hypertension section, obesity causes volume expansion that is due, in part, to increased salt reabsorption in the proximal tubule; this is mediated by increased sympathetic tone, Ang II, adipokines, and increased oncotic pressure of the tubular blood supply caused by glomerular hyperfiltration. By lowering tubular NaCl relative to GFR, these obesity-dependent changes disrupt the TGF response, preventing suppression of GFR. Given the high rate of hypertension in obese individuals, blunting of TGF feedback and failure to constrict the afferent arteriole may allow transmission of systemic BP to the glomerulus, contributing not only to increased GFR but glomerular hypertension and activation of growth factors and cytokines that promote renal damage [87]. Pharmacologic stimulation of TGF has been shown to decrease hyperfiltration in obese, nondiabetic men. Administration of acetazolamide, a diuretic acting in the proximal tubule that predicts increased sodium delivery to the macula densa, resulted in increased renal vascular resistance and a fall in GFR. By contrast, furosemide, which acts on nephron segments beyond the macula densa, did not alter renal hemodynamics, including GFR. Notably, the GFR-decreasing acetazolamide effect was more pronounced with increasing GFR, underscoring the maladaptive afferent arteriolar vasodilatation in obesity-associated glomerular hyperfiltration [88].

Importantly, the renal hemodynamic changes that characterize obesity precede the current definition of obesity (BMI $\geq$30 in adults) [89]. Thus, even in normal weight individuals, central body/abdominal adiposity correlates with the increasing filtration fraction that may confer increased renal susceptibility. A study of >1500 apparently healthy 18-year-old men reported decreased HDL (38%), elevated BP (24%), overweight (18%), increased triglycerides (13%), and elevated plasma glucose (8%) [90]. Critically, although glomerular hyperfiltration was observed in 4%, it correlated with several of the metabolic risks. Compared to young men with no risks and GFR of ~130 mL/min, the GFR was ~170 mL/min in those with 4–5 risks ($p < 0.0001$). Similarly, in children (age 10.6 years), estimated GFR rose with waist circumference and clustered with metabolic syndrome components [91].

Proteinuria

A hallmark renal manifestation of obesity/ORG is proteinuria. It is relatively modest and usually not associated with nephrotic syndrome.

Presentation with hypoalbuminemia and edema is rare [69, 78, 92]. Lack of edema may delay detection of proteinuria and increase the chance for progressive glomerulosclerosis and loss of renal function. Indeed, in one study, those who progressed to ESRD had elevated serum creatinine at presentation [78]. In a Chinese cohort of patients with ORG, protein excretion rose with increasing BMI yet the severity of glomerulosclerosis on biopsy was similar across the range of BMI. These observations suggest that additional intrarenal hemodynamic derangements contributed to excess proteinuria with increasing adiposity.

It should be emphasized, however, that a third of the cohort with biopsy-proven ORG had only mild proteinuria (400 mg/24 h). These findings suggest that the renal pathophysiologic processes that culminate in ORG are already present at the time when proteinuria is only modestly elevated or even before overt proteinuria is detected. Indeed, one study of extremely obese adults showing 41% with only microalbuminuria and 4% with low grade proteinuria nevertheless showed an identifiable glomerular lesion in 77%, increased glomerular size, and more globally sclerotic glomeruli compared to normal weight controls [79].

It is noteworthy that proteinuria in ORG can in some cases be dramatically lessened with weight loss [67, 78]. As noted above, pharmacologic agents that reduce blood pressure have been shown, in some cases, to reverse microalbuminuria and limit progression of renal disease in obese subjects. In some studies, bariatric surgery has also been shown to normalize protein excretion in adult and pediatric patients [70, 93]. Ongoing studies will clarify the utility of these interventions on proteinuria and kidney function in obesity.

Renal Morphology

Glomerulomegaly is the foremost obesity-related renal structural alteration. It is also the critical feature that differentiates ORG from primary FSGS (Fig. 27.5). Increased glomerular filtration due to increased transcapillary hydraulic pressure likely contributes to glomerulomegaly. Although increased glomerular size may not directly cause sclerosis, it may be an early manifestation of processes that promote cell growth and extracellular matrix synthesis.

Importantly, the link between glomerulomegaly and sclerosis may reflect the limited capacity of mature podocytes to hypertrophy and divide. Thus, increasing glomerular size causes a reduction in the relative podocyte density that may be a stimulus for further injury. Indeed, a study of patients with ORG found that glomerulomegaly was accompanied by a 45% reduction in podocyte density. Increased Bowman's space cross-sectional area and proximal tubule lumen size in proteinuric obese patients underscores the role of glomerular hyperfiltration in structural changes of ORG [94]. Segmental sclerosis of ORG is more often at the hilum of the glomerulus than idiopathic FSGS, observations that suggest the close relationship to glomerular blood flow [68, 95]. ORG-associated podocyte rarefication has also been linked to several podocyte abnormalities including microvillous degeneration with foot process effacement, retraction, separation from the basal lamina, as well as podocyte detachment and capillary adherence to the parietal epithelium of Bowman's capsule leading to the development of the segmental sclerotic lesion (Fig. 27.5) [96].

Progressive glomerular destruction, regardless of cause, will culminate in tubulointerstitial fibrosis. It is therefore of interest that compared with idiopathic FSGS, obesity-associated FSGS has less interstitial alpha smooth muscle actin and TGF beta and lower interstitial volume, suggesting relative preservation of the tubulointerstitium. These observations may explain the lower rates of progression to ESRD of ORG compared to idiopathic FSGS. Lipid droplets have been observed in cells of the renal tubules as well as glomeruli of patients with obesity-related FSGS [95]. Recently renal cortical triglyceride accumulation has been correlated with increasing BMI [97].

It is interesting that glomerular pathology has been observed in obese patients without clinically apparent renal disease. Thus, autopsies of

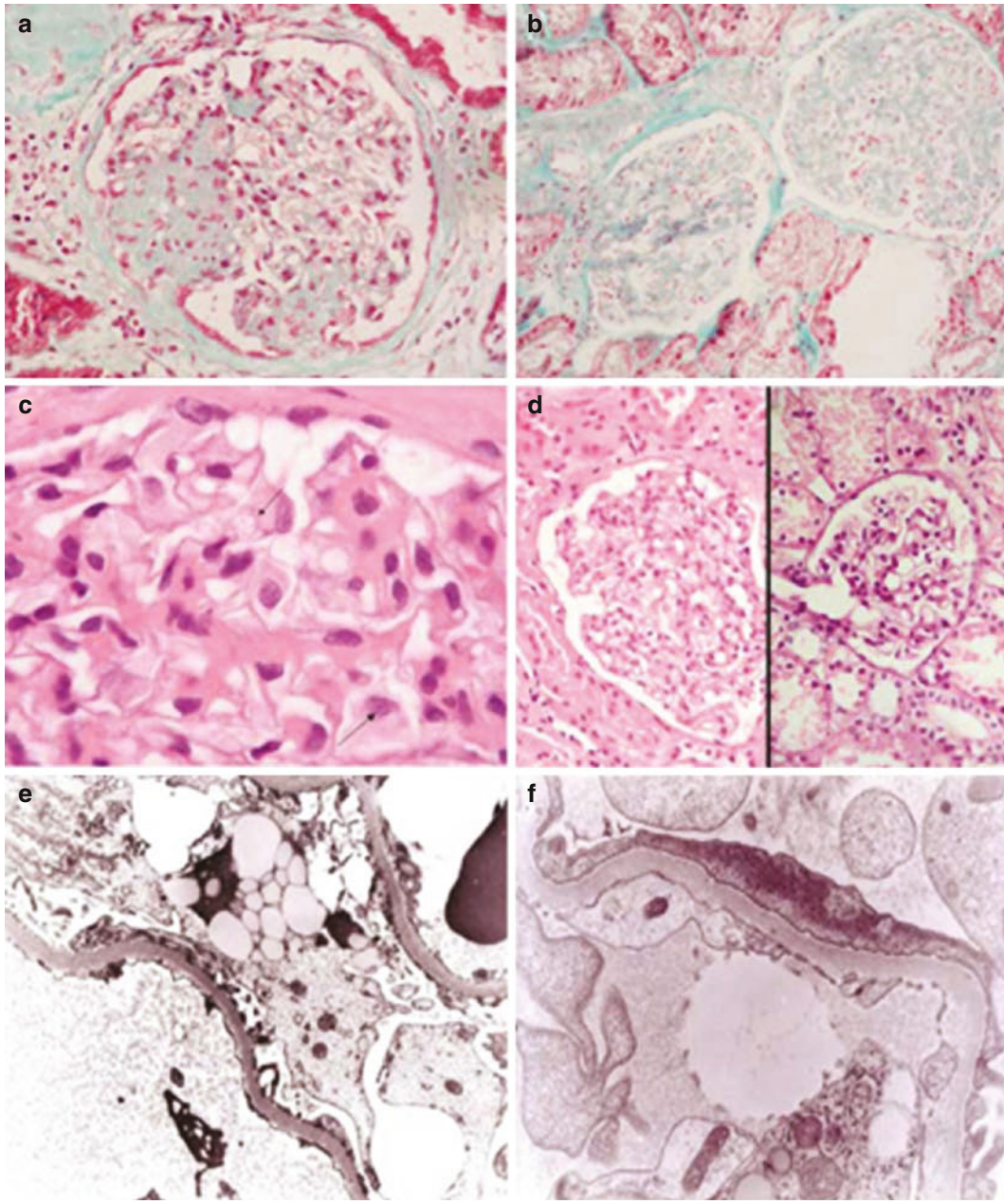


Fig. 27.5 Morphologic changes of obesity-related glomerulopathy. Upper Left Panel (**a**): two peripheral segmental sclerotic lesions showing focal adhesions to Bowman's capsule (Masson trichrome stain, ×400). Upper Right Panel (**b**): global mesangial matrix increase in two glomeruli (Masson trichrome stain, ×200). Middle Left Panel (**c**): Hypertrophic podocytes that contain intracytoplasmic droplets of fat resorption (arrow) and prominent nucleoli (arrow) (H&E stain, ×1000). Middle Right Panel (**d**): Glomerulus with glomerulomegaly from an extremely obese patient and glomerulus without glomerulomegaly from a control of the same age. (H&E stain, ×400). Lower Left Panel (**e**): Transmission electron microscopy showing large sized podocyte with intracytoplasmic lipids and focal foot process fusion (×4000). Lower Right Panel (**f**): Mild fusion of podocytes and condensations of cytoskeletal filaments with a parallel orientation to the glomerular basement membrane, indicative of podocyte decompensation (electron microscopy, ×10,000) (Used with permission of Elsevier from Serra A, Romero R, Lopez D, Navarro M, Esteve A, Perez N, Alastrue A and Ariza A. Renal injury in the extremely obese patients with normal renal function. Kidney Int. 2008;73:947–55)

two boys with Prader–Willi syndrome without renal dysfunction or proteinuria revealed marked glomerulomegaly. Similarly, examination of renal morphology in extremely obese adults (BMI 52 kg/m^2) with normal renal function revealed that only 5% had segmental glomerulosclerosis in 6% of glomeruli. Nonetheless, the mean glomerular planar area was 50% higher compared to normal weight controls [79]. Only 4% of these individuals had significant proteinuria (none >500 mg/day). These findings complement observations in otherwise healthy obese kidney donors who show no histological abnormalities but have glomeruli that are 15% larger than nonobese donors. No data exist as to persistence of glomerulomegaly in these donor kidneys in nonobese recipients, though the possibility of correction in a nonobese milieu seems plausible [98].

Pathogenesis of Renal Disease in Obesity

Obesity-associated metabolic abnormalities promote both systemic hypertension and renal injury; hypertension in turn results from, and contributes to, progressive renal damage. Obesity dramatically increases the risks of type 2 diabetes and diabetic nephropathy; yet even in the absence of diabetes, obesity predisposes to chronic kidney disease and accelerates its progression. The pathways involved in the pathogenesis of renal disease in obese subjects are explored below.

Renin-Angiotensin-Aldosterone System (RAAS)

The RAAS is a major regulator of systemic and renal vasomotor tone that affects renal blood flow and glomerular filtration and promotes the growth of renal cells. As noted previously, the adipocytes and infiltrating macrophages of adipose tissue constitute important sources of RAAS components. The Ang II type-1 receptor (AT1), primarily responsible for post-glomerular (efferent) anteriolar vasoconstriction, is dramatically elevated in the renal cortex of obese Zucker rats compared to lean Zucker controls [99]. Renal AT1 is also upregulated in transgenic mice overexpressing angiotensinogen exclusively in adipocytes [100]. These studies suggest that an adipose-derived increase in circulating RAAS ligands and an adipose-driven increase in renal AT1 receptor provide a powerful combination for increasing efferent arteriolar vasoconstriction, glomerular pressure, and cellular proliferation that promote structural damage. As with other chronic proteinuric glomerulopathies, inhibition of the renin–angiotensin system has been employed successfully to treat obesity-related glomerulopathy. Likewise, aldosterone blockade lessens renal injury in the vascular, glomerular, and tubulointerstitial compartments. These benefits are independent of its antihypertensive effects and likely block the effects of aldosterone on plasminogen activator inhibitor-1 and TGF-β, reactive oxygen intermediates, inflammatory mediators, and podocyte function [101]. Aldosterone antagonism attenuates obesity-induced glomerular hyperfiltration in high fat-fed dogs [102]. While the role of aldosterone in renal damage in obese humans has not yet been explicitly demonstrated, the compelling nature of animal data has prompted suggestions to use aldosterone antagonism for obesity-related kidney injury [103]. The antiproteinuric benefits of angiotensin-converting enzyme inhibition or aldosterone blockade may be reversed by progression of obesity or weight regain [70, 78, 92].

A recently characterized RAAS enzyme, ACE2, may prove to be particularly relevant for obesity-related renal alterations [104]. While ACE converts angiotensin I to angiotensin II, ACE2 degrades Ang II to Ang (1-7). Ang (1-7) acts through the Mas receptor to trigger vasodilatation and activate antifibrotic pathways, thus serving to restrain Ang II actions. Accordingly, genetic deletion of MasR or ACE2 leads to glomerular hyperfiltration and worsened renal functional and histologic outcomes after various injuries. Diminished renal ACE2 has been seen in a variety of renal diseases, including obesity. Obese Zucker rats show diminution of kidney ACE2, particularly during high sodium diet [105]. Likewise, kidney ACE2 is reduced in wild-type mice made obese by high fat diet [106].

Recent studies highlight the potential kidney benefits of Ang-(1-7). In cultured mesangial cells, Ang-(1-7) inhibited LDL uptake and the resultant upregulation of TGF-beta [107]. In high fat diet fed mice, exogenously Ang (1-7) blocked renal lipid accumulation pathways, which reduced renal inflammation (vide infra) [108]. Together these findings indicate novel pathways by which obesity-linked RAAS components may drive ORG.

Nephron Number

Overweight and obesity in adults with congenital solitary kidneys or surgical uninephrectomy is associated with poorer outcomes including proteinuria and decreased kidney function [76]. Recognition that reduced kidney parenchyma effects on outcome can be stratified by body mass index suggests that a mismatch in nephrons to metabolic demands may promote conditions for progressive glomerular stress. Given that glomerulogenesis ceases at 36 weeks gestation, preterm birth is an important setting which leads to a reduction in the complement of nephrons. Among a cohort of obese children with glomerulomegaly and FSGS (consistent with ORG), those born prematurely had significantly worse renal survival (15 years versus 23 years) despite lower BMI (*Z* score 2.3 ± 1.0) than the obese children born at term (BMI *Z* score 3.8 ± 1.8). These data indicate that the renal consequences of prematurity amplify the renal impact of obesity [71]. Experimentally, high fat diet induced obesity in uninephrectomized mice resulted in dramatic increases in urinary albumin, urinary reactive oxygen, glomerulosclerosis, and interstitial fibrosis compared to sham operated mice on high fat diet [109]. In another model of weight gain-induced podocyte failure, uninephrectomy caused proteinuria at significantly lower weight than mice without reduced renal parenchyma (two intact kidneys) [110].

Kidneys in otherwise healthy individuals demonstrate a wide variability in the number of nephrons, i.e., ~200,000–1.8 million. However, data suggest that individuals on the lower end of nephron number may be predisposed to renal disease. Renal biopsies in patients with ORG revealed that the density of glomeruli was about half of that observed in renal biopsies from patients with other renal diseases or individuals who were kidney donors. Interestingly, however, glomerular density from autopsy kidneys of obese subjects (without renal disease) was not lower [111]. While glomerular density assessed in a limited renal biopsy may not be a wholly adequate surrogate for total nephron number, the data raise the possibility that lower nephron number may be a critical factor that influences development of overt renal disease in the setting of obesity [111]. It is also possible that glomerular dysfunction depends on the interaction of a given nephron complement (the culmination of a variety of genetic, intrauterine, and acquired factors) and a given threshold of adiposity.

Podocyte Pathophysiology

Uninephrectomy potentiates adiposity-induced podocyte failure [110], including increase in areas of glomerular capillaries denuded of podocytes leading to increased adhesions to Bowman's capsule (the beginning of glomerulosclerosis). Thus, podocyte detachment follows progression from glomerulomegaly to podocyte hypertrophy. Recently, in a model of high fat diet induced obesity, progressive diminution of podocyte Cytochrome C (Cyt C, a marker of mitochondria) was seen before loss of nephrin. Cyt C and nephrin loss were not seen in podocytes from Smad3 knockout mice, implicating the TGF beta/Smad signaling pathway in the process of podocyte decompensation [112]. Smad 3 deficiency protects against obesity induced podocyte injury. In addition, a Smad3 inhibitor SIS3 was able to block podocyte toxicity caused by the fatty acid palmitate in vitro, raising potentially novel therapeutic implications for protecting podocytes in obesity. Importantly, podocyte shedding into the urinary space has been observed in obese humans. Urine of class III obese adults (BMI >40 kg/m2) showed mRNAs unique to podocytes at levels higher than other groups. Univariate and multivariate linear regression analyses strongly linked BMI and insulin level to the degree of urinary podocalyxin mRNA [113]. A similar study used flow cytometry to analyze urinary cells.

Podocalyxin positive cells were four times higher in the urine of obese patients compared to non-obese [114].

Adipocytes/Metabolic Factors

Receptors for *leptin* have been demonstrated in the renal inner medulla and in vascular structures of the renal corticomedullary region. Leptin promotes diuresis and tissue remodeling by regulating cellular growth and proliferation. For example, glomerular endothelial cells proliferate when stimulated by leptin and increase TGF-β production. In mesangial cells, leptin increases collagen type I production, cellular hypertrophy (but not proliferation), and also increases expression of TGF-β receptors, thereby sensitizing them to TGF-β produced by adjacent glomerular endothelial cells [115]. Chronic leptin infusion increases glomerular type-IV collagen and causes proteinuria in rats. Conversely, leptin deficiency has been shown to be protective in a mouse model of renal tubulointerstitial injury caused by unilateral ureteral obstruction, together with reduced TGF-β expression, less alpha smooth muscle actin and fibronectin staining than wild-type controls [116].

Circulating *adiponectin* levels decline with increasing obesity in adults as well as children and rise again with weight loss. In the kidney, podocytes express one of two adiponectin receptors (AdipoR1), which appear to support normal podocyte function [117] Adiponectin-null mutant mice show podocyte foot process effacement and albuminuria, both of which normalize with adiponectin treatment. The crucial role of adiponectin in normal glomerular structure and function was demonstrated in a recent model of podocyte apoptosis injury [118]. Mice overexpressing adiponectin recovered more rapidly after podocyte injury and had less renal fibrosis. Conversely, the same injury in adiponectin knockout mice produced much higher albuminuria compared to normal adiponectin controls, lower GFR, and worse interstitial fibrosis. Not surprisingly, adiponectin null mutant mice have poorer outcomes following renal injury, including increased inflammatory mediators, increased TGF-β, increased glomerular collagen deposition, glomerulomegaly, and albuminuria [119]. Taken together, these findings suggest that adiponectin is renoprotective and hypoadiponectinemia of obesity contributes to renal, especially podocyte, injury. Indeed, among obese African-Americans and Caucasian Europeans, a strong negative correlation was demonstrated between plasma adiponectin levels and albuminuria, highlighting the likely contribution of podocyte injury [117, 120]. Mechanistic studies reveal that adiponectin deficiency leads to an increase in NADPH oxidase; renal injury augments this deleterious response with increases in urinary reactive oxygen species [117, 119]. Conversely, adiponectin stimulates phosphorylation of glomerular AMPK (AMP-activated protein kinase), which inhibits oxidative stress and maintains normal podocyte architecture (Fig. 27.6) [117, 121, 122]. Similar salutary benefits of adiponectin to mesangial cells through increased AMPK phosphorylation were also recently demonstrated. Cultured mesangial cells treated with adiponectin showed reduction in angiotensin II-induced TGF-beta and fibronectin elaboration [123]. These observations raise the possibility that hypoadiponectinemia of obesity may contribute as well to accumulation of extracellular matrix in ORG.

Chemerin, a recently discovered adipokine elevated in obesity, is involved in inflammation and chemotaxis by acting on the G protein coupled receptor, chemokine receptor-like 1 (CMKLR1) on macrophages and dendritic cells. Chemerin also interacts with peroxisome proliferator-activated receptor-gamma to promote adipocyte differentiation and regulation of insulin and lipid metabolism. Chemerin may link adiposity with vascular disease. Among healthy lean and obese pediatric patients, chemerin levels correlated with BMI, CRP, as well as elevated levels of ICAM-1 and E-selectin, suggesting a role in endothelial activation. Complementary in vitro data confirmed that chemerin induced expression of ICAM-1 and E-selectin (but not eNOS or VCAM-1) in human coronary artery endothelial cells [124]. In another study of nearly 500 adults undergoing elective coronary angiography, chemerin correlated positively with BMI and waist circumference and negatively with

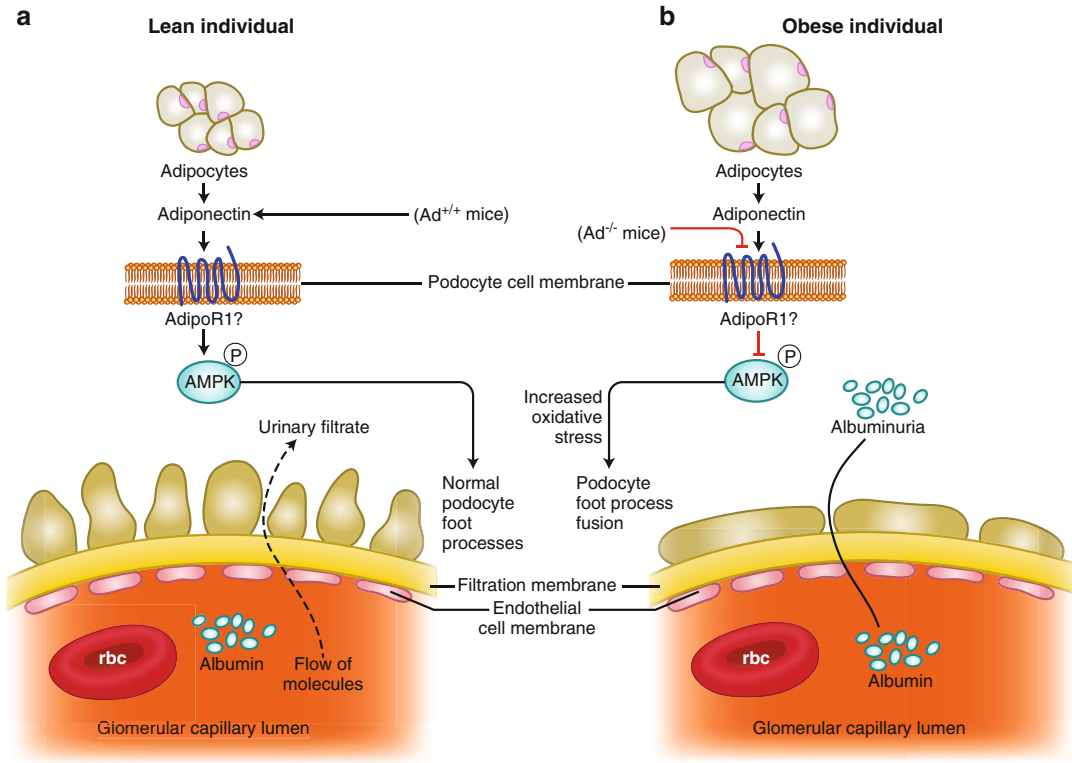


Fig. 27.6 Adiponectin is essential to normal podocyte function. Low adiponectin in obesity (Ad−/− mice) triggers glomerular podocyte effacement and albuminuria through decrease in AMPK phosphorylation and resultant increase in oxidative stress (Used with permission of Springer Science from Bayliss G, Weinrauch LA and D'Elia JA. Pathophysiology of obesity-related renal dysfunction contributes to diabetic nephropathy. Curr Diab Rep. 2012;12:440–6)

GFR. In those in the highest tertile of chemerin levels, 49.7% had CKD ≥ 2 at the study outset which increased to 63.9% over 3.5 years follow-up. By contrast, in those in the lowest tertile of chemerin levels, the CKD stage remained stable (31.1–34.1%). Interestingly, even after exclusion of those with preexisting CKD, the highest chemerin tertile had an incident development of CKD ≥ 2 of 36.5% versus only 15.4% for the lowest chemerin tertile. Albumin-to-creatinine ration (ACR) followed the same pattern. Those in the highest chemerin tertile ACR increased from 48 mcg/mg to 117 compared to the lowest tertile where no increase was noted from a baseline of 29 mcg/mg. The association of high chemerin levels with CKD remained significant even after adjustment for multiple other confounding variables [125].

Renal tissue chemerin and ChemR23 have been observed in severe human renal lupus as well as animal models of streptozocin induced diabetes. In the latter, renal overexpression of ChemR23 was ameliorated by both PPAR gamma agonists rosiglitazone and pioglitazone as well as the ARB irbesartan [98, 126].

Other adipocytokines have been implicated in ORG. Glomeruli from ORG patients have increased expression of TNF-α and a doubling in the expression of TNF receptor 1 [127]. These observations suggest that TNF-α may directly contribute to obesity-induced renal damage, possibly through stimulation of TGF-β, macrophage infiltration, and apoptosis. Circulating levels of interleukin-6 (IL-6) increase with obesity, with as much as 30% derived from adipose tissue [128].

IL-6 is the most important regulator of the hepatic acute phase response, which includes C-reactive protein (CRP). Strong epidemiologic data connect CRP with poor cardiovascular outcomes, and CRP may participate directly in vascular wall pathology [129]. Visceral adipose volumes were highly correlated with circulating IL-6 and CRP levels in Framingham subjects, and even obese children show dramatic elevation of CRP compared to normal weight controls [130]. Evidence for IL-6 involvement in vascular and renal disease beyond CRP is found in IL-6 induction of AT1 receptor in vitro and in vivo and subsequent increase in angiotensin-mediated oxidative stress [131]. Glomeruli from patients with ORG show a twofold increase in expression of IL-6 signal transducer, pointing to the possibility of direct IL-6 pathogenicity in glomeruli [127].

Excess intracellular *free fatty acids* are thought to be shunted toward the production of reactive intermediates such as fatty acyl CoA, diacylglycerol, and ceramide, which are cytotoxic. *LDL* has numerous glomerular effects, promoting mesangial cell proliferation and mesangial cell production of extracellular matrix, plasminogen activator inhibitor (PAI-1), and TGF-β. Sterol regulatory element binding transcription factor-1 (SREBP-1) is upregulated in high-fat-fed, obese C57BL/6 J mice that develop glomerulosclerosis and proteinuria. Transgenic overexpression of SREBP-1a resulted in increased lipid accumulation in glomeruli and tubular cells as well as glomerulosclerosis. Conversely, mutant mice with inactivated SREBP-1c were protected from glomerulosclerosis when fed a high-fat diet.

Glomerular expression of these lipid-related transporters was upregulated in glomeruli from patients with ORG: fatty acid-binding protein was upregulated fourfold, LDL-receptor twofold, and SREBP-1 twofold [127]. Thus, lipid disturbances often associated with obesity provide additional mechanisms for glomerular injury. Interestingly, the Vitamin D agonist doxercalciferol ameliorated the kidney disease (structural and functional) of diet induced obesity in mice. Treated mice showed dramatic reduction in renal lipid accumulation as well as reduced renal cortical expression of SREBP-1c, SREBP-2, LDL receptor, and HMG CoA as well as significant augmentation of farnesoid X receptor (FXR) expression [132]. Additionally, in high fat induced obesity in mice, oil red O and cholesterol staining as well as kidney expression of LDL receptor and SREBP2 were dramatically reduced in those animals treated concomitantly with exogenous Ang-(1-7) (vide supra). This resulted in dramatic reduction in expression of the inflammatory mediators TNF-alpha, IL-6, and MCP-1 [108]. Importantly, SREBP antagonism and FXR agonist treatment have been postulated as potential pharmacologic targets for improving renal lipid accumulation and damage in obesity [68].

Recent evidence suggests kinases are important in ORG. Mitogen-activated protein kinase p38 (p38 MAPK) signaling has a key role in renal disease including injury resulting from obesity. Specific inhibition of p38 MAPK in experimental nephrotic syndrome reduced podocyte damage and actin cytoskeletal disruption [133]. Albumin overload in rats leads to proteinuria, decreased nephrin staining (reflective of podocyte injury), and p38 MAPK phosphorylation. In culture, albumin overloaded podocytes display marked increase in apoptosis, which was dramatically lessened by p38 MAPK inhibition [134]. In classic models of podocyte injury (rat puromycin aminonucleoside and mouse adriamycin), specific p38 MAPK inhibition led to preservation of podocyte foot process architecture, nephrin expression, and prevention of focal glomerulosclerosis [135].

It is intriguing that recent data point to p38 MAPK upregulation and activation in multiple locations of obesity-induced end-organ damage, including impaired vascular endothelium-dependent relaxation, cardiac hypertrophy, as well as renal disease [136, 137]. In obese Zucker rats, besides proteinuria and glomerular expansion, renal cortical tissue analysis revealed activation of p38 MAPK and ERK 1/2 MAPK which was ameliorated by angiotensin type 1 receptor blockade with Losartan [99]. In rats with high fat diet-induced obesity, renal histology revealed glomerulomegaly and increased matrix formation as well as increased p38 MAPK phosphorylation. In

mesangial cells in culture, PPAR delta antagonism increased p38 MAPK activation and increased laminin and collagen IV production. In the same cells, PPAR delta overexpression or agonist treatment reduced p38 MAPK activation and laminin and collagen IV [138]. Lastly, high fat diet-induced obesity in mice results in glomerulomegaly and inflammatory signaling which is worse in animals also fed a diet low in zinc. These zinc depleted animals show heightened activation of p38 MAPK. Specific inhibition of p38 MAPK blocks obesity-induced renal inflammation as well as the low zinc-induced amplification of the inflammation. Additionally, a diet high in zinc reduced renal p38 MAPK activation and inflammation. Taken together, these studies indicate firstly an important role for p38 MAPK in obesity-induced renal disease but also that the activity of p38 MAPK can be modulated by exogenous agents including specific inhibitors, ARBs, PPAR delta agonists, and supplemental zinc. It is important to point out that levels of zinc in obese children may be low in plasma and higher in urine [139].

Interventions for Obesity-Related Hypertension and Kidney Dysfunction

Treatment of hypertension in overweight/obese adults clearly reduces long-term morbidity and mortality related to cardiovascular and renal disease. Treatment of hypertension prior to reaching adulthood predicts additional benefit. Therefore, intervention during childhood and adolescence may be an optimal time to lessen or prevent the permanent consequences of obesity. What is currently unclear is the threshold at which intervention should start and what treatment strategy is best to avert obesity-driven hypertension and kidney injury. This uncertainty is complicated by the paucity of studies that document benefit of therapeutic interventions on BP and kidney function in children and adolescents. At present, there are three main categories of obesity interventions: (1) diet and exercise, (2) pharmacologic methods, and (3) bariatric surgery.

Diet, Exercise, and Behavioral Therapy

Currently, weight reduction remains the cornerstone of management of overweight children and adolescents. Caloric restriction, especially when combined with increased physical activity has been shown effective in reducing weight and BP in overweight children and adolescents. A study of 97 overweight adolescents followed for 1 year involving nutritional, exercise, and behavioral therapies found 21% and 12% reduction in systolic and diastolic BP, respectively [140]. Typically, however, intervention studies have been small (20–100 subjects), relatively short term (6–52 weeks), and have not included long-term cardiovascular and renal effects. Similar to adults, longer studies report that overall behavioral and diet/lifestyle therapies lead to only small absolute decreases in body weight, a shortcoming especially relevant in morbidly obese adolescents. Nonetheless, even short-term interventions in lifestyle such as increased physical activity/exercise that lead to only small degree of weight loss (e.g., 3–7%) can impart a beneficial effect on cardiovascular risk [141]. It is currently unknown how much or the duration of weight reduction that is beneficial to lessen CV risks including development of hypertension and kidney dysfunction.

Pharmacologic Agents

Disappointing results of diet, exercise, and behavioral therapies has led to development of pharmacologic agents to treat obesity. Reduction in weight remains the primary outcome of pharmacologic interventions, with the rationale being that if adolescent obesity can be halted or resolved, comorbidities like hypertension and albuminuria will resolve. Currently, Orlistat and metformin are the primary agents available but other agents may be on the horizon for testing in adolescents [142].

Orlistat blocks the function of intestinal lipases and has been approved to treat obesity. A multicenter, randomized, placebo-controlled

trial of Orlistat vs. placebo along with a hypocaloric diet, exercise, and behavioral therapy was conducted in obese 12–16-year-olds. The trial lasted 54 weeks. Orlistat decreased BMI by 0.55, compared to the placebo group who had an increase of 0.31 over the same time period and similar behavioral therapy, diet, and exercise [143]. This was a significant effect on BMI, but the clinical implications are uncertain. Less than 3% of children were hypertensive and there was no detectable effect of Orlistat on blood pressure. Kidney function was not directly assessed.

Metformin is an anti-hyperglycemic agent used to treat adults and children with impaired glucose tolerance and type 2 diabetes. Its mechanism involves partial inhibition of mitochondrial electron transport and oxidative phosphorylation that modulates lipid oxidation as well as improving hepatic insulin sensitivity and suppression of hepatic glucose output. Several studies have examined effects of metformin in addition to healthy lifestyle or dietary modifications. Similar to adults, in adolescents metformin show small albeit significant decreases in body weight and improvement in markers of insulin resistance. Thus far, there have been no reports on effects on BP or kidney parameters in childhood/adolescence.

Bariatric Surgery

In contrast to other therapeutic approaches, bariatric surgery appears to be an effective, long-term treatment for obesity in adults [144–146]. Currently, there are three types of bariatric operations performed in adolescents: adjustable gastric banding, vertical sleeve gastrectomy (VSG), and Roux-en-Y gastric bypass.

Adjustable gastric banding is a procedure in which a restrictive band is placed around the upper portion of the stomach, significantly limiting stomach capacity. Although there is a wide range of hypertension noted in adolescence undergoing gastric banding (12–90%), not all studies document both pre- and post-banding levels. Nonetheless, studies that follow blood pressure report remarkable resolution (i.e., >90%) [147–149].

Vertical sleeve gastrectomy has proven safe and efficacious for weight loss in adolescents [150]. In this operation, stomach volume is decreased by excision of approximately 70% of the stomach along the greater curvature. Studies examining VSG and hypertension report resolution rates ranging from 75% up to 100%. VSG is one of two bariatric operations being examined prospectively for treatment of obesity and other obesity-related comorbidities, including hypertension, in the Teen-LABS (Longitudinal Assessment of Bariatric Surgery) study. Hypertension resolution at 3 years is approximately 53% in the VSG cohort.

Roux-en-Y gastric bypass (RYGB) involves dividing the top of the stomach from the rest of the stomach and the first portion from the rest of the small intestine. The bottom end of the small intestine is connected to the newly created small stomach pouch while the top portion of the divided small intestine is anastomosed to the small intestine further down so that the stomach acids and digestive enzymes from the bypassed stomach and first portion of small intestine will eventually mix with the food. Surprisingly, only few studies have specifically reported outcomes related to hypertension and kidney disease in adults. Nonetheless, paralleling other metabolic improvements, resolution of hypertension appears to be even better than VSG and adjustable gastric banding. In adults, resolution rates range from 50 to 100% [151, 152]. Retrospective or case series studies of RYGB in adolescents report improvement or resolution rates between 80 and 100% [148, 153]. A series of adolescent RYGB patients a year postoperatively report a significant reduction in both systolic and diastolic blood pressure [154]. A more recent propensity matched cohort study looking specifically at kidney outcomes showed that bariatric surgery patients (96.5% RYGB and 3.5% VSG) had a 58% lower risk of a eGFR decline of >30% as well as a 57% decreased risk of doubling serum creatinine [155].

The Teen-LABS consortium is the largest ongoing, multicenter, longitudinal study examining the effects of bariatric surgery (VSG or RYGB) in adolescents. Among the many outcomes being examined, blood pressure and kidney function, i.e., urine albumin to creatinine ratio and cystatin C-based GFR, are being followed. Of the 242 patient cohort, 45% have clinically diagnosed hypertension prior to surgery, while approximately 26% are pre-hypertensive (systolic blood pressure >120 but <140) [156]. Further, 14% have microalbuminuria and 3% have macroalbuminuria [74] preoperatively, indicating that a significant number of these severely obese adolescents already have documented kidney dysfunction. In the three-year outcomes data, 74% of baseline hypertensive adolescents had complete resolution of their hypertension. Studies describing the effects on kidney function have just become available. In those with decreased kidney function at baseline (GFR estimated by Cystatin C under 90 mL/min/1.73 m^2) mean eGFR improved from 76 to 102 mL/min/1.73 m^2 3 years after bariatric surgery. Of those participants with albuminuria, mean albumin to creatinine ratio was 74 mg/g creatinine at baseline and decreased to 17 mg/g creatinine at 3 years. Of the seven patients with macroalbuminuria, three had normalization of urinary protein by 1 year post surgery with the highest level of macroalbuminuria dropping from 1677 mg/g creatinine at baseline to 173.7 mg/g creatinine after 3 years [157].

Summary

While hypertension and renal damage have long been recognized to be interrelated, obesity dramatically amplifies each of these abnormalities. The obesity epidemic, now well entrenched in the pediatric population, is expected to increase these complications. Current therapies aimed at lessening elevated blood pressure and slowing progressive renal damage will likely be supplemented by interventions aimed at obesity-specific targets.

Editor's Comments and Questions

1. Hypertension is a critical risk factor for future renal disease, myocardial infarction, and stroke. My experience, however, dictates that its identification in obese children is often overlooked as physicians focus primarily on BMI, glucose intolerance, and hyperlipidemia. Pediatricians in general tend to be less aggressive than their adult counterparts in treating mild-moderate hypertension, perhaps because they lack familiarity and comfort with the use of antihypertensive medications. We also lack a strong evidence base that proves that pharmaco-reduction of blood pressure in childhood and early adolescence will prevent long-term renal and cardiovascular complications.
2. I agree wholeheartedly that urine microalbumin should be measured in tandem with blood pressure in obese children. I have become accustomed to recommending an ACE (Angiotensin-Converting Enzyme) inhibitor in those with persistent hypertension *and/or* microalbuminuria confirmed on at least two independent measurements. ACE inhibitors are generally less costly than Angiotensin Receptor Blockers (ARBs) and may be endorsed as first-line agents by insurance agencies (including for example North Carolina Medicaid). I am careful to make teenage girls aware that ACE inhibitors can be teratogenic. In combination with weight reduction, an ACE or an ARB is usually effective in reducing blood pressure and often (but not always) decreases urine microalbumin concentrations. How strong is the evidence that such an approach will prevent progression of renal disease?
3. If the microalbuminuria persists despite control of blood pressure or the child has macroalbuminuria I refer to a

nephrologist, who typically increases the dose of the ACE inhibitor (or in some cases the ARB) and may add a second anti-hypertensive agent. In our institution few obese children with either microalbuminuria or macroalbuminuria undergo renal biopsy; exceptions are made when the magnitude of urinary albumin excretion is unusually high, the child is edematous, or the creatinine clearance is reduced. What criteria would you employ for performing a renal biopsy in an obese child with albuminuria?

Authors' Responses

1. Hard cardiovascular endpoints such as MI and stroke four to five decades are currently not available in the pediatric population. However, pediatric blood pressure strongly correlates with adult pressure, and adult hypertension is a strong predictor of increased cardiovascular disease. Moreover, there are excellent data linking pediatric hypertension to cardiovascular pathophysiologic processes that regress with treatment.[a] Thus, while expected cardiovascular endpoints may be speculative (albeit reasonable), observed end-organ changes seen in pediatric hypertension (increased carotid thickness, left ventricular hypertrophy, arterial stiffness, and microalbuminuria) can be considered midpoints on the way to life threatening outcomes and opportune for and responsive to pharmacologic intervention. We are convinced that pharmacologic amelioration of cardiovascular and renal pathophysiologic processes begun in childhood will accrue to improvement in overall cardiovascular health for those treated compared to their outcomes if not treated.

   In our experience, pediatricians screen and refer for hypertension but are not inclined to start treatment. Our practice receives five to ten new patient referrals for pediatric hypertension per week, most related to obesity. Indeed, this may only be a fraction of obese hypertensive children needing treatment. Regional differences in referral patterns of hypertensive children may relate to distance to tertiary pediatric centers, availability of specialized pediatric hypertension experts as well as training of local physicians. In a study of Michigan Medicaid data, 63% of adolescents on antihypertensive medication received their prescription from adult primary care physicians; only 24% of the teens were seen by pediatric subspecialists.[b] Hesitance in treating pediatric patients can be inferred from this study, in which only 23% of hypertensive adolescents were receiving antihypertensive medication.
2. Microalbuminuria in obese pediatric patients has several potential origins. Some patients referred for microalbuminuria turn out to have orthostatic proteinuria upon properly collected first morning urine. This scenario parallels the benign phenomenon of orthostatic proteinuria in nonobese children. Microalbuminuria in obesity may also reflect undiagnosed diabetic glomerular disease, particularly insulin-resistant diabetes, the appearance of which may deviate from the predicted time course. Microalbuminuria may also be the first evidence of an inadequate nephron mass relative to the obese body size that results in glomerular hyperfiltration and damage to the filtration barrier. In both diabetic nephropathy and reduced nephron mass, inhibition of the renin angiotensin system is established to lessen decline in kidney function.

It is also possible that angiotensin receptor antagonists (ARBs) may have benefits beyond angiotensin-converting enzyme inhibitors (ACEI) in obese patients. A large trial of several classes of antihypertensive medications in adults reported the incident diabetes to be lowest for ARBs and second lowest for ACE inhibitors. Notably, ARBs upregulate adiponectin (diminished in obesity and important to podocyte stability) and function as PPAR gamma agonists, which predict beneficial renal effects.

3. Balancing the risk of an invasive diagnostic procedure with the information to be gained is a frequent dilemma in clinical medicine. In our practice, an obese patient with overt proteinuria and no evidence of active processes beyond obesity-related renal disease would begin treatment with ACEi/ARB.

   Renal biopsy of a very obese patient is technically more challenging and often requires general anesthesia rather than conscious sedation, presenting more risk for the patient. Microalbuminuria generally does not warrant that risk while overt nephrotic syndrome requires a biopsy. For the patient with overt proteinuria/microalbuminuria who is not nephrotic, the degree of proteinuria and its progression constitutes the main factors in the decision to do a renal biopsy. Nonetheless, even modest proteinuria can indicate dramatic renal involvement. We reported a case where kidney biopsy was undertaken in an obese girl in whom escalating doses of ACEi and ARBs was ineffective in reducing proteinuria. The biopsy showed global glomerulosclerosis in nine of twenty glomeruli and segmental sclerosis in six. This rarefaction of non-scarred glomeruli in the face of treatment prompted referral for bariatric surgery. The procedure stabilized her kidney function, which still remains normal to this day [70].

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28 Sleep-Disordered Breathing and Sleep Duration in Childhood Obesity

Annelies Van Eyck and Stijn Verhulst

General Introduction

The increasing prevalence of childhood obesity during the past generation has been accompanied by profound changes in daily lifestyle. Computer-related activities, video games, cell phones, and other diversions have promoted a more sedentary existence, reducing energy expenditure and facilitating weight gain. Much of the screen and cell time is spent during the evening hours at the expense of sleep. Thus, behaviors that foster the development and progression of obesity in children may disrupt fundamental biological rhythms that are vital to child and adolescent health. Obesity in turn is a major risk factor for sleep-disordered breathing (SDB), which may facilitate further weight gain and promote the development of metabolic and cardiovascular morbidities in obese children as well as adults. This underscores the importance of exploring the relationship between childhood obesity and sleep.

The first part of this chapter will review the evidence that obesity is an anatomical and functional risk factor for SDB in children and discusses its consequences and management. The second part of the chapter discusses the relationship between sleep duration and the development of childhood obesity. Sleep duration may be an important determinant of body weight, as it modulates changes in several obesity-related hormones and affects daytime physical activity and the time available for food consumption. This suggests that good sleep hygiene should be added to the list of measures that may assist in the prevention of childhood obesity.

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Sleep-Disordered Breathing and Sleep Duration in Childhood Obesity

Introduction

Sleep-disordered breathing (SDB) is defined as a clinically relevant disturbance of breathing during sleep. The two most common respiratory events are apneas and hypopneas, which are documented by a formal sleep study or polysomnography. Apnea is defined as a complete cessation of respiratory airflow for at least two respiratory cycles. Hypopnea is defined as a reduction in respiratory airflow by 50% or more of baseline for at least two respiratory cycles. Apneas and hypopneas are then further classified as central, obstructive, or mixed. A respiratory event is classified as central

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when there is a cessation of all respiratory efforts (measured at the level of the thorax and abdomen). During an obstructive event, there is a continuous or even increased respiratory effort. A mixed event has both central and obstructive components. An example of a sleep study showing some of these respiratory events is presented in Fig. 28.1.

Much of the study of SDB has focused on obstructive sleep disorders. Obstructive sleep apnea syndrome (OSAS) is characterized by recurrent events of partial and/or complete upper airway obstruction that disrupt normal ventilation and sleep patterns. The diagnosis of OSAS in children is based on normative data in healthy children without snoring or other symptoms suggesting sleep apnea. Based on these normative data, the current diagnostic threshold is two or more obstructive events per hour of sleep [1]. OSAS is distinguished from primary snoring, a more benign expression of abnormal upper airway resistance that occurs in 3–12% of the general pediatric population. Primary snoring is not associated with obstructive events or desaturations during sleep.

Central sleep apnea has not been studied extensively in children. Reference studies demonstrate that central apneas lasting less than 20 s occur normally in children. These events are rarely accompanied by serious oxygen desaturation; a level of oxygen saturation below 90% following a central apnea event is considered abnormal. We therefore classify children as having central sleep apnea if they present with central events lasting more than 10 s and are accompanied by more than one bradytachycardia event or more than one desaturation below 90%.

Obesity as a Risk Factor of Sleep-Disordered Breathing in Children

Various studies have shown that obese children and adolescents have a higher prevalence of all types of SDB compared to their normal-weight peers. For example, an Italian review of questionnaires from more than 2000 teenagers found that the frequency of snoring was significantly higher in children with body mass index (BMI) in the 90th percentile or greater. Furthermore, subjects with a BMI exceeding the 95th percentile were 2.6 times more likely to snore than children with a BMI below the 75th percentile [2]. Similar findings were noted in a German study, which demonstrated that obese children had more than four times the risk of snoring when compared to their peers with a BMI in the 75th percentile or less [3].

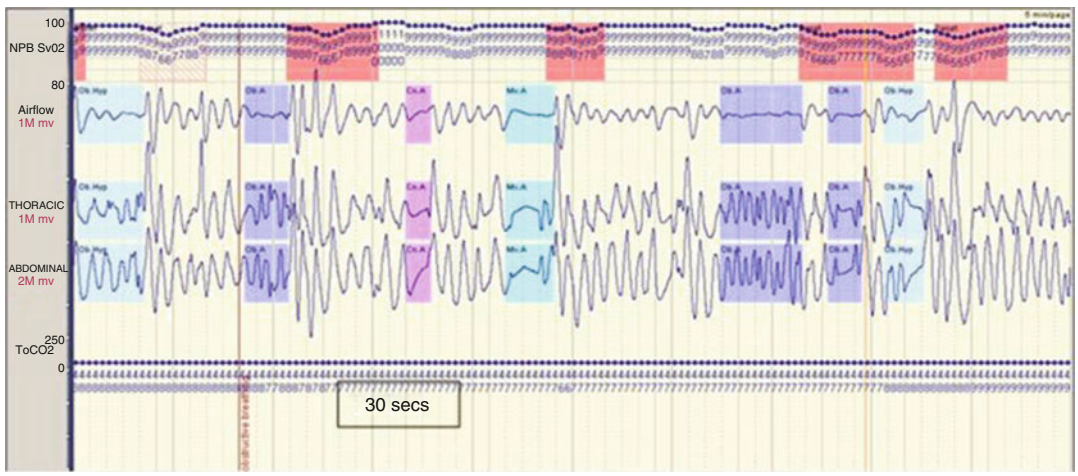

Fig. 28.1 Screen print of a polysomnography showing an obstructive apnea (purple box) and hypopnea (light blue box), central apnea (pink box), and mixed apnea (blue box). Following repetitive apneas and hypopneas oxygen saturation intermittently drops (red box), which is also referred to as intermittent hypoxia

A number of population-based studies have used nocturnal cardiorespiratory monitoring or polygraphy to delineate factors that predispose to OSAS in children. In the Cleveland Family Study, both African-American race and obesity in children aged 2–18 years were associated with a three- to fivefold higher likelihood of SDB [4]. The predisposition of African-Americans to OSAS was confirmed in a follow-up study of 8–11-year-old children; preterm birth was also a significant risk factor but obesity per se was not [5]. Sánchez-Armengol found that snoring adolescents, as assessed by questionnaire, expressed higher weights and higher waist-to-hip ratios and were more frequently obese as a group than their non-snoring peers [6].

Various studies have used nocturnal polysomnography in hospital settings to determine the prevalence of OSAS [7]. Three general conclusions are warranted.

First, obese children are at greater risk of OSAS, and the risk for developing OSAS is proportional to the degree of obesity [8]. In fact, Redline and colleagues showed that for each 1 kg/m^2 increase in BMI beyond the mean for age and gender, the risk for OSAS increases by 12% [4]. However, there are large variations in observed prevalence rates for OSAS among studies in obese pediatric populations, ranging from 13 to 59%. The observed differences in prevalence probably reflect a number of factors, including differences in the ethnicity, age, and pubertal status of the studied subjects and, more importantly, the use of different diagnostic criteria for childhood obesity and for childhood OSAS. These factors make the calculation of a pooled estimate for the prevalence of OSAS in childhood obesity very difficult, if not impossible.

Second, in the majority of cases the OSAS is generally mild and non-debilitating.

Finally, not all studies found the expected association between BMI and the apnea–hypopnea index—the classical marker of the severity of OSAS. However, the apnea–hypopnea index may correlate more strongly with the distribution of body fat than with BMI per se. For instance, we reported a significant association between waist-to-hip ratio and the apnea–hypopnea index in one of our studies but failed to find a significant association with BMI.

Moreover, the apnea–hypopnea index is not the only marker of the severity of sleep apnea; various studies have demonstrated that the degree of obesity is associated with other consequences of SDB, such as oxygen desaturation. Our study, for instance, reported a correlation between BMI and the minimal oxygen saturation during sleep; this finding had been described previously by Marcus and colleagues [9]. From a pathophysiological point of view, an association with oxygen desaturation is perhaps more important than a correlation with the number of apneic events, because intermittent hypoxia is the primary mediator of most of the complications associated with sleep apnea.

In contrast to evidence that OSAS is more prevalent in obese children, there are limited data on the prevalence of central apnea. We found that 13% of obese children had central sleep apnea; of all the groups of children we studied, those with central apnea had the most severe oxygen desaturation events [10]. Marcus and colleagues also described three subjects with central apneas associated with desaturation [9]. A recent investigation found that high body mass index (BMI) predicted central sleep apnea in a mixed cohort of normal-weight and overweight children [11].

Pathogenesis of Sleep Apnea in Obesity

The classical risk factor for obstructive sleep apnea in normal-weight children is enlargement of the adenoids and/or tonsils. In obese children, both lymphoid hypertrophy and adiposity can compromise the upper airway. For example, obese children with OSAS were seven times more likely to have enlarged tonsils and four times more likely to have enlarged adenoids [12], while subjects without adenotonsillar hypertrophy had a milder spectrum of respiratory abnormalities [13]. In a mixed group of normal-weight and overweight subjects, Brooks and coworkers demonstrated that the degree of obesity was the

only predictor of the apnea–hypopnea index, but lymphoid hyperplasia affected the duration of the obstructive apneas and the severity of the subsequent desaturation [14]. Data from the Cleveland Family Study also showed the importance of both obesity and respiratory disorders (sinusitis and a history of bronchiolitis, bronchitis, or asthma) as risk factors for sleep apnea in children [4].

Numerous studies in adults have shown that waist circumference or visceral fat content correlates strongly with the severity of OSAS and often more so than BMI [15–18]. However, little is known about the importance of fat distribution as a risk factor for sleep apnea in obese children and adolescents. A questionnaire study in children documented that waist circumference correlated with the risk of SDB [19]. In a population-based study of 101 adolescents, snoring was associated with a higher waist-to-hip ratio, reflecting a more central body fattening [6]. In a study by Li and coworkers, the association between the waist circumference and the presence of OSAS was borderline significant [20]. In a more recent study by Canapari and coworkers, the deposition of fat in a visceral distribution was found to be an independent predictor of OSAS severity in obese children [21].

In our prevalence study, tonsillar hypertrophy was the only significant covariate for obstructive sleep apnea. On the other hand, BMI z-score, waist circumference, waist-to-hip ratio, and percent fat mass predicted central apnea [10]. Moreover, abdominal adiposity was associated with increasing values of the "respiratory disturbance index (RDI)," which combines all central and obstructive events (Fig. 28.2).

Although a number of imaging studies in children with SDB have been performed, only two studies included overweight subjects. Fregosi and coworkers failed to find any correlation between BMI and sleep apnea severity, pharyngeal airway dimensions, and soft tissue anatomy [22]. In contrast, an MRI study by Arens and colleagues found significant upper airway lymphoid hypertrophy in obese children with OSAS [23]. However, data from our laboratory (see below) show narrowing of the airway in the region of the adenoids in some obese children with OSAS. It

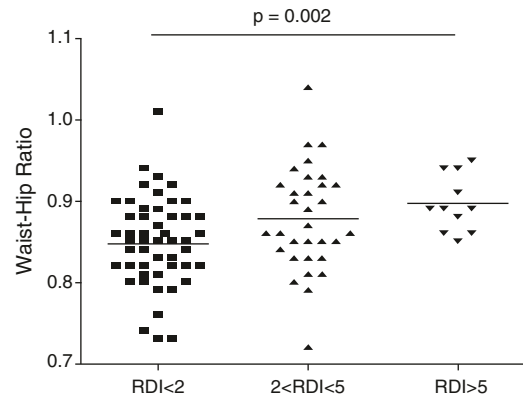

Fig. 28.2 The severity of sleep-disordered breathing is associated with abdominal obesity, as expressed by the waist-to-hip ratio (RDI, respiratory disturbance index, which is defined as the total number of apneas and hypopneas per hour of sleep) (Used with permission of Elsevier from Verhulst SL, Van Gaal L, De Backer W, Desager K. The prevalence, anatomical correlates and treatment of sleep-disordered breathing in obese children and adolescents. Sleep Med Rev. 2008;12(5):339–46)

seems likely therefore that the severity of sleep apnea in obese children is mediated both by adenotonsillar hypertrophy and by fat distribution. Recent data suggest that adenotonsillar hypertrophy is particularly important in the development of OSAS in young obese children, while progressive upper body fat deposition plays a major role in the obese adolescent. Normal variations in craniofacial anatomy may also contribute to the higher risks of OSAS in certain ethnic groups.

The pathogenesis of central apnea in obese children is unexplained except in children with central nervous system dysfunction following hypothalamic surgery for brain tumors and genetic obesity disorders such as the Prader–Willi syndrome.

Complications of Sleep-Disordered Breathing

The main consequence of repetitive apneas and hypopneas during sleep is intermittent hypoxia, which is a potent trigger of oxidative stress and inflammation [24]. Indeed, several studies have documented increased markers of oxidative stress and inflammation in obese children who exhibit

sleep apnea [25–29]. SDB is also associated with increased sympathetic activity [30, 31], higher serum cortisol levels [32], and other hormonal changes resulting from secondary sleep debt [33–35] (see below). However, these associations are not found in all studies, especially in the context of childhood obesity [36, 37]. It could be that obesity triggers an array of downstream effects that overwhelm those caused by mild intermittent hypoxia as seen in childhood SDB.

The neurocognitive and behavioral consequences of SDB in children are the best studied. Common problems include restless sleep, morning headache, and daytime fatigue and sleepiness. Furthermore, children with sleep apnea are at higher risk for concentration problems and learning disabilities, deficits in school performance, and behavioral problems including hyperactivity [38].

In obese children, sleep apnea may augment metabolic and cardiovascular morbidity. Cross-sectional studies indicate that increasing severity of SDB in obese children and adolescents is associated with an increased risk of the metabolic syndrome [39, 40], increases in diastolic blood pressure, blunting of the nocturnal fall in blood pressure [41, 42], and increases in left ventricular mass and decreases in function [43, 44]. Moreover, several studies show a positive correlation between sleep apnea and insulin resistance and dyslipidemia in children [39, 40, 45]. However, it must be noted that other studies failed to find similar relationships [46–48]. These conflicting results could be explained by variations in the magnitude of obesity and the ages of study subjects, reflecting varying severity and/or duration of disease; in addition, pubertal status likely plays an important role.

In general, SDB appears to have modest effects on metabolic function in children, and the long-term consequences of childhood sleep apnea on metabolic morbidity in early adulthood remain to be demonstrated in longitudinal investigations. To date, one randomized controlled trial investigated the effect of adenotonsillectomy compared to watchful waiting on cardiometabolic parameters in children with OSAS but could not find an effect of the treatment on glucose, lipids, insulin, CRP, blood pressure, and heart rate [49]. Cross-sectional studies of patients prior to and following treatment have yielded conflicting results [50–52].

Treatment of Sleep-Disordered Breathing in Obese Children and Adolescents

Because obese children have a high prevalence of OSAS, and because OSAS can exacerbate the comorbidities of obesity, an optimal treatment strategy should target OSAS and obesity simultaneously. A multidisciplinary approach to treatment is essential: an obese child with OSAS should be evaluated by a pediatric sleep physician, an ENT specialist, and a pediatric endocrinologist and should be enrolled in a weight management program staffed by physicians and nutritionists, exercise physiologists, and counselors providing psychological support.

Treatment should be individualized. Adenotonsillectomy can be considered in obese children with adenotonsillar hypertrophy and other signs compatible with chronic upper airway problems, including mouth breathing, chronic rhinitis, recurrent ear infections, and respiratory allergies. In such cases, surgery can provide immediate benefit, though long-term resolution of OSAS may depend on concurrent weight loss. Other treatments are preferred when there is little or no obvious upper airway obstruction; these include weight loss for mild cases and continuous positive airway pressure (CPAP) plus weight loss for more severe cases.

Adenotonsillectomy is the first-line treatment for sleep apnea in the child with significant adenotonsillar hypertrophy. But a recent meta-analysis showed that adenotonsillectomy reverses OSAS in less than half of obese children with the condition [53]. Moreover, several studies indicate that obese children may gain weight after adenotonsillectomy [7]. This postoperative weight gain can result in treatment failure and an increase in insulin resistance after surgery [52, 54].

This does not imply that adenotonsillectomy should be completely abandoned. However,

additional studies are required to identify those children most likely to benefit from adenotonsillectomy. In our center, we have begun to use ultra-low-dose CT scans and functional imaging to identify the subset of obese children who are most likely to benefit from surgery. Figure 28.3a, b presents a CT scan from an overweight child with moderate OSAS; it clearly shows that airway narrowing is most severe at the level of the adenoids. Using sophisticated mathematical techniques, we can simulate flows through a 3D computer model generated from the CT scan and calculate velocities, pressures, and resistances across the airway. The second part of the figure shows that the pressure drop indeed coincides with narrowing in the region of the adenoids. Such a finding would suggest that adenotonsillectomy is warranted. It is our intention to implement this technique in future clinical practice in order to create an individualized treatment plan for each obese child with OSAS. Should the child undergo adenotonsillectomy, it is mandatory to assess the efficacy of the procedure with a follow-up sleep study.

Systematic studies of the effect of weight loss on the severity of SDB in children are scarce. However, Kalra and colleagues studied 34 morbidly obese adolescents who underwent bariatric surgery [55]. Prior to surgery, 55% of the subjects

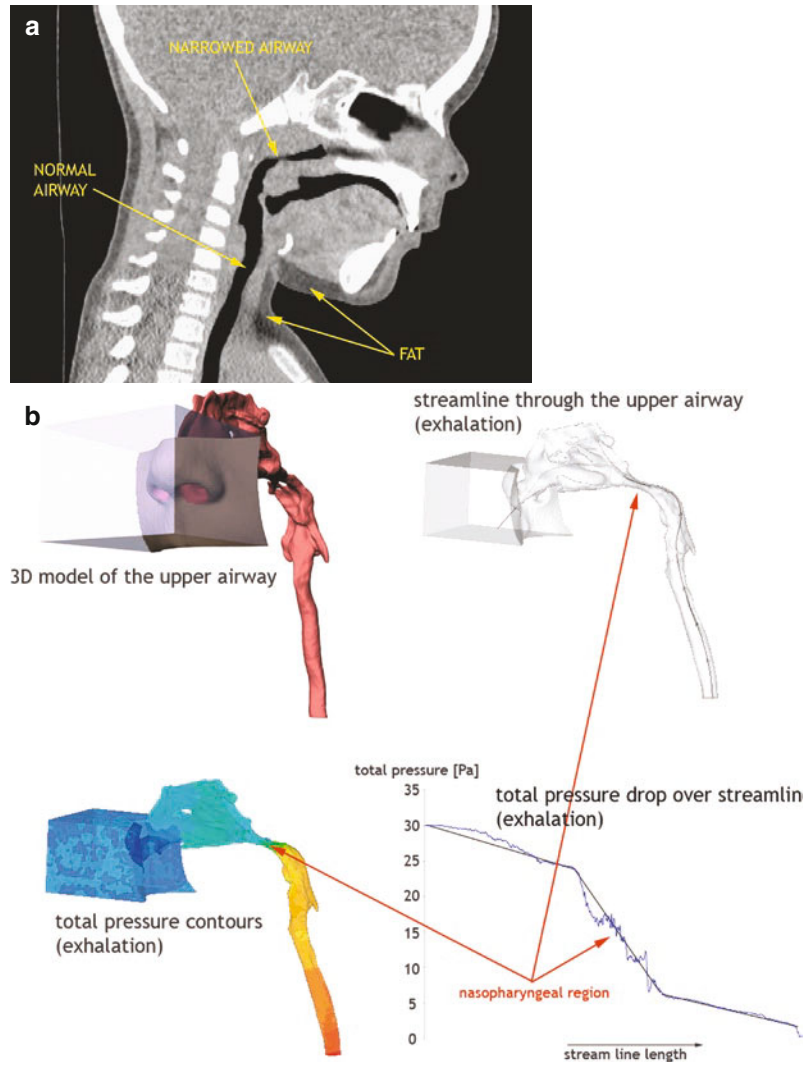

Fig. 28.3 CT scan (**a**) and 3D reconstruction with velocity and pressure profile (**b**) of an overweight child with OSAS

were diagnosed with OSAS. After surgical weight loss, only one subject had sleep apnea. In another study by Alqahtani and colleagues, 226 obese children underwent bariatric surgery. At baseline 43% of the children were diagnosed with OSAS; after 2 years of surgical weight loss, OSAS persisted in only 16% of the patients who had OSAS at baseline [56].

Our group studied the effect of weight loss on sleep-disordered breathing in obese teenagers enrolled in an inpatient weight loss program in two studies [25, 57]. In the first study, 61 patients were included, of which 37 were diagnosed with sleep apnea; SDB resolved in 23 of the 37 subjects, but 14 had residual sleep-disordered breathing despite a median weight loss of 24 kg. In the second study 114 patients were included, of which 41 were diagnosed with sleep apnea. After weight loss 12 subjects showed residual sleep apnea. Interestingly, the apnea–hypopnea index of the baseline screening study correlated significantly with the amount of weight loss that was achieved during the treatment program, suggesting that children with sleep apnea lost more weight than their peers without sleep apnea. Although our weight loss data seem promising, we have no data from obese children less than 10 years of age and no long-term results thus far. Nevertheless, weight loss is an essential component of any treatment regimen for obese children with sleep apnea and represents the first-line approach in those without adenotonsillar obstruction. Whether or not adenotonsillectomy is indicated in subjects resistant to weight loss remains to be determined.

Finally, the use of noninvasive ventilation (CPAP) should be considered in children with severe OSAS. However, CPAP is often poorly tolerated in children. Therefore, children using CPAP should undergo close follow-up to ensure maximal compliance. The additional value of upper airway surgery and/or weight loss in these subjects requires further study.

Conclusions for Daily Practice

1. Childhood obesity is associated with an increased prevalence of all types of sleep-disordered breathing (SDB), including habitual snoring, obstructive sleep apnea, and central sleep apnea. At this moment, there are no valid screening instruments for pediatric SDB. Pediatricians should therefore be aware of its presence in obese children and screen for it through a detailed history, physical examination, and timely referral for polysomnography.
2. The severity of obstructive sleep apnea syndrome (OSAS) in obese children is determined both by adenotonsillar hypertrophy and by adiposity. Future imaging studies are necessary to sort out the individual contribution of these risk factors.
3. Adenotonsillectomy is indicated for adenotonsillar hypertrophy, but its success rate is highly variable and there is a risk of postoperative weight gain.
4. Weight loss seems to be a promising alternative as first-line treatment. However, there are no data on its effects in young obese children and its long-term success rates.
5. CPAP can be considered in children with severe SDB.
6. SDB is associated with the metabolic syndrome. Intervention and longitudinal studies are warranted to assess its effect on long-term metabolic and cardiovascular morbidity.

Sleep Duration and Childhood Obesity

Introduction

Calorie intake and energy expenditure are the two fundamental targets in the prevention and treatment of childhood obesity. In recent years, sleep has received much attention since it might affect both energy intake and expenditure. Indeed, sleep plays a major role in the growth and general health of children through its effects on the diurnal rhythms of many hormones related to growth and energy homeostasis. In this section, we review epidemiological evidence suggesting an association between shortened sleep and childhood obesity and discuss possible pathophysiological mechanisms and recommendations for daily clinical practice.

Epidemiological Evidence

A meta-analysis published in 2008 showed that children with shorter sleep duration had a 58% higher risk for overweight or obesity; children with the least sleep had an even higher risk (92%) when compared with children who slept for longer periods of time [58]. For each hour increase in sleep, the risk of overweight/obesity was reduced on average by 9%. The study found a significant linear dose–response relationship only in children less than 10 years of age. Boys had a stronger inverse association than girls. More recent meta-analyses also confirmed the relationship between shorter sleep duration and obesity [59, 60].

Mechanisms Linking Short Sleep Duration to Obesity

Figure 28.4 presents a concise overview of possible mechanisms linking sleep curtailment to obesity in children [33, 61].

Epidemiological investigations and laboratory studies that subjected young adults to experimental sleep restriction have shown that sleep disruption is associated with adverse changes in several obesity- and appetite-regulating hormones; these include reductions in leptin and growth hormone and increases in ghrelin, insulin, and cortisol [33, 61–63]. The fall in leptin and rise in ghrelin, insulin, and cortisol promote food intake and fat deposition; the fall in growth hormone limits fat breakdown. In concert, these changes might promote the development of obesity and insulin resistance.

Sleep deprivation may also cause emotional distress and daytime fatigue and sleepiness, which may limit daytime physical activity. Interestingly, physical activity has a positive influence on sleep [64]; conversely, obesity and emotional distress can disrupt sleep. Thus, sleep deprivation may generate a vicious cycle that initiates or perpetuates weight gain.

It is important to note that much of the above evidence originates in studies in adults; little is known about the effects of sleep restriction on hormonal status in children. However, two recent cross-sectional studies in children found that sleep duration was negatively associated with insulin resistance [34, 35]. It also remains unclear if sleep disruption is a cause or a consequence of obesity; no studies to date have demonstrated that prolongation of sleep can prevent or reverse childhood obesity or reduce its severity [64].

Conclusions for Daily Practice

As noted above, no studies to date have shown that an increase in sleep duration can reduce body weight in obese children; indeed, it is unclear how much a person's sleep would have to be prolonged to exert such an effect. Nevertheless, it seems reasonable to include good sleep hygiene as a preven-

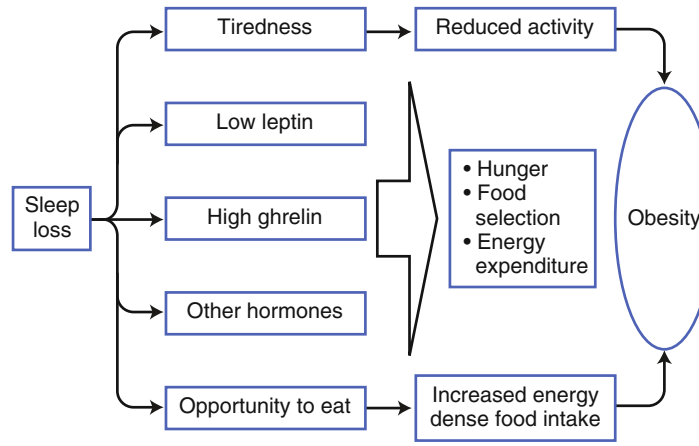

Fig. 28.4 Possible mechanisms linking sleep restriction with obesity. Data from [33, 61]

tive measure or as one of the general lifestyle changes necessary to treat childhood obesity. In our opinion this is warranted in view of the consistent epidemiological relationship between sleep duration and obesity in children. General recommendations for good sleep hygiene for children should include: assume a regular bedtime routine; provide a quiet, dark, and relaxing bedroom environment in which there is no place for other activities (television, computer, cell phone); avoid caffeinated drinks during evening hours; avoid bright light in the evening but provide exposure to bright light on awakening in the morning; and, finally, do not disrupt the circadian clock by staying up all night and sleeping in during weekends.

Editor's Comments and Questions

1. "Teenagers 13–18 years of age should sleep 8–10 h per 24 h on a regular basis to promote optimal health. Sleeping the number of recommended hours on a regular basis is associated with better health outcomes including: improved attention, behavior, learning, memory, emotional regulation, quality of life, and mental and physical health." So sayeth an expert consensus committee of the American Academy of Sleep Medicine.[a]

   Achieving this goal, however, can be quite difficult, as many teenagers, beset with homework, extracurricular activities, and the demands of social networking, get insufficient sleep on school days. Compensating (inadequately) for an accumulated sleep deficit, they tend to "sleep in" on Saturdays and Sundays. Is there any evidence that extra sleep on weekends can attenuate the effects of weekday sleep deprivation and reduce the risk of obesity?
2. As you rightly note, the association between sleep duration and adiposity is likely bidirectional and multifactorial. Lack of parental oversight and family disorganization can disrupt daily sleep patterns and meal regimens and may promote a dependence on fat-forming fast food. Conversely, sleep deprivation can limit daytime physical activity and may increase off-hour food intake. Studies of mice forced to eat during the day[b] (they are normally nocturnal feeders) and of human adults with shiftwork[c] suggest that disrupted feeding (and sleep) patterns can wreak havoc on circadian genes and hormones and cause weight gain and metabolic dysfunction.
3. Asthma is particularly common among obese children. How do asthma and obesity interact to impair sleep health?

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(b) Opperhuizen AL, van Kerkhof LW, Proper KI, Rodenburg W, Kalsbeek A. Rodent models to study the metabolic effects of shiftwork in humans. Front Pharmacol. 2015;6:50.

(c) McHill AW, Melanson EL, Higgins J, Connick E, Moehlman TM, Stothard ER, Wright KP Jr. Impact of circadian misalignment on energy metabolism during simulated nightshift work. Proc Natl Acad Sci U S A. 2014;111(48):17302–7.

Authors' Responses

1. Only a limited number of studies have investigated the relationship between catch-up sleep and obesity. In a cross-sectional study by Kim and colleagues,[a]

an increase in catch-up sleep in the weekend was associated with decreased odds of being overweight in children. However, the effect of weekend catch-up sleep varied according to weekday sleep duration, suggesting that overall sleep duration remains the major determining factor. Wing and colleagues[b] found similar results in their study, where children who compensated for their sleep deficit had lower BMI z-scores than those without sleep compensation during weekends or holidays. They also found that the effect of weekday sleep duration on obesity differed on the basis of weekend (or holiday) sleep duration.

2. But the pendulum can swing in the opposite direction as well: exercise training increases sleep duration and sleep efficiency in obese children; increasing sleep duration, in turn, can increase daytime physical activity energy expenditure. This can turn a vicious cycle into a virtuous one.[c]
3. Both children with asthma and children with obesity are at an increased risk for developing OSAS. Since both OSAS and asthma share the presence of activated regional airway inflammatory pathways, they could contribute to mutually exacerbating each other. Furthermore, it could be expected that OSAS in obese children is associated with more frequent oxygen desaturations because of a more restrictive pulmonary function[d,e] compared to normal-weight children. Therefore, it is possible that patients with both asthma and obesity will present with more severe OSAS compared to patients with only one of the latter.

   Fedele and colleagues found that children with both obesity and asthma had a shorter sleep duration than children with only obesity.[f] Furthermore, in an adult study by Zidan and colleagues a higher BMI was found to be an independent predictor of the development of OSAS in asthmatics.[g] In one of our own studies,[d] we found that obese patients with asthma had a significantly lower SaO_2 nadir compared to obese patients without asthma. Furthermore, there was also a trend for higher oxygen desaturation index in the obese children with asthma. In contrast, we could not confirm this finding in a larger cohort of obese adolescents as we could not find any difference in OSAS severity between obese adolescents with asthma and those without asthma (*unpublished data*).

   However, the relationship among obesity, OSAS, and asthma remains complex and further studies are warranted around this subject for a better understanding in the mechanisms behind these relationships.

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Pediatric Metabolic Syndrome: Long-Term Risks for Type 2 Diabetes and Cardiovascular Disease

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Abbreviations

cMetS	Continuous metabolic syndrome
CVD	Cardiovascular disease
MetS	Metabolic syndrome
T2DM	Type 2 diabetes mellitus

Introduction

In the late 1980s, Gerald Reaven coined the term "syndrome X" in his Banting Lecture at the American Diabetes Association to describe the grouping or clustering of metabolic disturbances that had been observed among certain adult populations who were insulin resistant [1]. He hypothesized that the clustering of these metabolic disturbances in an insulin-resistant individual might be involved in the development of type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and hypertension. Following his Banting Lecture, there was increased scientific and clinical interest in the clustering of these abnormalities, their interacting relationships, and its value in identifying individuals at increased risk for future cardio-metabolic disease (a collective term that includes both cardiovascular and metabolic complications) [2, 3].

The terms to refer to syndrome X evolved over time with most major organizations settling on "metabolic syndrome" (MetS). With major organizations such as the World Health Organization [4], International Diabetes Federation [5], and other European [6] and North American [7, 8] groups issuing an adult definition by the late 1990s or early 2000s, research into MetS rose sharply. As an example of the increased attention to the condition, a PubMed search using the terms "syndrome X" or "metabolic syndrome" or "insulin resistance syndrome" restricting to the 12 years from end 1988 to end 2000 returned approximately 1200 citations. In the 12 years from end 2000 to end 2012, it returned more than 26,500 citations.

The definition of MetS also changed over this time, with debate concerning the core metabolic disturbances included in the definition, the cutoff points for the included metabolic components, and whether any particular factor was an essential component of any definition. One example was the International Diabetes Federation [5] definition that required excess abdominal adiposity (a high waist circumference) as an essential component of MetS. Interestingly, Reaven never included excess adiposity in his description of syndrome X [1].

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In response to calls from clinicians and researchers for synchronization of the MetS definitions, the major stakeholders in earlier definitions and other authoritative groups (International Diabetes Federation Task Force on Epidemiology and Prevention; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity) joined forces to issue a "harmonized" adult definition of the MetS in 2009 [9]. The group agreed that the MetS definition encompasses elevated blood pressure, abdominal obesity, hyperglycemia, and dyslipidemia (low high-density lipoprotein cholesterol or high triglyceride levels), but not insulin resistance, and that no single component be requisite; instead, at least three of the five components must be present.

As the literature on MetS gained pace from the 1980s to the 2000s, so too did evidence from prospective cohort studies of children and adolescents on the long-term association of early-life risk factors with adult risk factors, early (or preclinical) signs of overt disease, or cardiometabolic outcomes [10]. Building on autopsy data from children and young adults spanning back to the 1950s [11–18], these studies showed evidence that although the major health complications and economic costs of cardio-metabolic disease do not typically occur before midlife, the disease process begins early in life and progresses through adolescence and young adulthood.

Current evidence suggests that child and adolescent risk factors including adiposity, blood pressure, smoking, blood lipid levels, markers of glucose homeostasis, and parental and socioeconomic factors associate with adult cardio-metabolic disease [19–21]. Although presentation of overt adult disease is very distant from the pediatric setting, the risk seems to be defined by the combined effect of early-life and later-life exposures [22]. For example, data from cohorts part of an international consortium have shown exposure to some child risk factors to be more strongly associated with markers of adult cardio-metabolic health than adult measures of the same exposure [10, 20, 23, 24].

Given the concomitant increase in interest in the MetS and accumulating evidence of the importance of early-life risk factors for later cardio-metabolic outcomes, it was only a matter of time before long-term studies of MetS in children with adult outcomes began to appear in the literature. The following section will overview the relevant literature that have accrued to date in this area. We will delineate some of the major findings, the existing challenges, and overview areas for future research priority.

Defining Metabolic Syndrome in the Pediatric Setting

A summary of the various definitions of MetS and the challenges in defining a pediatric definition is succinctly detailed by Ford and Li [25], Eisenmann [26], and Brambilla [27]. Although there have been attempts to define MetS for the pediatric setting, a consensus statement from the American Heart Association did not issue a pediatric definition of MetS and called for additional research [28]. One important part of this consideration by the writing group was the apparent short-term instability of pediatric dichotomous definitions (either you have or do not have MetS). This was exemplified in a cohort of adolescents aged 15 years studied by Goodman and colleagues [29], where only approximately 50% of those diagnosed with MetS maintained this diagnosis after 3 years. Later, Gustafson and colleagues [30] showed a high degree of instability in the dichotomous definition of MetS over shorter periods of 20 days and 1.5 years. In a group of obese children aged 6–17 years, only 31% maintained their MetS diagnosis after 20 days. This is remarkable given the short duration and that one would expect obese children, already meeting one criterion of MetS, would be more stable in their MetS profile. In a separate cohort of obese and nonobese children, Gustafson showed that only 45% maintained their MetS diagnosis after 1.5 years [30]. A long-term follow-up of the Cardiovascular Risk in Young Finns and Bogalusa Heart studies showed that between 40 and 60% of individuals originally diagnosed with MetS in childhood would maintain this status 24 years later [31]. The data from these studies are presented in Fig. 29.1. Although different MetS definitions were used in these studies, the data suggest a high degree of variation in rates of MetS diagnosis in the short term that tends to stabilize over time.

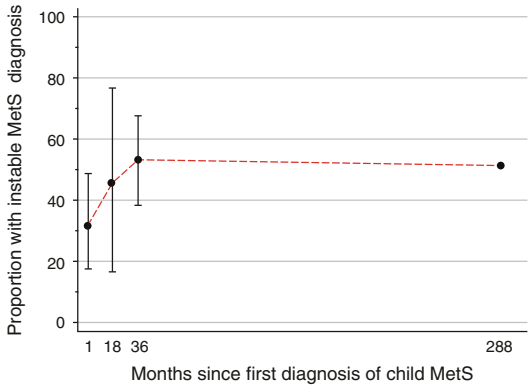

Fig. 29.1 Proportions of participants that lose their MetS diagnosis as a function of time. Error bars represent 95% confidence intervals. Data from 1 and 18 months were extracted from Gustafson et al. [30]. Data from 36 months were extracted from Goodman et al. [29]. Data from 288 months were extracted from Magnussen et al. [31]. Ninety-five percent confidence intervals are not provided for the 288-month point estimate, as this value was the mean from four different MetS definitions

There are several factors that may explain the observed short-term instability. First, physiological changes that occur in adolescence, particularly during puberty, have been shown to affect all components of the MetS [32–34]. Second, the cutoff points for components used in the MetS definitions do not always reflect pubertal stage, age, race, or sex differences in their distribution. Third, there may be misclassification of the components [35, 36], particularly as lipid and blood pressure guidelines for the pediatric setting recommend multiple rather than single measures prior to assigning a classification [37, 38]. Finally, the relative tracking, or persistence, of a cluster of risk factors does not seem to be as high as the individual risk factors themselves. In unpublished data from the Cardiovascular Risk in Young Finns Study, tracking of the individual MetS components over a 15-year period from 1986 to 2001 was much stronger (correlation coefficient, $r = 0.56$ for body mass index, $r = 0.51$ for high-density lipoprotein cholesterol, $r = 0.41$ for systolic blood pressure, $r = 0.34$ for triglycerides, $r = 0.31$ for glucose) than tracking of the full complement of MetS components defined by the National Cholesterol Education Program criteria ($r = 0.21$) or International Diabetes Federation criteria ($r = 0.17$).

The value of continuous MetS (cMetS) risk scores over dichotomous MetS definitions has also been advocated for possible consideration in the pediatric setting [26, 27]. In one formulation, *z*-scores for each individual metabolic syndrome component are calculated based on standard values adjusted for sex, age, and ethnicity. Assigning a negative value to HDL cholesterol (since higher levels are protective), the *z*-scores are then summed to derive a metabolic syndrome score. Compared with dichotomous definitions, cMetS scores reflect the entire continuum of metabolic and cardiovascular risk and do not require arbitrary cutoff points. Indeed, several studies have shown construct validity for cMetS in children and adolescents, with a higher cMetS score increasing as the number of components used in dichotomous MetS definitions increase [39–42]. Like the dichotomous definition, a number of different approaches have been used to construct cMetS scores, with a major limitation of most approaches being that scores are constructed based on cohort-specific *z*-scores, or distributions; unless the values are published, these cannot be replicated by others [26, 42]. Values derived from the National Health and Nutrition Examination Survey, if more widely applied, could avert this limitation [43].

Observational Data on the Association Between Child Metabolic Syndrome and Adult Cardio-metabolic Outcomes

Pediatric Metabolic Syndrome Predicts Adult Metabolic Syndrome, Type 2 Diabetes, and Cardiovascular Disease

Despite conjecture around a prevailing definition of MetS in the pediatric setting, a number of papers have examined the apparent utility of both dichotomous and continuous MetS in childhood in predicting future cardio-metabolic outcomes. An overview of the long-term studies that have examined the association between pediatric MetS and adult MetS, T2DM, preclinical markers of atherosclerosis, and CVD is presented in Table 29.1. Most studies report that individuals with MetS, a higher number of MetS components, or a higher cMetS score in childhood or adolescence are more likely to have adult-defined

Table 29.1 Overview of previous longitudinal studies that have examined the association between pediatric MetS and adult MetS, T2DM, preclinical markers of atherosclerosis, and CVD

Adult outcome	Author, publication year	Sample size	Childhood MetS definition	Baseline age	Follow-up age	Results summary
Metabolic syndrome	Chen, 2005 [65]	1474	Defined by the number of components (BMI, HOMA-IR, SBP, total-to-HDL-C ratio) in the bottom quarter of the sample distribution	Range: 4–17 years	Range: 19–41 years	Children with ≥3 variables in the bottom quarter had significantly lower prevalence of adult MetS (defined by the upper three quarters in adulthood) compared to children with <3 variables (3.8% vs. 14.6%, $p < 0.001$). Clustering of childhood risk variables at low levels was associated with decreased odds of MetS (OR = 0.29, $p = 0.008$) in adulthood, independent of family history of cardiovascular disease
	Morrison, 2007 [66]	771	MetS was defined if ≥3 of 5 abnormal values were recorded (triglycerides (≥110 mg/dL), BMI (age-specific 90th percentile on CDC 2000 growth charts), blood pressure (SBP or DBP ≥the age- and height-specific 90th percentile), HDL-C (≤50 mg/dL (female), or ≤40 mg/dL (male)), or glucose (≥110 mg/dL))	Range, 6–19 years; mean (SD), 12.9 (3.4) years	Range, 30–48 years; mean (SD), 38.4 (3.6) years	Childhood MetS was associated with increased odds of adult MetS (OR = 6.2, 95% CI = 2.8, 13.8)
	Morrison, 2008 [67]	814	MetS defined in two ways: (1) ATP III criteria; (2) using pediatric standards if ≥3 abnormal factors were recorded (triglycerides (≥110 mg/dL), BMI (age-specific 90th percentile on CDC 2000 growth charts), blood pressure (SBP or DBP ≥the age- and height-specific 90th percentile), and HDL-C and glucose cutoffs as per ATP III)	Range, 5–19 years; mean (SD), 12.8 (3.4) years	Range, 30–48 years; mean (SD), 38.4 (3.6) years	MetS in childhood predicted adult MetS (OR = 9.4, 95% CI = 4.0, 22.2)
	Schubert, 2009 [45]	1789	Defined by the number of components that reached threshold values (ranged from 1 to ≥4, Group 1, BMI (≥90th percentile), fasting glucose (≥100 mg/dL), triglycerides (≥90 mg/dL), HDL-C (<45 mg/dL), or SBP or DBP (≥90th percentile) and Group 2, BMI (≥85th percentile), fasting glucose (≥100 mg/dL), triglycerides (≥90th percentile), HDL-C (<45 mg/dL), or SBP or DBP (≥85th percentile))	Range, 6–20 years; mean (SD), 13.8 (3.1) years	Range, 25–55 years; mean (SD), 41.5 (5.8) years	Identifying multiple childhood components increased the specificity and positive predictive value of adult MetS (Group 1, ≥1 component, specificity = 57.2%, PPV = 37.9%; ≥4 components, specificity = 99.6%, PPV = 81.8%, Group 2: ≥1 component, specificity = 60.3%, PPV = 37.4%; ≥4 components, specificity = 99.8%, PPV = 66.7%)
	Magnussen, 2010 [31]	1781	Five MetS definitions were used. A modified NCEP definition, if ≥3 of 5 components were present (BMI, SBP, or DBP, triglycerides, glucose (≥75th percentile), or HDL-C (≤25th percentile)), and a modified IDF definition required elevated BMI to be present in addition to ≥2 of the remaining 4 components. Age- and sex-standardized pediatric cut points available in the literature were used to create a pediatric NCEP definition (≥3 of 5 components) and a pediatric IDF definition (obesity must be present in addition to ≥2 other components). A cMetS score was created following methods described by Wijndaele [68]	Range: 9–18 years	Range: 24–41 years	Children with MetS had 2.7–3.4 times increased risk of adult MetS, compared with children without MetS (all $p < 0.05$). A 1SD increase in childhood cMetS score increased the risk of adult MetS (RR = 1.5, 95% CI = 1.4, 1.6). Child BMI had similar predictive utility to child MetS status (modified NCEP: AUC = 0.62, 95% CI = 0.59, 0.64; modified IDF: AUC = 0.61, 95% CI = 0.59, 0.64; BMI: AUC = 0.65, 95% CI = 0.62, 0.68)

	Kelly, 2011 [54]	265	ATP III criteria were modified based on a previous study using NHANES data and adult criteria modified for children by the IDF to provide a dichotomous definition [69, 70]. A MetS cluster score was calculated by the average of deviates of MetS components standardized by their mean and SD	Range: 11–15 years; mean (SD): 13 (1.2) years	Range, 19–24 years; mean (SD), 21.6 (1.6) years	Dichotomous MetS was not a predictor of adult MetS; although those with MetS had a larger adult MetS cluster score (MetS present = 0.78 ± 0.71; MetS absent = 0.09 ± 0.70). Further, MetS cluster score tracked into adulthood (r = 0.51), and larger childhood MetS cluster scores were associated with larger adult MetS cluster scores (p-trend < 0.0001)
	Koskinen, 2014 [49]	1617	Categorized first by weight status (overweight/obese or normal weight (age- and sex-specific international BMI percentiles of Cole et al. [71])) and the number of metabolic disturbances (SBP, DBP, LDL-C, triglyceride, glucose (≥90th percentile), or HDL-C (≤10th percentile); classified as 0 or ≥1 metabolic disturbance)	Range: 9–24 years	Range: 30–45 years	Compared with healthy weight children with no metabolic disturbances, children with normal weight and ≥1 metabolic disturbance (RR = 1.8, 95% CI = 1.4, 2.4), overweight and no metabolic disturbances (RR = 2.3, 95% CI = 1.5, 3.5), and both overweight with ≥1 metabolic disturbance (RR = 5.2, 95% CI = 3.8, 7.1), all had an increased risk of developing MetS in adulthood
Type 2 diabetes mellitus	Franks, 2007 [72]	1604	An optimally weighted, standardized, continuously distributed, multivariate score was used that included fasting glucose, 2-h glucose, A1c, BMI, waist circumference, fasting insulin, HDL-C, triglycerides, SBP, and DBP	Range, 5–19 years; mean (SD), 12.1 (3.7)	Range: 10.5–24.5 years[a]	A 1SD increase in the score was associated with young onset T2DM (all participants: HRR = 3.4, 95% CI = 2.7–4.1). All HRR for the score were higher than any MetS component individually. A partial summary score (including only fasting glucose, 2-h glucose, HDL-C, and BMI) had similar predictive utility to the full score (including fasting glucose, 2-h glucose, A1c, BMI, waist circumference, fasting insulin, HDL-C, triglycerides, SBP, and DBP) (AUC = 0.77 vs. AUC = 0.78, p = 0.33)
	Morrison, 2008 [67]	814	MetS defined two ways: (1) ATP III criteria; (2) using pediatric standards if ≥3 abnormal factors were recorded (triglycerides (≥110 mg/dL), BMI (age-specific 90th percentile on CDC 2000 growth charts), blood pressure (SBP or DBP ≥the age- and height-specific 90th percentile), and HDL-C and glucose cutoffs as per ATP III)	Range, 5–19 years; mean (SD), 12.8 (3.4) years	Range, 30–48 years; mean (SD), 38.4 (3.6) years	Childhood MetS predicted adult T2DM (OR = 11.5, 95% CI = 2.1, 63.7)
	Schubert, 2009 [45]	1789	Defined by the number of components that reached threshold values (ranged from 1 to ≥4, Group 1: BMI (≥90th percentile), fasting glucose (≥100 mg/dL), triglycerides (≥90 mg/dL), HDL-C (<45 mg/dL), or SBP or DBP (≥90th percentile) and Group 2: BMI (≥85th percentile), fasting glucose (≥100 mg/dL), triglycerides (≥90th percentile), HDL-C (<45 mg/dL), or SBP or DBP (≥85th percentile))	Range, 6–20 years; mean (SD), 13.8 (3.1) years	Range, 25–55 years; mean (SD), 41.5 (5.8) years	Identifying multiple childhood components increased the specificity and maintained high negative predictive value of predicting adult T2DM (Group 1: ≥1 component, specificity = 52.4%, NPV = 98.2%; ≥4 components, specificity = 99.0%, NPV = 95.5%; Group 2: ≥1 component, specificity = 56.2%, NPV = 97.7%; ≥4 components, specificity = 99.7%, NPV = 94.9%)

(continued)

Table 29.1 (continued)

Adult outcome	Author, publication year	Sample size	Childhood MetS definition	Baseline age	Follow-up age	Results summary
	Magnussen, 2010 [31]	1781	Five MetS definitions were used. A modified NCEP definition, if ≥3 of 5 components were present (BMI, SBP, or DBP, triglycerides, glucose (≥75th percentile), or HDL-C (≤25th percentile)), and a modified IDF definition required elevated BMI to be present in addition to ≥2 of the remaining 4 components. Age- and sex-standardized pediatric cut points available in the literature were used to create a pediatric NCEP definition (≥3 of 5 components) and a pediatric IDF definition (obesity must be present in addition to ≥2 other components). A cMetS score was created following methods described by Wijndaele [68]	Range: 9–18 years	Range: 24–41 years	Children with MetS had 2–3 times the risk of developing adult T2DM compared with children without MetS. A 1SD increase in childhood cMetS was associated with 30% increased risk of adult T2DM. However, the predictive utility of childhood MetS (modified NCEP, AUC = 0.58, 95% CI = 0.50, 0.66; modified IDF, AUC = 0.61, 95% CI = 0.53, 0.69) was similar to BMI (AUC = 0.64, 95% CI = 0.56, 0.72)
	Morrison, 2011 [73]	556	MetS was dichotomously defined if ≥3 abnormal values of 5 measures were recorded (triglycerides (≥110 mg/dL), waist circumference (race- and age-specific 85th percentile), blood pressure (SBP or DBP ≥ the age- and height-specific 90th percentile), HDL-C (≤50 mg/dL), or glucose (≥100 mg/dL))	Mean: 10 years	Mean: 24 years	Those with MetS at age 10 years had increased risk of adult IFG and T2DM (RR = 2.72, 95% CI = 1.79, 4.13)
	Magnussen, 2012 [46]	1757	Using age-, sex-, race-, cohort-, and study year-specific *z*-scores, MetS was defined if ≥3 of 5 abnormal values were recorded (BMI, SBP, or DBP, triglycerides, glucose (≥75th percentile), or HDL-C (≤25th percentile))	Range: 9–18 years	Range: 24–39 years	Participants with MetS in childhood and adulthood had 12.2 times the risk (95% CI = 6.3, 23.9) of adult T2DM compared with those who did not have MetS at either time point. Participants who had MetS in childhood but not in adulthood had similar risk to those who never had MetS in childhood (RR = 1.1, 95%; CI = 0.3, 3.7)
	Koskinen, 2014 [49]	1617	Children were categorized by weight status (overweight/obese or normal weight (age- and sex-specific international BMI percentiles of Cole et al. [71])) and number of metabolic disturbances (SBP, DBP, LDL-C, triglyceride, glucose (≥90th percentile), or HDL-C (≤10th percentile); classified as 0 or ≥1 metabolic disturbance)	Range: 9–24 years	Range: 30–45 years	Overweight children with no metabolic disturbances (RR = 6.9, 95% CI = 3.0, 15.8) and children who were both overweight and had ≥1 metabolic disturbance (RR = 6.6, 95% CI = 2.9, 15.1) had an increased risk of adult T2DM compared with normal weight children with no metabolic disturbances
	DeBoer, 2015 [74]	629; 354	MetS defined if ≥3 of 5 components were reached (triacylglycerol (110 mg/dL), HDL-C (40 mg/dL), BMI (≥90th percentile), glucose (100 mg/dL), or SBP or DBP (≥90th percentile)). This definition was a modification of NCEP ATP III criteria whereby BMI replaced waist circumference and different triglyceride, SBP, and DBP cut points were used. A MetS-severity *z*-score was created from each individual MetS component *z*-score based on equations specific to sex and racial subgroup [43]	Range, 6–19 years; mean (SD), 12.9 (3.3) years	Mean (SD), 38.4 (3.5) years; mean (SD), 49.6 (3.5) years	Childhood MetS was associated with T2DM in adulthood (age 38.5 years, OR = 4.4, 95% CI = 1.2, 16.4; age 49.6 years, OR = 7.8, 95% CI = 1.4, 43.8). For every one-unit increase in childhood MetS *z*-score, the OR for developing future T2DM was 2.7 by age 38.5 years (95% CI = 1.6, 4.4) and 2.8 by age 49.6 years (95% CI = 1.3, 6.0)

	Magnussen, 2016 [42]	1453	Dichotomous MetS was defined if ≥3 of 5 components were met using age- and sex-specific *z*-score cut points (BMI, SBP, or DBP, triglycerides, glucose (≥75th percentile), or HDL-C (≤25th percentile)). Numerous continuous MetS definitions were used. These were derived from principal component analysis, sum of standardized *z*-scores, sum of standardized residual, and a modified NHANES definition using sex- and race-specific equations	Range, 9–18 years; mean (SD): male, 13.3 (3.3) years; female, 13.5 (3.3) years	Range, 24–43 years; mean (SD): male, 36.5 (4.9) years; female, 36.9 (4.9) years	A 1SD increase in childhood cMetS score was associated with a 30–49% increased risk of T2DM. Children with MetS (defined dichotomously) had increased risk of developing T2DM in adulthood (RR = 2.54, 95% CI = 1.25, 5.17). The predictive utility of dichotomous and continuous MetS was similar (dichotomous, AUC = 0.59, 95% CI = 0.50, 0.67; continuous, range AUC = 0.59, 95% CI = 0.49, 0.69 to AUC = 0.62, 95% CI = 0.52, 0.72)
Preclinical markers of atherosclerosis	Chen, 2005 [65]	1474	Defined by the number of variables (BMI, HOMA-IR, SBP, total-to-HDL-C ratio) that had levels in the bottom quarter of study sample	Range: 4–17 years	Range: 19–41 years	As the number of childhood variables in the bottom quarter increased, mean values of adult cIMT decreased (p-trend = 0.013)
	Magnussen, 2010 [31]	1781	Five MetS definitions were used. A modified NCEP definition, if ≥3 of 5 components were present (BMI, SBP, or DBP, triglycerides, glucose (≥75th percentile), or HDL-C (≤25th percentile)), and a modified IDF definition required elevated BMI to be present in addition to ≥2 of the remaining 4 components. Age- and sex-standardized pediatric cut points available in the literature were used to create a pediatric NCEP definition (≥3 of 5 components) and a pediatric IDF definition (obesity must be present in addition to ≥2 other components). A cMetS score was created following methods described by Wijndaele [68]	Range: 9–18 years	Range: 24–41 years	Children with MetS had approximately double the risk of developing high cIMT in adulthood, and increased childhood cMetS was associated with increased risk of high cIMT in adulthood compared with children without MetS. BMI had similar predictive utility (modified NCEP, AUC = 0.57, 95% CI = 0.53, 0.60; modified IDF, AUC = 0.56, 95% CI = 0.53, 0.60; BMI, AUC = 0.60, 95% CI = 0.56, 0.64)
	Koivistoinen, 2011 [47]	945	Values of age- and sex-specific cut points were used for each MetS component, and MetS was defined if ≥3 of 6 risk factors were present (BMI (≥85th percentile), triglycerides, SBP, fasting insulin (≥75th percentile), fasting blood glucose (≥6.1 mmol/L), or HDL-C (≤25th percentile)). The second MetS definition required hyperinsulinemia and ≥2 of the remaining 5 risk factors to be present	Range: 9, 12, 15 or 18 years	Range: 30–39 years	Children with MetS had higher pulse wave velocity in adulthood, compared to those without MetS ($p < 0.007$). As the number of MetS components in childhood increased, so did pulse wave velocity (p-trend = 0.005). Participants that resolved their MetS from childhood to adulthood had lower pulse wave velocity compared to those who had persistent MetS ($p < 0.001$)
	Magnussen, 2012 [46]	1757	Using age-, sex-, race-, cohort-, and study year-specific *z*-scores, MetS was defined if ≥3 of 5 abnormal values were recorded (BMI, SBP, or DBP, triglycerides, glucose (≥75th percentile), or HDL-C (≤25th percentile))	Range: 9–18 years	Range: 24–39 years	Participants with MetS in childhood and adulthood had 3.4 times increased risk (95% CI = 2.4, 4.9) of high cIMT in adulthood compared to those who did not have MetS at either time point. Those who resolved their MetS between childhood and adulthood had similar risk to those who never had MetS in childhood (RR = 1.3, 95% CI = 0.9, 2.1)

(continued)

Table 29.1 (continued)

Adult outcome	Author, publication year	Sample size	Childhood MetS definition	Baseline age	Follow-up age	Results summary
	Koskinen, 2014 [49]	1617	Children were categorized by weight status (overweight/obese or normal weight (age- and sex-specific international BMI percentiles of Cole et al. [71])) and the number of metabolic disturbances they have (SBP, DBP, LDL-C, triglyceride, glucose (≥90th percentile), or HDL-C (≤10th percentile))	Range: 9–24 years	Range: 30–45 years	Compared to children who were normal weight and had no metabolic disturbances (mean = 0.616, SEM = 0.003 mm), children who had normal weight and ≥1 metabolic disturbance (mean = 0.627, SEM = 0.005 mm), overweight and no metabolic disturbance (mean = 0.647, SEM = 0.010 mm), and those both overweight with ≥1 metabolic disturbances (mean = 0.670, SEM = 0.010 mm), all had larger cIMT values (p-trend <0.0001)
	Magnussen, 2016 [42]	1453	Dichotomous MetS was defined if ≥3 of 5 components were met using age- and sex-specific z-score cut points (BMI, SBP, or DBP, triglycerides, glucose (≥75th percentile), or HDL-C (≤25th percentile)). Numerous continuous MetS definitions were used. These included principal component analysis, sum of standardized z-scores, sum of standardized residual, and a modified NHANES definition using sex- and race-specific equations	Range: 9–18 years; mean (SD): male: 13.3 (3.3) years; female: 13.5 (3.3) years	Range: 24–43 years; mean (SD): male: 36.5 (4.9) years; female: 36.9 (4.9) years	A 1SD increase in childhood cMetS scores increased the risk of high cIMT by 12–32%. When defined dichotomously, children with MetS had increased risk of developing high cIMT in adulthood compared with children without MetS (RR = 1.76, 95% CI = 1.26, 2.43). The predictive utility of dichotomous and continuous MetS definitions was similar (dichotomous, AUC = 0.55, 95% CI = 0.52, 0.59; continuous, range AUC = 0.55, 95% CI = 0.50, 0.60 to AUC = 0.58, 95% CI = 0.52, 0.63)
Cardiovascular disease	Morrison, 2007 [66]	771	MetS was defined if ≥3 of 5 abnormal values were recorded (triglycerides (≥110 mg/dL), BMI (age-specific 90th percentile on CDC 2000 growth charts), blood pressure (SBP or DBP ≥ the age- and height-specific 90th percentile), HDL-C (≤50 mg/dL (female) or ≤40 mg/dL (male)), or glucose (≥110 mg/dL))	Range: 6–19 years; mean (SD): 12.9 (3.4) years	Range: 30–48 years; mean (SD): 38.4 (3.6) years	Childhood MetS was associated with increased odds of adult CVD (OR = 14.6, 95% CI = 4.8, 45.3)
	DeBoer, 2015 [75]	629; 354	A MetS-severity z-score was created using BMI z-score, SBP, fasting triglycerides, and fasting glucose within an equation which summed the product of constant values and each individual MetS component, based on equations specific to sex and racial subgroup [43]	Mean: 12.9 years	Mean: 38.4 years; mean: 49.6 years	Larger childhood MetS-severity z-scores were associated with adult early-stage CVD (AUC = 0.91) and later-stage CVD (AUC = 0.65)

[a]Follow-up age not explicitly stated in this study. This range was calculated from baseline ages plus median length to follow-up of all participants (baseline age, 9–15 years + median length to follow-up, 5.5 years)

Abbreviations: *ATP III* Adult Treatment Panel III report, *AUC* area under the curve, *A1c* glycated hemoglobin, *BMI* body mass index, *CDC* Centre for Disease Control, *CI* confidence intervals, *cIMT* carotid intima-media thickness, *cMetS* continuous metabolic syndrome score, *CVD* cardiovascular disease, *HDL-C* high-density lipoprotein cholesterol, *HOMA-IR* homeostatic model assessment of insulin resistance, *HRR* hazard rate ratio, *IDF* International Diabetes Federation, *IFG* impaired fasting glucose, *LDL-C* low-density lipoprotein cholesterol, *MetS* metabolic syndrome, *NCEP* National Cholesterol Education Program, *NHANES* National Health and Nutrition Examination Survey, *NPV* negative predictive value, *OR* odds ratio, *PPV* positive predictive value, *r* partial Pearson's tracking correlation coefficient, *RR* relative risk, *SD* standard deviation, *SEM* standard error of the mean, *T2DM* type 2 diabetes mellitus

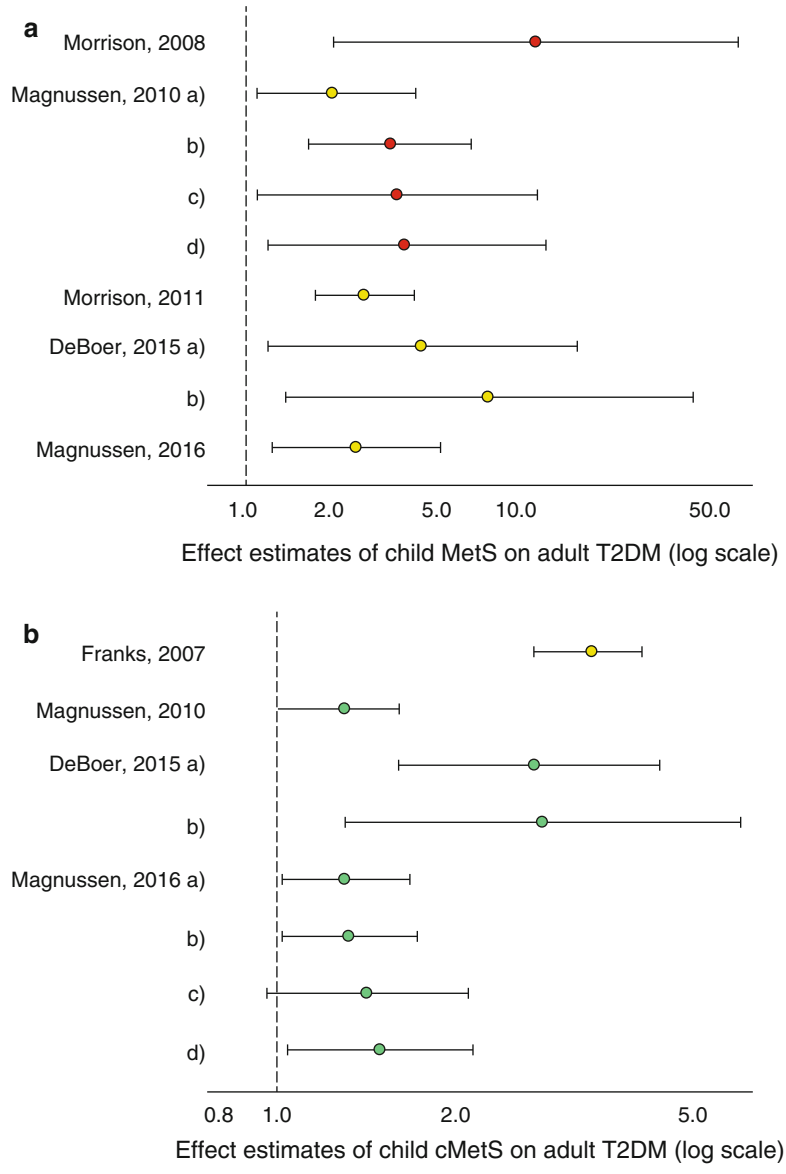

Fig. 29.2 (**a**, **b**) Plot showing the association between childhood (**a**) dichotomous and (**b**) continuous scores of MetS with adult T2DM extracted from studies reporting relative frequency estimates (odds ratio, relative risk, or hazard risk ratio). The data presented are for illustrative purposes only as we have combined different effect estimates that are not directly comparable. The point estimates are color coded according to effect magnitudes as small (green), moderate (yellow), and large (red) [44]. Error bars represent 95% confidence intervals

MetS, T2DM or impaired fasting glucose, early (preclinical) markers of atherosclerosis, and prevalent CVD. In compiling these data, it was evident that although a reasonable amount of evidence has amassed examining the association between pediatric MetS and important long-term cardio-metabolic outcomes, there has been no uniform reporting of effect estimates or exposure in the outcome groups from these studies. Combining this with a nonuniform definition of MetS in the pediatric setting will make meta-analysis of these studies challenging in the future.

Because most data were available for the association between child dichotomous and continuous MetS with adult T2DM, we extracted effect estimates and confidence intervals from studies reporting relative frequency estimates and displayed these in Fig. 29.2a, b. As we have combined different effect estimates (odds ratios, relative risks, hazards rate ratios) that are not directly comparable, the data presented in Fig. 29.2a, b are strictly for illustrative purposes. However, we have color coded the point estimates as small (green), moderate (yellow), and

large (red) effect magnitudes to aid interpretation [44]. The data displayed suggest that pediatric populations with MetS (Fig. 29.2a) or a higher cMetS score (Fig. 29.2b) are more likely to develop T2DM in adulthood across samples of participants with different baseline ages, length to adult follow-up, and definitions of pediatric MetS.

To date, only two papers have reported on the association between pediatric MetS and adult CVD (Table 29.1). Both papers report data from the Princeton Lipid Research Cohort Study. Morrison and colleagues reported an increased odds of adult CVD 25 years after baseline assessment among those with pediatric MetS, whereas DeBoer reported an increased odds of adult CVD for each one-unit increase in a cMetS score 25 years and 38 years later. Although these data are limited by use of self-report outcomes and relatively small case numbers, they do lend support to the hypothesis of a long-term increased risk of CVD among those children and adolescents with MetS or those with a heightened clustering of MetS components. A number of papers from the Cardiovascular Risk in Young Finns and Bogalusa Heart studies support a role of MetS in the development of CVD, whereby higher carotid artery intima-media thickness and pulse wave velocity were reported among adults who had MetS or a higher MetS load in childhood (Table 29.1). These markers of atherosclerosis precede overt CVD and are able to be examined noninvasively among free-living populations to provide an indication of the burden of atherosclerosis. It is expected that a large international consortium of seven prospective cohort studies (International Childhood Cardiovascular Cohort, i3C, Consortium) will soon be able to provide more robust data on the utility of child MetS in predicting confirmed adult CVD [10].

Taken together, these prospective data linking child exposure to MetS with adult cardio-metabolic outcomes are largely consistent with what has been observed in adult studies. Beyond confirming the link between child exposure and adult outcomes, many of these observational studies provided additional information on the potential clinical utility of MetS in the pediatric setting.

Clinical Utility of Pediatric Metabolic Syndrome in Predicting Adult Cardio-metabolic Diseases

With the instability of a pediatric "point-in-time" MetS diagnosis well recognized, several observational studies expanded on what clinical utility a MetS diagnosis might provide in the pediatric setting for predicting future cardio-metabolic outcomes. Schubert and colleagues [45] proposed that a dichotomous MetS definition in the pediatric setting could rule out those children and adolescents at very low likelihood of developing adult MetS and instead focus prevention efforts on those at *unclear* potential (those who met the MetS criteria in childhood). They based this suggestion on observational data from three prospective cohort studies (Fels Longitudinal Study, Muscatine Study, and Princeton Follow-up Study) where a high proportion of participants without MetS in childhood persisted without MetS into adulthood (negative predictive value, non-MetS tracking) and a high proportion of those without MetS in adulthood also did not have MetS in childhood (specificity). These data were later confirmed by Magnussen and coworkers in pooled analyses of the Cardiovascular Risk in Young Finns and Bogalusa Heart studies [31].

Building on these data, analyses from the Cardiovascular Risk in Young Finns Study examined what lasting impact a diagnosis of MetS in childhood had on adult cardio-metabolic outcomes based on whether or not the diagnosis was maintained into adulthood [46–48]. The results from these studies showed no residual, or lasting, effect of child MetS on these outcomes, but a substantially higher risk was observed among those who had acquired MetS in adulthood or those who had maintained MetS from childhood to adulthood. Though these data reinforce the idea that prevention of MetS or improvement in the risk factor profile may cause a loss of MetS diagnosis in the time between childhood and adulthood, they are also consistent with the term *unclear potential* that Schubert and coworkers described for those with a childhood MetS diagnosis.

One of the most important findings came from a joint analysis with data from the Cardiovascular

Risk in Young Finns and Bogalusa Heart studies. Magnussen and coworkers [31] found that classification of children and adolescents into body mass index categories of normal weight vs. overweight or obese was an equivalent or better predictor of adult T2DM and high carotid intima-media thickness than multiple dichotomous MetS definitions. From a clinical perspective, these data suggested that to identify youth at risk for important future cardio-metabolic outcomes, a simple, cost-effective, and time-efficient measure could be used in place of MetS. Consistent with these data were those from Koskinen and coworkers [49] who showed that overweight or obese children were at increased risk for future cardio-metabolic outcomes irrespective of other metabolic risk factors. The role of excess adiposity in early life as an antecedent to subsequent development of other cardio-metabolic risk factors, including insulin resistance or heightened insulin levels, has been suggested in several cohorts [31, 50–53]. Indeed, excess adiposity seems to be the major initiating factor in the development of subsequent cardio-metabolic disease and therefore may be a critical first target for identifying those at risk in the pediatric setting.

Because the dichotomous approach to MetS had low clinical utility and was thought to exclude too much clinically important information, alternative approaches to assessing MetS in children and adolescents were explored, including the utility of dichotomous vs. continuous MetS scores in childhood for prediction of subsequent MetS in adulthood. Kelly and coworkers [54] concluded that a cMetS score tracked ($r = 0.51$) much more strongly than a dichotomous definition between age 13 and 22 years. They again showed a high degree of instability in the dichotomous definition even though it did associate with adult cardio-metabolic risk factor levels [54]. However, they did not provide any direct comparison of the dichotomous vs. continuous approach. In contrast, Magnussen and coworkers [42] directly compared four different childhood cMetS scores with a dichotomous MetS definition but did not show any substantial improvements in the prediction of adult cardio-metabolic outcomes 23 years later. Importantly, confidence intervals for the area under the receiver operating characteristic curves often included 0.5, suggesting that prediction of adult cardio-metabolic outcomes using either continuous or dichotomous child MetS definitions performs no better than flipping a coin.

Collectively, the available data consistently suggest that despite the observed short- and long-term instability in a pediatric MetS diagnosis, children and adolescents with MetS do have increased risk of adult cardio-metabolic outcomes. However, what seems equally consistent in the current evidence is that, from a clinical standpoint, there is only limited support for predicting individual future risk on the basis of a single point-in-time diagnosis of MetS in childhood or early adolescence. Predictive value increases dramatically, however, if the metabolic syndrome in childhood persists into late adolescence and adult life.

Future Research Directions

A call for additional research into different ways of defining pediatric MetS and other early-life risk factors that predispose to adult cardio-metabolic outcomes probably seems too obvious. However, other questions must also be addressed. For example, there has been some suggestion [55, 56] that adding genetic information to conventional risk factors in childhood may incrementally improve prediction for later cardio-metabolic outcomes. Although this has not been observed for all components of MetS [57, 58], no study has yet determined if adding risk alleles for MetS identified from large genome-wide association studies to conventional risk factors improves risk prediction. Indeed, there have been conflicting reports of genes for MetS with suggestions for and against pleiotropic genetic effects across traits [59, 60]. There has been some attempt to examine the utility of other child risk factors [61–64], with those most promising including family history, fasting insulin and insulin resistance, and inflammatory markers. However, consideration of other factors

including possible protective factors need to be better considered. Another important area for enquiry is to identify when in the life course, or at what age, components of MetS other than adiposity begin to influence later cardio-metabolic outcomes. The work by Magnussen and coworkers [31] showed that BMI in children and adolescents is adequate to stratify individuals into risk categories but there must be a time in the life course when these risk factors become operative. Identifying when in the life course this critical or change point occurs could be important for prevention and intervention programs and would provide guidance for assessing risk factors in addition to adiposity. It may be that this tipping point occurs in adolescence but one limitation of the observational data currently available is that they do not attempt to stratify by childhood age. Most studies do not have a substantial enough sample size to stratify by age and sex, but future data from the International Childhood Cardiovascular Cohort Consortium [10] might be the first to provide comprehensive data on this issue.

Conclusions

Risk factors commensurate with the MetS do seem to cluster in children and adolescents, and those with a greater MetS load appear at increased likelihood of developing important cardio-metabolic outcomes in adulthood such as T2DM and preclinical or overt CVD. However, dichotomizing children and adolescents according to their MetS status seems to be highly unstable, with observational studies showing that high proportions of those diagnosed with MetS do not have it a matter of weeks or months later. While debate continues as to whether an ideal definition of MetS for the pediatric setting exists, and what that incorporates, current evidence is not sufficient to support any routine clinical monitoring of the MetS among children and adolescents. Future research needs to examine other factors that may improve prediction and at what age these factors should be measured. If new factors are found, they should be routinely assessed for their clinical utility and compared to more simple measures of risk in children and adolescents such as excess adiposity. Although more data on hard clinical end points are needed linking child MetS to adult outcomes, in many respects the data for the utility of MetS in the clinical pediatric setting is reflecting what has been shown in the adult setting. That is, though it predicts future cardio-metabolic outcomes, MetS may not provide additional clinical utility beyond other risk factors.

Editor's Comments

The concept of the metabolic syndrome is attractive because its components can be explained, at least in part, by complications of insulin resistance and the compensatory hyperinsulinemia that commonly result from progressive weight gain; see discussion in Chap. 1. It is perhaps not surprising, then, that the most reliable determinant of future metabolic risk in adolescents is adiposity, which tends to be more stable than single point-in-time measurements of blood pressure, glucose tolerance, or triglycerides and HDL cholesterol.

But simple measures of adiposity have limitations, as Asian patients develop metabolic complications at relatively low BMI (presumably because of higher ratio of fat mass to lean body mass) and the levels of triglycerides and liver enzymes are characteristically lower in African American than in Caucasian and Hispanic children for any given BMI. The long-term risks of type 2 diabetes and cardiovascular disease are also modulated by sex steroids through mechanisms that remain poorly understood. The use of a continuous MetS risk score adjusted for sex, age, and ethnicity would therefore seem to make good sense.

It should also be noted that the clinical value of biochemical risk factor measurements extends beyond their ability to predict future diabetes or cardiovascular disease. They can identify patients who

currently have glucose intolerance, dyslipidemia, microalbuminuria, and/or fatty liver disease that may require immediate intervention. Moreover, in some cases the detection of metabolic dysfunction can motivate patients and their families to make the difficult behavioral changes that will reduce body weight and attenuate their long-term risks of chronic metabolic disease.

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Childhood Obesity, Atherogenesis, and Adult Cardiovascular Disease

30

Amy S. Shah and Elaine M. Urbina

Atherosclerosis Development

The process of atherosclerosis (Fig. 30.1) begins in childhood, progresses in adolescence, and can result in complications by middle adulthood. Atherosclerosis commences with the development of fatty streaks, deposits of cholesterol and its esters that can be detected in the intima of the aorta by 3 years of age [1]. As lipids continue to accumulate in fatty streaks, the resulting core of extracellular lipid becomes covered by a cap of smooth muscle and connective tissue to form a fibrous plaque. Fibrous plaques can then undergo various modifications. They may continue to increase in thickness and protrude into the arterial lumen, but since the artery is simultaneously remodeled, obstruction to blood flow is minimized. Fibrous plaques may also become calcified, a change that renders them detectable by X-ray but does not cause obstruction to blood flow. Finally, small vessels may grow into the plaque and rupture, causing hemorrhage, rapid swelling of the plaque, and obstruction to blood flow [2].

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Autopsy Studies

Spurred by data from Korean and Vietnam War veterans demonstrating significant atherosclerosis in young men, both the Bogalusa Heart study and the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study aimed to determine the impact of acquired and inherited cardiovascular risk factors on early atherosclerosis.

The Bogalusa Heart Study performed autopsies on 204 young participants between the ages of 2 and 39 years (mean age 19.6 years) who died from accidental injury, homicide, or suicide. They found fatty streaks in 60% of cases between 2–15 years of age and in 85% of cases between 21–39 years of age [3] and raised fibrous plaques in the aorta and coronary arteries in approximately 20% of cases 2–15 years of age and 70% of cases 26–39 years of age. Furthermore, they observed that the prevalence and the extent of atherosclerosis in the aorta and coronary arteries not only increased with age but was greater in those with higher body mass index (BMI), blood pressure, and serum levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C).

The PDAY study examined the right coronary arteries and aortas in 2876 individuals' ages 15–34 years [4, 5]. By 15–19 years of age, fatty streaks were evident and occupied approximately 25% of the aortic intima in both the thoracic and abdominal aortas. In adults 30–34 years of age, fatty streaks occupied nearly 40% of the abdomi-

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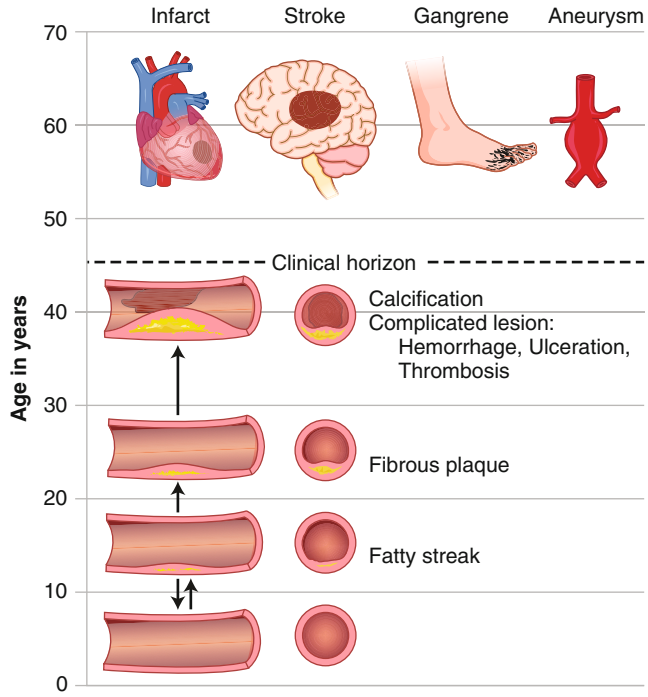


Fig. 30.1 Natural history of atherosclerosis beginning with the development of the fatty streak in childhood and adolescence. Some fatty streaks accumulate more lipid with age and begin to develop a fibromuscular cap, forming the lesion termed a fibrous plaque. In subsequent years, fibrous plaques enlarge and undergo calcification, hemorrhage, ulceration or rupture, and thrombosis. Thrombotic occlusion precipitates one of the clinical diseases, depending on which artery is affected (Adapted with permission from McGill, H.C., Jr. The pathogenesis of atherosclerosis. Clin Chem 1988;34:B33–39)

nal aorta. In the right coronary artery, fatty streaks increased from approximately 2% of the intimal surface at the age of 15–19 years to approximately 8% at the age of 30–34 years. Furthermore, there was greater surface involvement of both fatty streaks and raised lesions in the coronary arteries in males with a higher BMI (BMI >30) compared to those with a lower BMI (BMI <30). These autopsy studies documented that atherosclerosis begins in childhood, progresses with age, and is accelerated by obesity and obesity-related comorbidities [6–14].

Obesity as a Risk Factor

The concept that obesity is related to atherosclerosis and heart disease has a controversial history. Early reviews concluded that, except through its contribution to hypertension and type 2 diabetes, obesity had no effect on cardiovascular disease [15–17]. However, as the prevalence of obesity has increased and as the results of long-term (>25 years) follow-up studies have become available [18–20], evidence of an independent association has been confirmed [21].

Longitudinal studies in children and adolescents, such as the Muscatine Study, Bogalusa Heart Study, and Cardiovascular Risk in Young Finns Study, have shown that obesity in childhood tracks to adulthood and that a higher BMI during childhood increases the risk of cardiovascular disease in adulthood [22–24]. This concept was also illustrated in a large prospective cohort study of 277,000 Danish children born between 1930 and 1976 for whom childhood BMI measurements were available from mandatory school examinations [25]. BMI measured at 7–13 years of age was positively associated with coronary heart disease in adults older than 25 years of age, such that each

1-unit increase in BMI Z-score increased the risk of both fatal and nonfatal cardiovascular events by 33% [25]. In addition, in a meta-analysis of 21 cohort studies involving 300,000 persons, overweight (BMI-25-30) compared to normal weight individuals showed a risk ratio for coronary heart disease events of 1.32 (95% CI, 1.24–1.40); and obesity (BMI > 30) compared to normal weight, a risk ratio of 1.81 (95% CI, 1.56–2.10) [26] adjusted for age, sex, physical activity, and smoking. As such, both overweight and obesity are now firmly established as independent determinants of cardiovascular disease.

Obesity-Related Risk Factors

Obesity clusters with other metabolic diseases such as dyslipidemia, hypertension, hyperinsulinemia, inflammation, and diabetes mellitus, each which is independently associated with cardiovascular disease [27]. The National Health and Nutrition Examination Survey found that the prevalence of any cardiovascular disease risk factor increases with higher BMI as follows: 37, 49, and 61% for normal weight, overweight, and obese adolescents, respectively [28]. Others have shown that children or adolescents who are overweight or obese are more likely to be hypertensive, have dyslipidemia and insulin resistance, develop type 2 diabetes mellitus, and be overweight as adults [29]. Given that individuals often have more than one risk factor and their effects are cumulative, the PDAY study developed a coronary artery score using demographic and risk factor data (age, sex, BMI, non-HDL and HDL cholesterol, smoking and blood pressure) to predict advanced atherosclerotic lesions found on histology [30]. The PDAY risk score has been shown to be associated with all stages of histological lesions including the transition from normal tissue to the earliest detectable anatomic lesion [30]. Furthermore, this score has been shown to predict the presence of coronary artery calcification detected by computed tomography [31]. As a result, targeting both obesity and its associated risk factors is necessary to prevent adult cardiovascular disease.

Recent work demonstrates that the degree of obesity is also important [32]. Severe obesity, defined as an absolute body mass index (BMI) >35 (class II or III obesity in adults) or a BMI >120% of the 95th percentile for age and sex, is the fastest growing category of obesity among US adolescents and currently affects about 6% of all youth or 4 million adolescents [33]. Emerging data show that compared to less obese youth, those with severe obesity have higher numbers of cardiovascular risk factors, a greater extent of dyslipidemia, and earlier evidence of cardiac and vascular dysfunction [34]. Youth with severe obesity have been shown to have higher arterial thickness, higher vascular stiffness, higher left ventricular mass index, and worse diastolic function [34]. Furthermore, after adjustment for age, race, sex, blood pressure, lipids, and inflammatory markers, severe obesity in youth has been shown to be independently associated with each of the outcomes listed above [34]. These findings suggest that reductions in the severity of obesity may be beneficial even if the resultant BMI remains above the normal range.

Noninvasive Atherosclerosis Imaging

As children with obesity progress to adulthood, there is continued need to monitor the development of subclinical atherosclerosis. This is possible using noninvasive imaging techniques. During the last several decades, numerous modalities have emerged and several have proved to be valid and reliable markers to predict future cardiovascular disease in adults. While noninvasive imaging has largely been reserved for research purposes in pediatrics, these methods provide a means to document the presence of subclinical atherosclerosis, track cardiovascular risk over time, and monitor improvement with interventions [35]. Changes in the vasculature can be anatomical (i.e., increased intima media thickness [IMT]), mechanical (i.e., increased stiffness), or physiologic (i.e., endothelial dysfunction) [36]. Below, we describe some of the most widely

used imaging modalities in pediatrics and summarize the studies where noninvasive imaging has been used to assess the effects of obesity on early cardiovascular disease.

Carotid Intima Media Thickness

In adults, increased carotid intima media thickness (IMT) is associated with coronary artery disease and predicts future cardiovascular events, including stroke and myocardial infarction [37–39]. As such, carotid IMT is one of the more powerful tools to assess early atherosclerosis. Using high-resolution B-mode ultrasonography and a high frequency transducer the far wall intima-media layer of the blood vessel is imaged. See Fig. 30.2a, b.

In cross-sectional studies, youth with obesity have higher cIMT compared to normal weight children [40, 41]. Longitudinal studies show that cardiovascular risk factors in childhood are associated with increased cIMT in young adults. Specifically, the Bogalusa Heart Study, Muscatine Study, and Young Finns Study each found that pediatric obesity independently predicts adult IMT after adjustment for other risk factors [42–44]. Furthermore, obesity has a linear and positive relationship with carotid IMT, such that individuals with the largest increase in BMI during childhood and adolescence and those that remain overweight have the greatest cIMT as adults [45, 46]. A meta-analysis published by Silva and colleagues summarized the pediatric studies conducted between 2000 and 2009 that have evaluated obesity and its association with carotid IMT. In all 16 studies evaluated, obese youth showed higher values of IMT than those in control groups; in 12 studies this difference was significant [47].

In addition to thickness in the carotid artery, stiffness can also be assessed. Youth with obesity also have higher carotid stiffness (β-stiffness index) compared to normal weight youth [48, 49].

Aortic IMT has also been studied. In the Muscatine offspring study the relationships between cardiovascular risk factors and aortic IMT and cIMT were compared [50]. Although cardiovascular risk factors were associated with both measures in a similar pattern, the strength of associations were greater for aortic IMT in those <18 years of age. These results suggest aortic IMT may allow detection of the atherosclerotic process at an earlier age than cIMT [50]. Further studies are needed to confirm this.

Despite the clear value of IMT as a tool in the assessment of cardiovascular risk, its application has been limited in pediatrics for several reasons. First, cIMT measurements require trained vascular technicians and appropriate ultrasound equipment. Second, variability in protocols for data acquisition and data analysis has limited comparability across research centers [35]. Third, no normative data exist in chil-

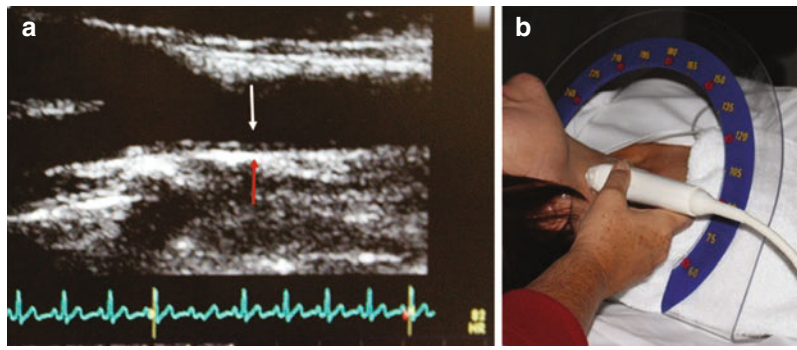


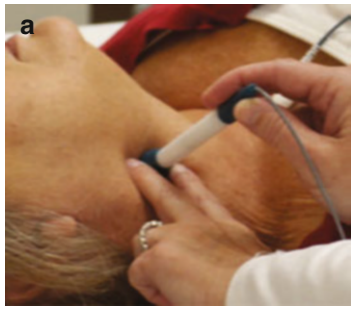
Fig. 30.2 (**a**) Ultrasound image taken from the carotid artery demonstrating the intima-medial layer. The intimal-medial thickness is measured (in mm) from the border between the echolucent vessel lumen and the echogenic intima (white arrow) and the border between the echolucent media and echogenic adventitia (red arrow). (**b**) Meyer's arc device can be used to record angle of insonation when measuring carotid intima-media thickness measurements

dren and adolescents [51]. Finally, there is paucity of data to show that reduction of carotid IMT in adolescents translates to decreased cardiovascular events in adulthood.

Arterial Stiffness Measurements

Arterial compliance, distensibility, and stiffness are all measures of artery mechanics. Although both compliance and distensibility are measures of stiffness, distensibility is a measure of the elastic properties of an artery, whereas compliance is a measure of the local vessel capacity to respond to changes in blood volume [52]. Arterial stiffness is the reciprocal of distensibility. Many pediatric studies have used these techniques to evaluate obesity-related changes in artery mechanics.

Two commonly used measures of arterial stiffness include pulse wave velocity (PWV, Fig. 30.3a, b) and augmentation index (AIx, Fig. 30.4a–c). PWV is a derived gradient velocity calculated from noninvasive pulse waveforms at two separate peripheral loci (commonly the carotid and femoral arteries) and the distance between them (with greater PWV indicating a higher arterial stiffness). AIx is derived from pulse waveforms at a single arterial site, calculated as the difference in the augmented and forward waves in an arterial waveform, divided by the overall pulse pressure of the waveform (with a higher AI a proxy of greater arterial stiffness). PWV is reproducible [53] and in adults predicts degree of arterial



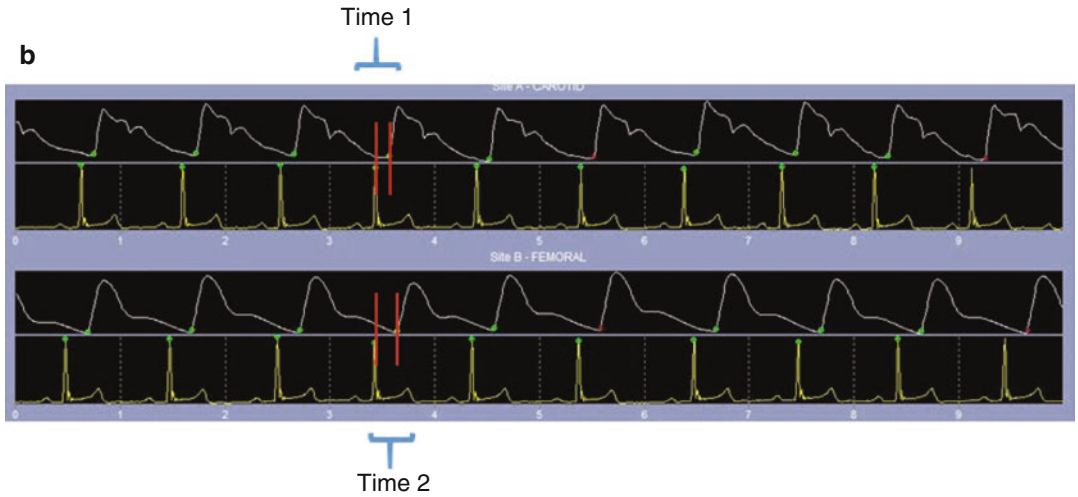


Fig. 30.3 (**a**) Pulse wave velocity is obtained from tonometry placed at a proximal (i.e., carotid—shown) and then distal artery (i.e., femoral—not shown). (**b**) The time from the peak of the R wave on the ECG to the foot of the pressure curves is used to calculate the difference in time of arrival of the pressure wave between the two sites. The physical distance between the two arteries is measured manually and entered into the device. Pulse wave velocity is calculated in m/s

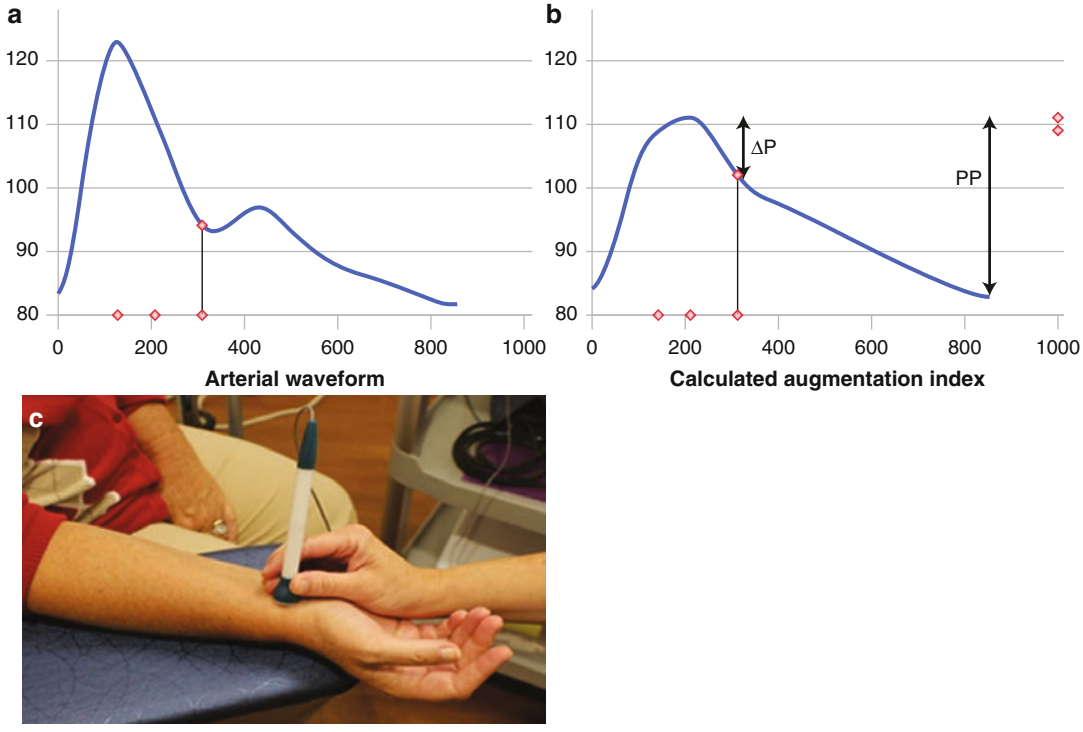


Fig. 30.4 (**a**) Pulse waveform analysis obtained from a tonometer placed on the radial artery. (**b**) Calculated central aortic trace. (**c**) Tonometer placed over the radial artery to obtain the measurement. Augmentation index is a measure of the enhancement (augmentation) of central aortic pressure by a reflected pulse wave and is calculated as the $\Delta P/PP \times 100$ and is expressed as *a%*

plaques [54] and future cardiovascular disease mortality [55]. Less evidence exists for the relationship between AIx and cardiovascular events [56].

Brachial distensibility (BrachD) is another reproducible [52] and validated noninvasive measure of arterial function [57] that has been linked to the development and progression of atherosclerotic vascular disease in adults. BrachD assesses resting vascular function in a medium muscular artery [26] and is derived from pressure curves generated from arterial pressure signals obtained from a standard blood pressure cuff sphygmomanometer. A lower BrachD indicates increased vascular stiffness. Prior work has shown that obesity is associated with a lower BrachD in adults [58] and children [41, 59].

Using all three measures of arterial stiffness PWV, AIx, and BrachD, Urbina and colleagues found that adolescents with obesity had higher arterial stiffness compared to normal weight youth [60]. In multivariate regression models, obesity was an independent predictor of PWV and BrachD (but not AIx) after adjustment for risk factors [60]. However, not all studies show that obesity in children is associated with greater arterial stiffness. A recent meta-analysis published by Hudson and colleagues summarized data from 14 pediatric studies that included 1120 obese and 5557 nonobese youth and found that across all studies, obese children had higher PWV than nonobese children (weight mean difference 0.45, 95% confidence interval 0.10–0.81 m/s) [61]. Using five studies that included 411 obese and 317 nonobese children for AIx, no significant difference was found in obese versus nonobese participants (weighted mean difference 4.75, 95% confidence interval −3.95 to 13.45) [61]. This may be because not all studies have consistently found AIx higher in obese children or because AIx may be a poorer marker of future cardiovascular disease compared to PWV. Longitudinal studies are needed to establish this.

Endothelial Dysfunction

In the early 1980s, the role of endothelial cells in relaxation of arterial smooth muscle in response to increased blood flow was discovered [62] and traced to release of nitric oxide [63]. Intense interest in endothelial function led to an enormous number of related publications during the three decades since its discovery. As currently measured, the brachial artery is briefly occluded by a pneumatic cuff and released, and dilation of the distal artery normally occurs and the resultant increased blood flow and diameter are assessed by ultrasound [64]. The percent change in flow after ischemic stress is called flow-mediated dilation (FMD) and diminution of the response is termed endothelial dysfunction. Endothelial dysfunction in adults is associated with the cardiovascular disease risk factors and coronary artery atherosclerosis [65].

Overweight and severely obese children show reduced FMD compared with control subjects even when matched for blood pressure, cholesterol, and glucose levels [41]. Ryder and colleagues found that FMD was associated with higher BMI, body fat percentage, and visceral adipose tissue measured by computed tomography [66]. Improved endothelial function has been seen with increased physical activity and fitness [67]. However, this improvement in endothelial function was observed without a change in BMI [67–69]. These findings have led to a working hypothesis that perhaps variety of condition that causes systemic inflammation (including obesity, infection, trauma, periodontitis, or low birth weight [70]) or that reverses inflammation may influence endothelial dysfunction. Thus, a number of factors may explain impaired vascular function in an obese child.

Prevention

As evidence has accumulated showing that adult risk factors are present in youth and track into adulthood, suggestions have been made that heart disease prevention should begin in childhood [70]. The validity of these recommendations was strengthened when longitudinal studies such as the Bogalusa Heart Study and Young Finns Study found that low levels of cardiovascular risk factors from childhood result in improved measures of vascular structure (i.e., IMT [71, 72]) and function (i.e., PWV [73]).

Preventive measures adopted in early middle age, as recommended by programs targeting adults, are too late because advanced plaques, vulnerable to rupture and thrombotic occlusion, have already formed by this age and the opportunity for prevention is limited. Furthermore, calcifications which develop in adulthood limit the ability to induce regression. Therefore, focus should be shifted to preventing obesity in the first place. This idea is defined as "primordial prevention"—broad health initiatives aimed at minimizing or preventing obesity (i.e., physical activity in school, healthy school lunch programs) [70]. However, most health care providers are forced to work on "primary prevention" that is treating obesity and its associated comorbidities including dyslipidemia, hypertension, obstructive sleep apnea, fatty liver disease, and smoking to prevent early onset cardiovascular disease. Studies of atherosclerosis in youth demonstrate that no risk factor can be safely ignored. Thus, current guidelines for cardiovascular risk reduction focus on primary prevention of obesity and targeting its comorbidities [74].

Conclusions

Obesity poses a major health concern for cardiovascular mortality and death in adulthood [75]. Obesity begins in childhood and adolescence is associated with the development and progression of atherosclerosis and increases the risk of future cardiovascular complications. Noninvasive imaging modalities have opened the possibility to monitor the development and track atherosclerosis prevention but are not yet ready for clinical use. Thus, limiting obesity and adult comorbidity continues to focus on obesity prevention and treatment.

Editor's Comments and Questions

1. The findings of the Bogalusa, PDAY, and Young Finns studies demonstrate that atherosclerosis is a progressive disease that begins in childhood. It is therefore clear that identification of high-risk children

and institution of preventive measures at an early age are of critical import. Stratification of risk could be facilitated by detection of early atherosclerotic lesions. In that regard, an increase in carotid intimal medial thickness (cIMT) may be a marker of early atherosclerosis and has been associated with higher risks of cardiovascular disease in adulthood.

But as you rightly note, the procedure for measuring cIMT may vary across centers and normative data are currently limited to postpubertal subjects.[a] In addition, the role of obesity as a determinant of cIMT is complex, as numerous other factors, some (but not all) of which are related to excess fat deposition, may contribute. These include:

Insulin resistance
Diabetes mellitus
Hypertension
Dyslipidemia
Inflammatory diseases (prominent examples include Kawasaki syndrome and systemic lupus erythematosus)
HIV and protease inhibitors
Male sex
Increasing age

2. Very limited data suggest that statin treatment of adolescents with familial hypercholesterolemia can reduce progression of cIMT over a 2 year period.[b] Large-scale studies examining the effects of treatment (of any sort) on cIMT in obese children or adolescents are thus far lacking, though recent investigations suggest that dietary modifications (such as reductions in saturated fat[c,d]) may reduce cIMT in association with increases in insulin sensitivity. Importantly, we thus far have no proof that therapeutic interventions that reduce or prevent progression of cIMT in childhood will also reduce rates of cardiovascular events in adulthood. The absence of such an evidence base makes it more difficult (in the minds of some) to justify universal screening for cardiovascular risk factors such as LDL and HDL.

The availability of a diagnostic procedure that could: (a) reliably identify and quantify the extent of early atherosclerotic lesions in children; (b) monitor the progress of treatment; and (c) predict the risk of future myocardial infarction and/or stroke would provide an extraordinarily useful tool for management and counseling of children and their families.

From my reading of your chapter, I suspect that cIMT does not yet fulfill these (rather demanding) criteria; would you agree? Do you foresee new developments in the fields of echocardiography, electrophysiology, and nuclear medicine that might provide a more detailed view of atherosclerosis during its early phases of development?

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Authors' Response

We agree that cIMT is not yet ready to be employed as a clinical tool in the pediatric population. Standardization of protocols, normative data, and studies establishing whether reduction in cIMT translates to a decrease in adult cardiovascular disease are needed. While, we do not see any new developments on the horizon that may be a better tool than cIMT, we are hopeful in the coming years, results of ongoing studies will be published that will provide normative cIMT data for adolescents and answer the question of whether obesity intervention reduces cIMT.

Acknowledgements We thank Drs. Henry C. McGill Jr, Alex McMahan and Samuel S. Gidding for writing the first version of this chapter. While much of the original content was preserved, several additions were made to reflect current knowledge of the effects of pediatric obesity on cardiovascular disease.

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Childhood Obesity and Cognitive Function

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Abbreviations

BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
HPA	Hypothalamic-pituitary-adrenal
MetS	Metabolic syndrome
OSA	Obstructive sleep apnea
SDB	Sleep disordered breathing
SES	Socioeconomic status

Introduction

Approximately one out of every three children living in the United States is overweight or obese, placing them at risk for significant medical and physical comorbidities [1, 2]. Recent research suggests that obesity may be associated with changes in cognition, although additional study is needed [3, 4]. Executive function, a critical component of cognition, refers to a set of cognitive processes necessary for goal directed behavior, which are important for managing eating and physical activity behavior. Children's brains are developing throughout childhood and adolescence, and some areas particularly important for executive function (e.g., prefrontal cortex) continue to develop into adulthood. Due to ongoing neural maturation and growth, these periods may be more vulnerable to biological or environmental insults that interfere with proper development. Furthermore, childhood and adolescence also represent key opportunities to intervene to promote healthy cognitive development and/or prevent excess weight gain. Thus, it is important to understand the connection between obesity and cognitive impairment.

Human and animal research is beginning to elucidate the mechanisms that may provide links between cognition and obesity. However, this field is in its infancy, especially with regard to youth, and many studies are correlational with only a few longitudinal studies available. To date, it is unclear if: (1) cognitive impairment serves as a vulnerability to develop obesity; (2) obesity causes cognitive impairment; or (3) individuals with cognitive impairment are vulnerable to develop obesity AND excess weight exacerbates cognitive impairment. Understanding the connection between obesity and cognitive impairment could highlight etiological and maintenance mechanisms and illuminate potential prevention and treatment targets. This chapter will review the current literature on the relationship among biological and environmental risk factors, overeating/overweight/obesity, and cognition. Next, it

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will review the literature on the empirically supported facets of cognition that are affected in children with overweight/obesity. Finally, implications for treatment development will be proposed.

Biological Mechanisms That Contribute to Cognitive Dysfunction and the Impact of a Western Diet

Research shows that intake of a Western diet (i.e., a diet high in saturated fat and refined sugar) is not only associated with weight gain but also with impairments in cognitive functions. Several studies have shown that consuming a Western diet can have adverse effects on the hippocampus (see below) and potentially other brain circuits and structures that contribute to the cognitive inhibitory control of behavior. The hippocampus is a limbic system structure that is important in forming and consolidating new memories, connecting emotions and senses, emotional responses, navigation, and spatial orientation. The famous case of H.M., whose hippocampus was removed to control epilepsy, demonstrated significant memory impairment. Interestingly, H.M. was also observed to eat multiple meals in succession due to a lack of memory for previous food intake and an inability to interpret hunger and satiety cues [5]. Thus, damage to the hippocampus not only is associated with cognitive impairment, but may also impact one's ability to detect hunger and satiety. Although H.M. was not obese, these observations shed light on the numerous functions of the hippocampus and its potential implication in overeating.

Several lines of evidence suggest that diet can modulate neural structure and function and facilitate weight gain. Consumption of a Western diet in laboratory studies of animals (i.e., high saturated fat, high refined sugars) is associated with hippocampal inflammation, reduced hippocampal neurogenesis, decreased synaptic plasticity, and increased permeability of the blood–brain barrier, all of which have been connected to cognitive impairment in both humans and animals (see [6] for review). Increased permeability of the blood–brain barrier can result in the passage of toxic or other agents typically precluded from entering the brain, which can result in neurological damage; the hippocampus is especially susceptible to this insult [6]. Moreover, animal studies suggest that a high fat diet can induce changes in hippocampal functioning (i.e., associated memory and inhibition processes) that promote responsiveness, rather than inhibition, to food-related environmental cues when physically sated [6, 7]. This could be mediated or amplified by changes in functioning of other neural areas interconnected with the hippocampus, such as the orbitofrontal cortex, striatum, and lateral hypothalamus [8]. In this paradigm, neural dysfunction caused by dietary overload may precede, cause, contribute to, and/or maintain overeating and weight gain. This has been termed the "vicious cycle of obesity and cognitive decline" by Kanoski and Davidson [6].

Alternatively, weight gain itself could precede, cause, or contribute to cognitive dysfunction. In that regard, a study in animals found that the impact of a Western diet on cognitive function was a good predictor of subsequent weight gain and increased adiposity; however, the effect of that diet on weight gain and adiposity did not reliably predict subsequent cognitive deficits [9]. Thus, cognitive impairment may precede excess weight gain in certain cases and serve as a potential indicator of children at risk of developing overweight or obesity.

Overweight and obesity are also associated with a number of metabolic and hormonal changes that are linked with deficits in hippocampal and other types of cognitive functioning. These include changes in brain-derived neurotrophic factor (BDNF), glucoregulation, leptin resistance, and inflammation. BDNF is essential for maintenance and growth of neurons and reduces food intake; Chaps. 2 and 9, respectively, on hypothalamic obesity and syndromic obesity. Consumption of a Western diet reduces levels of BDNF, which limits neurogenesis and synaptic plasticity particularly in the hippocampus [6]. Indeed, decreases in BDNF are associated with hippocampal dysfunction and weight gain in animal and human studies [10, 11].

Visceral obesity (i.e., abdominal or central) is tied to metabolic syndrome and associated with hyperleptinemia, insulin resistance, and production of proinflammatory cytokines. All of these are associated with cognitive decline [12–14]; for example, insulin resistance impairs hippocampal-dependent memory processes [15]. Abdominal adipose tissue secretes proinflammatory cytokines known to be neurotoxic [16]. Inflammation of the hypothalamus impairs feeding-related pathways, disrupting the ability of leptin and insulin to modulate hunger and food intake [14]. Inflammation may also stimulate the hypothalamic-pituitary-adrenal (HPA) axis, which in turn releases higher levels of glucocorticoids [17]. This effect may be exacerbated by induction of adipose 11 beta HSD 1, which increases local adipose cortisol concentrations. Together these promote central adiposity, insulin resistance, and, ultimately, hippocampal atrophy [18]. Thus, there are a number of biological processes associated with overeating and overweight and obesity which can secondarily impact cognition.

In summary, data suggest that consumption of a Western diet triggers a cascade of physiological and neural changes that impact hippocampal functioning and interconnected circuits in the brain. Ultimately, changes in hippocampal functioning can result in impaired memory and inhibition, as well as increased susceptibility to food cues in the environment. One study to date suggests that consumption of a Western diet precedes changes in cognitive functioning, although more research is needed to confirm causality. Considering the impact on the developing brain, consumption of a Western diet in childhood can have lasting implications on cognitive functioning and obesity in adulthood.

Obesogenic Environment Interacts with Cognition

Dramatic societal changes have created an "obesogenic" environment that encourages excess energy intake and discourages energy expenditure [19, 20]. Children are at a particularly high risk for overeating beyond nutritional need because the prefrontal cortex, which is involved in cognitive control, is not fully developed until the third decade of life [21]. Calorically dense meals reinforce environmental cues that promote food intake even in the absence of hunger.

Indeed, the strongest correlate of future weight gain is habitual overeating, or the susceptibility to overeat in response to everyday cues within the environment [22]. However, not all children overeat or become overweight or obese. This suggests that there are individual differences in how children respond to the environment.

Individual differences in cognitive-inhibitory control may predict one's susceptibility to environmental food cues; indeed, the ability to control one's impulses may serve as a risk factor for overeating, overweight, and obesity. Admittedly there is much to be learned in this area. For some children, food cues build powerful relationships with eating; when present, these food cues drive their attention, elicit memories of previous experiences with the food, and excite the motor system to reach for the food, sometimes automatically. Children who have strong associations with food cues may need to reduce or inhibit the impulse to eat throughout the day. In human research, poor cognitive performance predicts subsequent excess body weight gain [23, 24]. Executive functioning processes—including attentional control, inhibitory control, working memory, cognitive flexibility, reasoning, problem solving, and planning—may all contribute to individual differences in how each child responds to the current food environment. While all children exhibit some impairments in executive function as it continues to develop, greater difficulties are seen among overweight or obese children, whose executive function is impaired compared to their peers [25, 26].

Childhood Obesity and Cognitive Function

The next sections will summarize the research on the relationship between obesity and cognitive function in youth. We detail correlational research on specific aspects of cognitive and executive

function including learning, memory, attention, inhibition, reward, cognitive flexibility, and achievement. Wherever possible, longitudinal research and treatment are discussed.

Learning and Memory Performance

The ability to learn new information depends on the ability to encode or store information into long-term memory and to retrieve that information later when needed. Recent work on overeating has shown that episodic memory for recent meals can influence how much a person consumes at a later meal [27]. As discussed earlier, Western diets have been associated with hippocampal damage in animals [6, 7]. Given the critical role of the hippocampus in memory encoding, it is important to explore memory performance in children with obesity to determine if deficits exist.

The research on memory performance among children with overweight or obesity is inconclusive. A study using the 5–15 questionnaire, which asks parents to indicate whether their children exhibit problems in multiple domains of development found double the number of reported memory problems in obese children compared to healthy-weight children [28]. Conversely, two large-scale studies of preschoolers and older children directly tested verbal memory performance and found no differences between children with overweight and obesity and their healthy-weight peers [29, 30], a finding consistent with studies of verbal learning in adult studies (see Vainik and colleagues [31] for a review). Although these child studies tested verbal memory, they did not test episodic memory or memory for general knowledge, both of which were addressed on the 5–15 questionnaire. It is possible that obese children may have memory deficits in areas that are not detected by a verbal memory task.

Although they do not show deficits on general verbal learning tasks, overweight children are more likely to show biased memory for food words. On a recall task that included both food and nonfood words, overweight children recalled a higher proportion of food words, whereas healthy-weight children showed no differences in recall proportion [32]. These results are consistent with attention bias findings showing that overweight and obese children will pay more attention to food cues [33–35]. In fact, higher recall of food words may be related to increased attention to those words at the time of encoding. In sum, obese children have not been shown to have global verbal memory deficits, but they may be more likely to remember food stimuli than their healthy-weight counterparts.

Working Memory

Learning new information depends on storing information in long-term memory (as measured by verbal memory tests). In contrast, decision-making, which is a necessary component of executive function, depends on working memory. Working memory is the ability to temporarily store information in memory so that it can be used in the present moment. A well-functioning working memory is a critical component of making good decisions, such as what and how much food to consume. Overweight and obese children have not been shown to exhibit working memory deficits [29, 36]. However, there is evidence to suggest that behaviors associated with obesity are associated with poorer working memory performance. For instance, children who are sedentary and consume high fat/high sugar snacks reported more working memory problems on a self-reported Behavioral Rating Inventory of Executive Function than children who were active and ate healthy snacks [37].

There is also evidence that better working memory may contribute to greater success at keeping weight off after a weight-loss intervention. Obese children who completed a 6-week executive function training regimen (as a part of a weight-loss intervention) improved their working memory performance compared to children who did not get the training. Eight weeks after treatment, children who completed the training were able to maintain weight loss more effectively than children who did not get the training, although the difference was no longer significant

12 weeks after treatment [38]. Executive function training may need to be continued for the benefits in weight maintenance to persist. These results suggest that working memory plays a role in weight maintenance and that it is possible to improve working memory through training.

Attention Deficits and Bias

Attention involves the ability to concentrate on a given task. Difficulties with global attention are related to obesity in that inattention may be associated with poorer awareness of food intake and greater difficulty adhering to regular eating patterns and dietary regimens. Furthermore, inattention may be related to decreased inhibitory control (described below).

Adolescents with severe obesity are more likely to exhibit deficits in attention measured by performance on a computerized task compared with normative data [39]. Likewise, boys [40] and girls [30] with obesity performed worse on attention tasks than normal-weight peers. Deficits in attention can predict the presence of obesity at a later age [23] and greater inattention predicts poorer weight loss outcomes in treatment [41]. Moreover, a recent meta-analysis showed that a diagnosis of Attention Deficit Hyperactivity Disorder is more common in obese than non-obese children and adults [42]. In sum, global attention deficits appear to be related to and may contribute to childhood obesity.

In addition to global attention deficits, research suggests that obese children have an unconscious attention bias towards food cues. An attention bias towards food cues is related to overweight since the more a person attends to food, the more times that person needs to decide whether or not to eat it. With greater exposure, the person will be more likely to opt to eat the food. One study comparing overweight children to healthy weight peers demonstrated an attention bias towards food pictures; this was manifested as a slower reaction time in the presence of food pictures [33]. However, another study showed no differences in attention bias towards food pictures [43], although, among children with overweight, those who had an attention bias towards food cues lost less weight than those who did not have the bias in a treatment program [43]. Further, a pilot study using a one-session attention modification program to train attention away from food cues influenced eating behavior in the lab among children with overweight or obesity, such that those who were trained to always look away from food cues ate less than those who were equally trained to look towards and away from the food cues [44].

Mixed results also exist in studies examining attentional interference by the presence of food stimuli among overweight children. One investigation utilizing a Stroop-task adapted with food stimuli found an attention bias towards food, as overweight children were slower at naming the color of words that were the food stimuli [34]. Another study employed an Imbedded Word Task in which participants were instructed to find as many words as possible hidden in a grid (comparable to a word search puzzle) in a specified amount of time. This study did not find attentional interference of food words as participants found equal amounts of food and nonfood words during the search task [32]. Differences in outcomes may be due to the different methodologies. Among adolescent girls, body mass index (BMI) was correlated with an attention bias towards appetizing food cues but not with neutral stimuli [35]. Taken together, results suggest that children with obesity are more likely to display an attention bias towards food cues. Training programs that target this attention bias may impact eating behavior and thus might be a potential treatment component for childhood obesity.

Inhibition and Discounting of Reward

Inhibition requires self-regulation and refers to the ability to withhold a behavioral response. To avoid weight gain or to promote weight loss, it is essential to inhibit the urge to eat high caloric foods. Typically, these high caloric foods are perceived as being highly rewarding and the more rewarding something is perceived to be, the more difficult it will be to inhibit one's

behavior. Accordingly, sensitivity to reward interacts with one's ability to inhibit action. This is often referred to as the ability to discount rewards (or delay discounting). Children with obesity have impairments in delay discounting as they exhibit a tendency to demonstrate preference for smaller, immediate rewards over larger rewards in the future. This is believed to be linked to opting for a highly palatable food without thinking about how eating that food (e.g., cookie) would have negative consequences on the long-term goal of losing or maintaining one's weight.

Research clearly demonstrates an association between greater BMI and reduced behavioral inhibition in children [25, 45, 46]. Inhibition is most commonly measured using either the Stop Signal Task or the Go/No-Go task. The difference between the tasks is the point in the process at which inhibition is required, with the stop signal task measuring the ability to inhibit action after action has already been initiated. Overweight children exhibited greater difficulties with inhibition than normal-weight peers on a Stop Signal Task involving both toy and food stimuli combined [25]; however, they were especially ineffective at inhibiting response to food cues. Further, on a Go/No-Go task using animal stimuli, overweight children performed more poorly than normal-weight peers on accuracy of No-Go responses, suggesting a greater difficulty with inhibiting response [47]. Performance on the Stop Signal Task (all neutral stimuli) was related to weight loss in treatment such that those who performed more poorly lost less weight during treatment [45]. Similarly, those who demonstrated greater improvements in inhibition (all nonfood stimuli) over the course of treatment lost more weight [46]. Inhibition training using a Go/No-Go paradigm decreased food consumption in the lab and was associated with modest weight loss outcomes in adults [48]. More research is needed to determine the effects of inhibition training on child weight loss; however, preliminary evidence suggests that inhibition training may reduce laboratory food consumption of stimuli used in the training [49].

Delay of gratification is similar to delay discounting, in that those who have difficulty with delaying gratification will be much more likely to eat highly caloric, appetizing foods immediately, and have difficulty resisting temptation. Delay of gratification was reduced among overweight children compared to normal-weight peers; however, some suggest that this deficit is found only in response to food rewards [26], whereas others suggest a more general difficulty with discounting rewards [50]. Longitudinal studies suggest that delay discounting predicts BMI at a later age such that those who demonstrate greater difficulties discounting reward have greater BMIs in the future [23, 51]. Poorer delay discounting of food among overweight children was associated with poorer weight loss outcomes following treatment [52]. A strategy that may improve delay discounting involves encouraging individuals to engage in episodic future thinking or mentally imagining how one will experience future events. Interventions using episodic future thinking have been successful at improving delay of gratification in adults and have been preliminary successful at reducing food intake in children [53].

In sum, research suggests that overweight children are more likely to respond to food cues and to have greater difficulty delaying gratification in response to food stimuli. Preliminary studies suggest that interventions designed to control food responses and delay gratification may prove successful in weight control.

Cognitive Flexibility

Cognitive flexibility is defined as the ability to shift from one thought to another. Importantly, cognitive flexibility enables people to change their behavior to adapt to new or different situations. It is possible that lower cognitive flexibility could impact food consumption decisions, making it harder for children to change unhealthy dietary habits. Overweight and obese children score worse than their healthy-weight peers on tests of cognitive flexibility. For example, boys with obesity performed worse than healthy-weight

boys on the Wisconsin Card Sort Test, a task that requires participants to discern pattern-matching rules based on feedback [40]. Overweight adolescents (13–16 years) performed significantly worse than their healthy-weight peers on both the Five Digit Test (a task that requires participants to shift from reading numbers to counting objects) and the Trail Making Test (a task that requires participants to shift from letters to numbers while connecting dots in sequential order) [54].

Regular exercise has been shown to improve cognitive flexibility [55] and overall executive function in adolescents with overweight/obesity [56]. One study assigned overweight adolescents to a 10-week competitive exergame regimen, a 10-week cooperative exergame regimen, or a control group that did not play exergames [55]. Exergames are video games that require the player to move around. Adolescents who competed in exergames showed improved cognitive flexibility compared to those in both the cooperative exergame group and the control group. Furthermore, improvement in executive function was positively correlated with weight loss [55]. Another study that tested cognitive flexibility before and after a single bout of vigorous exercise did not result in any improvement [57].

Academic Achievement and IQ

Several large-scale, cross-sectional investigations have examined the relationship between childhood overweight/obesity and academic achievement [47, 58–60]. In a cross-sectional study of over 2500 US children aged 8–16 years, those who were overweight performed worse (controlling for age and gender) than their healthy-weight peers on reading and arithmetic skills using the Wide Range Achievement Test, Revised [58]. However, when a measure of socioeconomic status (SES) was included, this difference disappeared [58]. Another study tested 126 US children aged 7–9 years using the Wide Range Achievement Test 3rd edition and found that BMI was negatively correlated with performance on tests of spelling and arithmetic (controlling for age, gender, and SES) [47].

Longitudinal studies also demonstrate that overweight children perform worse academically than healthy-weight children. A study of over 1000 Thai students over a period of 2 years found that 7th–9th grade students who became overweight over the prior 2-year period had significantly lower grade point averages than students who did not gain excess weight or students who lost weight [61]. This study also found that overweight 7th–9th grade students had lower language and math scores than their healthy-weight or underweight counterparts. Interestingly it did not find deficits for obese students in the 3rd–6th grades [61]. Another study found that overweight 3rd grade students performed worse on tests of reading and math [62]. Surprisingly, this study also found that healthy-weight kindergarteners who became overweight by the 3rd grade performed significantly lower on reading and math tests in kindergarten than students who maintained a healthy-weight in 3rd grade. In this study, decreased academic performance actually preceded weight gain [62]. However, a follow-up study on the same group of students revealed that the performance differences at 3rd grade disappeared when the analysis controlled for SES and maternal level of education [63].

Some studies found no relationship between overweight and academic performance deficits [64, 65]. A study of almost 800 Portuguese 6–12-year-olds found no differences in teacher evaluations and grades between children with overweight/obesity when controlling for SES [64]. Another study of 129 Spanish children showed that BMI was a significant predictor of IQ and that children who have obesity had significantly lower IQs than their healthy-weight counterparts [66]; however, this study did not control for SES.

When taken together, these studies suggest that while overweight may be associated with lower academic achievement, it may also be associated with other factors such as SES that may be more important in predicting academic success.

Food-Specific vs. Global Cognitive Impairment

Overall, the evidence summarized above suggests that childhood overweight is associated with cognitive impairments. However, there is mixed evidence as to whether these deficits are limited to food stimuli [32–35] or if they reflect more global cognitive impairment [40, 45, 54]. Nevertheless, food-specific impairments [52] as well as general impairments [45] predicted poor outcome in treatment. Research in adults is similarly mixed, with some finding deficits present only for food-specific tasks and others for general tasks [67]. The mixed results are likely due to variability in outcome metrics as well as heterogeneity of the research cohorts. Moreover, some evidence suggests that other factors, such as SES, may better explain differences in cognitive impairment than overweight alone [63, 64]. Accordingly, it is important to continue research in this area to determine whether there are global impairments in addition to food-specific impairments in cognitive function to better inform intervention development in the future.

Conditions Related to Obesity May Further Impair Cognition

Certain conditions related to overweight such as Obstructive Sleep Apnea (OSA), Type 2 Diabetes, and metabolic syndrome (MetS) may further impact cognitive performance above overweight but again research in children is limited. Although these conditions are more prevalent among overweight children, the findings of research studies may be difficult to interpret if they fail to account for body fat mass and other factors that may impact cognitive function, including SES.

In children, sleep disordered breathing (SDB) includes conditions that range from snoring to OSA and is more common in children with overweight/obesity. It may be accompanied by intermittent hypoxia and/or hypercarbia and is commonly associated with daytime fatigue. A meta-analysis of 16 studies found that SDB was associated with poorer academic performance in language arts, math, and science [68]. Another comprehensive review of 61 studies of SDB similarly found an association with poorer academic function; however, an association with overall intelligence was not found [69]. Furthermore, SDB was associated with greater difficulties with attention but findings regarding memory are inconsistent [69]. When considering children with both obesity and OSA, results of a recent study of adolescents with obesity did not show significant differences in verbal memory between those with OSA compared to those without [70].

One study compared children with three or more symptoms of)MetS to those with two or fewer symptoms of MetS on a large neurocognitive battery and examined functional and structural brain impairments in adolescents. This study found that adolescents with MetS performed significantly worse on tests of spelling and arithmetic (as measured by the Wide Range Achievement Test), cognitive flexibility (as measured by trail making test B), and attention (as measured by the Digit Vigilance Task), and showed a trend towards lower IQ ($p = 0.09$) [71]. A greater number of components of MetS were associated with poorer cognitive performance. However, no differences were found on tests of memory function, other components of executive function, and some additional measures of attention.

The study also examined the association between components of MetS and brain volume and found that insulin resistance was the only symptom of MetS associated with reduced hippocampal volume. These findings remained significant after adjusting for obesity [71]. Of note, both groups also had nonsignificantly different sleep apnea scores, further suggesting that the effects are due to the MetS itself or other related conditions. Given that these findings were found among nondiabetic adolescents, they suggest that childhood obesity and even mild-moderate MetS could impact neurological development.

A well-controlled, small study, comparing obese adolescents with type 2 diabetes to obese adolescents without type 2 diabetes

found that those with type 2 diabetes scored significantly lower on IQ, verbal memory, and attention than those without diabetes [72]. Additional areas including measures of executive function, reading, and spelling were trending towards significance with medium to large effect sizes. An imaging study comparing adolescents with obesity and type 2 diabetes to adolescents with obesity without type 2 diabetes found that adolescents with type 2 diabetes had significantly reduced hippocampal and frontal lobe volumes [73].

Taken together, preliminary evidence suggests that certain conditions associated with obesity may exacerbate cognitive impairment above and beyond overweight alone. Further, in addition to cognitive impairments, neurological differences in major brain centers associated with memory, learning, and executive function also correlate with comorbidities of obesity. Additional studies, especially well-controlled, prospective, longitudinal studies are needed to elucidate whether these neurological impairments emerge following the development of the related condition or are present prior to their development.

Treatment Implications, Future Considerations, and Conclusions

Cognitive development proceeds throughout childhood and adolescence. This marks a time of great neural plasticity, and interventions that target cognitive function may help prevent weight gain and aid weight-loss efforts. Preliminary research in children shows that cognitive and executive function training can influence eating behavior in the lab [44] and weight maintenance outcomes [38]. Some additional evidence supports the value of cognitive training and executive function in adults. Training attention away from food cues resulted in decreases in binge eating and weight among adults [74]. Training inhibition towards food cues has also been associated with weight loss [48].

Interventions, such as those described previously, should be tested more rigorously to determine whether they can be stand-alone treatments or serve as adjuncts to family-based behavioral treatment. It is important to evaluate both computerized training sessions and individual or group interventions targeting mechanisms of executive function such as organization, cognitive flexibility, memory, problem solving, and planning.

Longitudinal research is needed to fully understand the implications of the Western diet on the development of obesity. There is a strong heritability of overweight [75]. Thus, it is important to identify biomarkers associated with obesity risk to determine who to target with preventive interventions. Longitudinal research is also required to determine if neurological differences exist prior to the development of obesity; this should help decipher if cognitive impairment may exist as a precursor to the development of obesity due to a biological vulnerability, if the development of overweight causes the cognitive impairment, or if there is a bidirectional relationship between cognitive impairment and overweight. Further, it will be important to study whether reductions in overweight can reduce cognitive impairment in the long run and whether damage or dysfunction of the hippocampus and other affected brain centers can be reversed.

Altogether, there is substantial evidence that cognitive impairment is associated with childhood overweight and obesity. As childhood marks a critical neurodevelopmental window, it is especially crucial that we pursue early intervention and prevention. Given the strong evidence implicating a role of the Western diet in cognitive impairment, it is important to consider its implications for childhood nutrition. Interventions for childhood obesity should target cognitive impairments while reducing consumption of foods concentrated with sugars and saturated fats. This field of research is still in its early stages and future research should work to address the remaining questions to help improve prevention and treatment of childhood overweight and elucidate the mechanisms linking cognitive impairment to excess weight gain.

Editor's Comments and Questions

1. You present evidence that a "Western" diet high in saturated fat and simple sugars can cause hippocampal inflammation, reduce hippocampal neurogenesis, and impair hippocampal function. A *direct* effect of the nutrients might be suggested by demonstrating: (a) that the effects on hippocampal structure and function *precede* changes in body weight or glucose or lipid metabolism; (b) that nutrients exert direct toxic effects on hippocampal neurons in culture.

   A. What do we know about the time course of nutrient effects and weight gain on the hippocampus and other brain structures?
   B. What effects do fatty acids and sugars have on the behavior and function of hippocampal neurons in vivo?
   C. Is there evidence that other nutrients or composite diets may protect the hippocampus or prolong neuronal survival?

2. Syndromic and monogenic forms of obesity (examples include Prader Willi syndrome and mutations in the melanocortin 4 receptor) are accompanied by hyperphagia and intense and persistent focus on food availability and meal preparation. You argue that excessive weight gain in the general population may be associated with decreased impulse control and attention bias towards food cues. It is unclear (to me) if this reflects an intrinsic propensity to hyperphagia or the relative lack of ability to control a normal drive to eat. It is also unclear if this behavior is innate, acquired as a consequence of some environmental insult(s), or learned in response to familial and societal pressures or prior food deprivation. What are your thoughts about this very complex question?

Authors' Responses

1A. Although we do not yet have evidence in humans, in animals impairment on tests that depend on hippocampal function has been shown to precede and be independent of weight gain that is caused by a western diet. These results suggest that hippocampal damage occurs as a consequence of the nutritional characteristics of the diet rather than the increased adiposity stemming from the diet. For example, the blood–brain barrier integrity is compromised following consumption of a western diet. The disruption to the blood–brain barrier allows toxins to pass through and contribute to hippocampal damage and disrupts the transport of hormones related to energy balance like leptin and ghrelin. Animal models can provide insight into the potential processes that occur in humans, but they do not allow unequivocal conclusions to be drawn.

1B. In rats, a high sugar/high saturated fat diet has been shown to lower brain-derived neurotrophic factor[a] and reduce hippocampal dendritic spine density,[b] causing reduced synaptic activity. However, not all fatty acids are equal. Omega-3 fatty acids might actually encourage neurogenesis. Thus, not all fats have the same impact on hippocampal neurons.

1C. A ketogenic diet (calorie-restricted, high-fat, low-carbohydrate) has been shown to have a protective effect on the hippocampus in mice and rats.[c] There is nascent evidence that dietary fiber may be related to increased cognitive control in children.[d]

2. It is certainly a complex question—in short, any or all could be playing a role.

Biologically, when food is scare it is adaptive to be able to quickly seek out and overconsume food. However, in the current obesogenic environment that is filled with calorie-dense and abundant food sources, the very strategies that were adaptive in prehistoric times can result in excess weight gain today. It is likely that decreased impulse control can be both attributed to innate (i.e., potentially related to genetics) drives but also can potentially be learned behavior. More longitudinal research is needed in humans to better understand risk factors present in young children prior to weight gain.

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Part VIII

Treatment of Childhood Obesity: Lifestyle Intervention

32 Family-Based Behavioral Interventions for Childhood Obesity

Denise E. Wilfley and Katherine N. Balantekin

Introduction

The childhood obesity epidemic is a pressing public health concern, with approximately 31.8% of children with either overweight or obesity [1]. Childhood obesity represents a considerable cost to society through increased health-care burden and associated spending [2]. It has many negative health consequences, including both medical (e.g., increased risk of diabetes, hypertension) and psychosocial comorbidities (e.g., bullying, weight-based teasing, and stigmatization that leads to a reduced quality of life) [3]. Given that 82% of children with obesity become adults with obesity [4], these health-care costs and physical and psychological comorbidities will persist into adulthood if the obesity is not treated effectively.

Fortunately, when obesity is treated at an early age, due to potential for height growth, relatively small weight losses can have a significant impact [5]. Children ages 8–9 years old with a BMI at or above the 97th percentile for age and sex need to lose only 1.8 (girls) to 2.1 (boys) kg over 1 year to achieve a healthy weight, which is in contrast to the 5.5 (boys) to 7.6 (girls) kg weight loss necessary for a 12–13-year-old to reach a healthy weight. Furthermore, maintaining weight and preventing weight gain improve cardiovascular risk factors in children but not adolescents [6], further emphasizing the importance of early intervention. Intervention early in childhood also allows healthy eating and physical activity habits to be established before children become entrenched in obesogenic patterns. Thus, early intervention is critical to promote a healthy weight and cardiovascular health in adulthood. In this chapter we will (1) present current treatment recommendations for childhood obesity and provide a brief review of the literature in support of childhood obesity treatment, (2) describe the components of family-based behavioral treatments for childhood obesity, and (3) explore future directions for FBT research.

Current Treatment Recommendations for Childhood Obesity

The United States Preventive Services Task Force (USPSTF) recommends that clinicians start tracking BMI percentiles at 2 years of age to screen children aged 6 years and older for obesity and, if diagnosed with obesity, offer them or refer them to a comprehensive, behavioral intervention of ≥26 hours over a period of up to 12 months to improve weight status [7]. These recommendations

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are based upon the results of a rigorous, scientific review that demonstrated the efficacy of interventions of 26 or more hours of contact that include dietary, physical activity, and behavioral counseling components [8].

Underpinning these recommendations and guidelines is a significant body of research demonstrating the potency of intensive, multicomponent lifestyle interventions in inducing weight loss in children and in reducing medical and psychological comorbidities associated with obesity, as compared to no-treatment controls, education-only, or single-component conditions. The amount, or duration of treatment contact, has also been found to be a consistent predictor of long-term weight outcomes in children [9]. Furthermore, the inclusion of parents or caregivers in the treatment of childhood obesity improves weight loss outcomes in comparison with interventions that only target the child. In fact, interventions with a family-based component result in a 6% greater mean reduction in percent overweight compared to those without this component [10].

Family-Based Behavioral Weight Loss Treatment

Family-based behavioral weight loss treatment (FBT) is a multicomponent behavioral weight control intervention developed and refined by Leonard Epstein, Denise Wilfley, and colleagues [11, 12]. FBT targets both children and parents and is considered a first-line treatment for children with overweight and obesity [13]. FBT is effective at improving weight status in both the short and long term [12, 14] and has been shown to improve other obesity-related comorbidities such as cardiometabolic risk factors and improvements in psychological well-being [15, 16]. Although the majority of studies have been conducted with children in middle childhood [11], FBT has also been successfully adapted for use with both preschoolers [17] and adolescents [18].

Sustainable behavior change is associated with early treatment response; specifically, recent work highlights that children who lose weight by week 8 of a weight loss intervention have the greatest likelihood of sustained success [19]. It is important for providers to encourage weight loss early in the intervention to maximize the potential for long-term success.

To improve a child's weight status, FBT targets modification of energy balance behaviors (i.e., decreasing energy intake and increasing energy expenditure) through the use of behavior change strategies and the active involvement of a parent or caregiver. In FBT, the parent or caregiver, who often also has overweight or obesity, is charged with both changing his or her own energy balance behaviors and supporting the child in these endeavors. Furthermore, the parent or caregiver is encouraged to engineer the home environment so that it promotes these behaviors for the entire family. To facilitate long-term weight loss maintenance, treatment contact is extended to allow for the continued practice of behavioral change skills and the development of family and social networks in support of weight loss maintenance behaviors [12]. The components of FBT are described below.

Key Components of Family-Based Behavioral Weight Loss Treatment

Dietary Modification

There are three primary dietary modification goals in FBT: (1) decrease energy intake, (2) improve nutritional quality, and (3) shift food preferences toward more nutrient-dense choices. To facilitate a decrease in energy intake while improving nutritional quality, FBT uses a family-friendly method of categorizing foods according to traffic light colors shown in Table 32.1 [20]. In addition, families learn to gradually adopt healthier eating habits through decreasing portion sizes; reducing intake of energy-dense, low-nutrient-dense foods (red foods); increasing intake of lower-calorie, more nutritious foods (green foods); and regularly consuming three meals a day. To shift taste preferences from less nutritious to more nutritious food options, families are discouraged from swapping energy-dense foods with non- or low-calorie or fat

Table 32.1 Traffic light classification of foods/beverages and activities

	Examples of foods/beverages	Examples of activities
Green (go!) Highest in nutrients, lowest in calories Have 0–1 grams of fat per serving	• Fresh vegetables	• Bicycling • Weight training • Brisk walking
Yellow (slow down) Contain a good amount of nutrients and calories Have 2–5 grams of fat per serving	• Dried fruit • Low-fat milk and plain yogurt • Extra lean beef	• Non-strenuous household chores • Stretching • Yoga
Red (stop and think) Highest in energy density, lowest in nutrient density Have >5 g of fat per serving	• Fried foods • Full-fat dairy • Cakes and cookies	• Watching TV • Using computer • Playing video games

Note: Food/beverage and activity colors are subject to change based on updates in nutrition and physical activity guidance

substitutes (e.g., swapping out ice cream with frozen yogurt) because these latter foods are typically processed to taste the same as their high-calorie alternative.

Other dietary goals include reducing portion sizes of yellow and red foods, which have been shown to reduce intake [21], and reducing food intake away from home, which helps increase overall diet quality and has been shown to be associated with reductions in both child BMI and percent body fat during FBT [22]. FBT has also been shown to decrease food fussiness (i.e., the frequent rejection of both familiar and unfamiliar foods), which increases diet quality, and thus increases relative weight loss [23]. Following sufficient weight loss, children and parents are instructed to increase their caloric intake to a level appropriate for weight maintenance. Other dietary goals for weight maintenance are similar to the dietary goals during weight loss treatment. In fact, continued reduced red food intake predicts weight loss maintenance in both children and their parents [24], indicating that dietary factors that help influence weight loss during FBT are also important for sustained weight maintenance.

Energy Expenditure Modification

The primary energy expenditure goals in FBT are to increase moderate-to-vigorous physical activity and to decrease sedentary behaviors (e.g., non-school or work-related screen time). Shown in Table 32.1, the colors of the traffic light are also used to help families identify which activities to increase (green, moderate-to-vigorous physical activity) and to decrease (red, sedentary behaviors). Families are also encouraged to increase lifestyle activities such as using stairs instead of elevators or walking or riding a bike to school rather than taking a car. Eating is a complementary behavior to sedentary behavior for many people (i.e., they both increase or decrease in the same direction); thus, decreasing time spent engaging in sedentary behaviors not only creates opportunities for greater time spent being physically active but also decreases opportunities for eating [25]. Increasing physical activity not only facilitates weight change in the short term but is also crucial for weight maintenance following FBT; physical activity level is also predictive of sustained weight change 10 years after participation in FBT [14].

Behavior Change Strategies

Components of behavior therapy and behavior change are vital to family-based behavioral weight loss interventions; interventions that incorporate behavior change strategies are more successful at achieving weight loss and the prevention of excess weight gain than education alone [26]. Standard behavior change strategies include goal setting, self-monitoring, family-based reward systems, and stimulus control strategies.

Goal setting is the process of creating specific, measurable, and realistic targets (i.e., goals) for behavior change. Sample goals include consuming less than 15 servings of red foods per week, engaging in 60 min of activity per day, reducing time spent in sedentary behavior by 50%, or

achieving projected weight loss or weight maintenance. The frequency of goal setting is associated with sustained behavior change, and continued, frequent goal setting is an important component of weight maintenance [27]. All children and parents are given weight loss goals, but other goals are individualized to focus on specific behaviors most needing improvement. As the intervention progresses, goals change to accommodate participant progress.

Goals are accompanied by self-monitoring, which allows one to monitor progress and to determine which goals are being met. Those who participate in frequent self-monitoring are more aware of their energy balance behaviors and have more successful weight outcomes [28]. In FBT, both the parent and child are encouraged to participate in regular self-monitoring of weight-related behaviors by weighing at home and recording the weights, on a weekly basis, and parents are encouraged to help their child master this skill.

In FBT, reward systems are used to help reinforce behaviors. To develop a reward-based incentive system, parents and children work together to determine appropriate and appealing rewards. Children earn points for achieving their goals and can exchange their points for rewards. Ideal rewards are those that increase social support and reinforce the targeted behaviors (e.g., park visit with friends); it is strongly recommended that parents do not use food as a reward and instead try to increase the reinforcing value of physical activity or peer interactions.

Stimulus control is defined as using environmental enrichment to restructure the environment to increase the likelihood of engaging in desired behaviors and is a critical component of behavior change interventions for obesity [10]. Within a behavioral economic framework, people's choices to obtain commodities are influenced by the constraints placed on those commodities. As the constraints on the commodities change, so do choices. As such, stimulus control works by placing constraints on undesirable choices (i.e., red foods and activities) to help someone make the best choice thus making the healthy choice the easy choice. In FBT, it is necessary for parents to remove prompts for unhealthy foods and sedentary behaviors (e.g., removing chips and cookies from the home, keeping videogame equipment on a high shelf in the closet) and increase the prompts for healthy foods and physical activity (e.g., placing fruits in a basket on the kitchen counter, keeping sneakers by the door) in the home.

Family Involvement and Support

Given that greater degree of parental involvement leads to greater child weight loss and that targeting the parent and child together is more effective than targeting the child alone [29], family involvement is a critical component of FBT. In FBT, participating parents and caregivers are also taught to systematically use behavioral principles and positive parenting approaches to help shape and support their child's weight change efforts. Children's weight-related behaviors exist in the context of their home and family environment. The goal of including parents in their child's treatment is to capitalize on this parental influence to promote healthier behavior choices and maximize health outcomes for both parent and child. Parents are encouraged to create a healthy home environment and model healthy behaviors by purchasing healthier foods, planning healthier meals, developing a family-based reward system to reinforce healthy choices, participating in and encouraging increased physical activity, and using praise to reinforce healthy behaviors while simultaneously minimizing attention to unhealthy behaviors [30]. While parents are tasked with helping their child reduce their consumption of energy-dense foods, it is critical to do so without using overly restrictive feeding practices or using excessive control over when and how much food a child eats. Thus, as a part of the emphasis on parenting skills in FBT, parents are taught how to use limit setting to help create structure and routines around eating (and activity and sleep) behaviors to avoid conceptualizing certain foods

as forbidden. As such, FBT has been shown to decrease restrictive parent feeding practices, which is associated with reductions in child relative weight during treatment [31].

Parents participating in FBT are encouraged to actively work toward changing their own weight status in addition to supporting their child's efforts. By including parents as active treatment targets, they can model the healthier eating and physical activity behavior critical for weight loss success. According to social learning theory, modeling is a critical way for parents to socialize their children's behavior [32]. When children are learning a new behavior, observing a key socialization agent (i.e., a parent) engaged in this behavior reinforces it. In fact, children with overweight or obesity may be particularly sensitive to adult influence in the transmission of health behaviors [33], underscoring the importance of active parental involvement in FBT. As such, parent weight loss is a positive predictor of child weight loss in FBT [34].

Importance of Intervening Across Time and Contexts

While weight loss during family-based behavioral interventions has been clearly demonstrated, weight regain after lifestyle change is a common phenomenon among adults and is a challenge for children as well [35]. A child's weight-related dietary and physical activity behaviors are not just developed and maintained in the context of the family home but also the broader community within which children and their families live, work, and play. Thus, interventions that utilize a socioenvironmental approach are efficacious for weight loss because they extend the focus of behavior change beyond the individual to encompass the home, peer, and community contexts [36]. Bouton's work on context-specific extinction shows that when new weight control behaviors are acquired during the course of FBT, these new behaviors do not replace the old behaviors associated with weight gain but rather coexist with them [37]. Unfortunately, new behaviors are not very generalizable outside of the setting in which they were learned, and old behaviors are easily activated across the different contexts of our obesogenic world. Therefore, concerted efforts must be made to ensure that new learning is practiced across most or all relevant contexts, that appropriate support and cues for healthful behaviors are in place, and that there is sufficient time devoted to the mastery and practice of these strategies. As a result of this contextual influence on the acquisition and practice of energy balance behaviors, FBT takes a socioenvironmental or multilevel approach to behavior change to improve maintenance of weight losses over time [38]. To address challenges to the maintenance of these new behaviors, FBT teaches families to plan for the different constraints or barriers to maintaining a healthy energy balance across these different levels of influence, e.g., learn how to identify and capitalize on facilitators for healthy living within peer networks and the community.

Peer Level

The overarching goal of the peer component in FBT is to increase the number of peers that are supportive of a healthier lifestyle rather than to change the attitudes and behaviors of everyone within the social network. Peer interactions are naturally reinforcing to children, and good peer relationships have a positive influence on overall quality of life. When peers are supportive of healthy energy balance behaviors, weight loss maintenance efforts are enhanced [39]. Conversely, a lack of peer support for physical activity and healthy eating contributes to weight gain [12]. In FBT, heightened social problems (e.g., loneliness, jealousy, susceptibility to teasing) predict greater weight regain after FBT [40], and children with higher levels of social problems evidence poorer weight loss maintenance [12]. These findings may be partially explained by the fact that youth who experience social problems or rejection may be more likely to use food as a coping mechanism [41] and less likely to engage in physical activity [42]. These findings highlight the need to

include training in pro-social techniques as part of treatment. Therefore, in FBT, families are encouraged to establish healthy peer networks and to disentangle socializing from unhealthy activities (e.g., encourage active playdates and birthday parties). In an effort to improve children's confidence in their ability to relate positively to peers, FBT also includes training in pro-social techniques for dealing with teasing and cognitive behavioral techniques to improve body image and self-esteem.

Community Level

At the community level, aspects of the built environment may affect an individual's choice to engage in energy balance behaviors. Environmental features of one's neighborhood are associated with rates of obesity and physical activity in children [43]. Important environmental factors include access to healthy foods (i.e., proximity of grocery stores), proximity to fast-food restaurants, relative cost of healthy and unhealthy foods, perceived safety and neighborhood walkability, and access to community recreation facilities and local parks [44]. For example, the built environment influences children's weight loss success in FBT; access to parks and open spaces predicted greater weight loss success at a 2-year follow-up, whereas reduced access to parks and greater access to supermarkets and convenience stores predicted poorer outcome [45]. In FBT, families engage in a number of activities to help increase their familiarity with how their built environment can both help and interfere with the establishment of healthy habits over the long term. It is also important that families learn to create a lifestyle that capitalizes on healthful environmental opportunities (e.g., local parks) while limiting access to obesity-promoting aspects of the environment (e.g., fast-food restaurants). Problem-solving, goal setting, and stimulus control are techniques that families can use in FBT to better work around or with their built environments. In addition, families are encouraged to become advocates for increased access to healthy foods and activity choices in their schools, their work places, and other community settings. Families are encouraged to build a culture of health in their homes, in their relationships, and in their communities to provide support for the difficult challenge of healthy weight maintenance in our obesogenic world.

Future Directions in the Behavioral Treatment of Obesity

Although FBT is a very effective treatment for childhood obesity, transdisciplinary research is needed to facilitate our understanding of individual, modifiable factors that can affect treatment response and to contribute to the development of even more potent, personalized, and efficient forms of FBT.

Personalized and Adaptive Treatment Designs

Previous work has identified predictors of FBT treatment success [46]; predictors of better child relative weight loss at the end of FBT included lower child baseline zBMI and age, higher baseline parent-reported self-efficacy at reducing calories, and greater parent BMI reductions across treatment [46]. Additionally, it has been shown that a child's weight loss by the eighth week of FBT predicts long-term treatment success [19]. Given this knowledge, advances in educational and systems sciences [47, 48] could be brought to bear to assist in the development of mastery learning models [49] or adaptive treatment algorithms [50] that would allow the intensity or direction of FBT to adjust to the needs or characteristics of individual families, thus conserving resources and improving treatment outcomes.

The varying intervention needs of individuals may not be met by uniform intervention dose, content, or frequency; thus, adaptive interventions deploy intervention content depending on specific individual needs [51]. For example, adaptive interventions can change or enhance treatment dose for non-responders, reintroduce

treatment for those who experience relapse, and decrease or alter dose for those who are early responders. Sequential, multiple assignment, randomized trials (SMARTs) allow one to simultaneously test multiple adaptive interventions [52]. Specifically, a SMART framework has been proposed for weight loss research [53]. SMARTs use decision roles for deciding when to adapt treatment [51]. For example, weight loss at week 8 of FBT could be used to adapt treatment; those who have not achieved their weight loss goal by week 8 could have their treatment frequency increased or enhanced to identify whether this potentiates treatment response.

Another option to enhance outcomes may be to tailor treatment using a mastery approach, which calibrates content and dose to the needs of the individual and has been shown to enhance weight loss outcomes [49]. Like many protocol-based interventions, FBT is designed to ensure that all participants receive the same dose of treatment. This ensures standardization of the protocol but may not ideally allocate treatment resources to meet participant's needs. An alternative approach, based on education research [54], is to use mastery teaching that takes into account different learning rates and does not present new information until patients master previous information. To examine whether a mastery-based learning approach to FBT improved treatment outcomes relative to standardization of FBT, families were randomized to mastery or usual FBT. The same information was presented to both groups, but the mastery group had to demonstrate mastery of information and mastery of behavioral goals. Results showed significantly better changes for the mastery group at 1 year in comparison with usual FBT [49]. While the terms "personalized" or "precision" medicine have traditionally been associated with medical treatments [55, 56], the use of mastery-based FBT for treating childhood obesity may serve as a model to efficiently and effectively match treatment "dose" or intensity to patient progress across a wide variety of behavioral health problems.

Co-location Within Primary Care Settings

Currently, FBT is typically only offered in specialty clinics or as part of research studies. One way to increase the availability of FBT while preserving its potency would be to conduct FBT with individual families within primary care settings. Co-location is a model of coordinated health care that places a behavioral health-care provider within the same location as the primary care physician. Primary care offers an optimal setting for timely, continuous delivery of evidence-based obesity treatment by capitalizing on the established and ongoing relationship between primary care providers and families [57] and reducing fragmented care that can occur through multiple providers and offices. As such, integrated care has been associated with improved treatment outcomes and patient satisfaction with treatment for other diseases [58]. Preliminary research suggests that FBT interventionists can be successfully co-located within pediatric primary care practices and achieve both child and parent weight losses [59]. However, this study used an abbreviated form of FBT in terms of both treatment content and intensity. Although further research is needed to test the efficacy of full-dose FBT in primary care, the co-location of a behavioral health interventionist within primary care would allow pediatricians to more easily refer appropriate families to comprehensive behavioral treatment for weight loss while still retaining them within the familiar practice setting. Furthermore, co-location would also allow for easier coordination of care, which is important given the comorbidities associated with obesity.

Need for Centers for Excellence

While FBT has proven to be effective for treatment of childhood obesity, access to care remains a challenge. Barriers include time and cost of training providers in FBT delivery, lack of reimbursement for treatment, and limited specialty clinics to which providers can refer their patients [60]. As insurers and medical service delivery

systems shift toward a health-care market that incentivizes prevention and the effective management of complex, multilevel diseases such as obesity, interventions such as FBT will be in demand to meet this need. In anticipation of this shift in the health-care system, it will be necessary to determine how best to scale up FBT for broader implementation without losing its potency. To achieve the broadest reach, professionals must be equipped to deliver FBT across multiple settings. One proposed approach to address this gap is creating regional centers of excellence in which FBT experts train center leaders to deliver FBT and supervise delivery. Such centers would have the potential to bridge the gap between treatment experts and interventionists to ensure proper delivery of FBT on a large scale [60].

Influence of FBT on the Microbiome

The gut microbiome, the set of genes accompanying the microbiota in the human gut, provides important metabolic capabilities and offers a promising new avenue for childhood obesity research. Seminal work in mice demonstrated that the microbiome in mice with obesity is more efficient at harvesting energy than the microbiome of mice without obesity [61], and human twin data support that the microbiome impacts host energetics [62]. Diet plays a large role in shaping the gut microbiome. Promising research in mice has shown that the diet affects the microbiome; switching from a low-fat, high-fat diet to a "Western" diet (i.e., high fat, high sugar) changed the metabolic pathways and shifted the structure of the mouse microbiome relatively quickly [63], indicating that the microbiome is responsive to changes in the diet. A recent meta-analysis highlights the importance of a diet higher in fruits, vegetables, and fiber for microbial health, integrity, and richness [64]. Given that FBT targets changes in the diet so that the diet is higher in fiber-containing foods such as fruits and vegetables, it follows that FBT would favorably alter the microbiome. As such, if FBT alters the microbiome, this may bolster and reinforce the weight loss seen in treatment. However, the impact of behavioral treatment for obesity on the gut microbiome has yet to be tested and remains an important next step in FBT research.

FBT with Comorbid Psychiatric Conditions

Rates of low self-esteem, anxiety, and depression are higher among children with overweight and obesity than among the general population [3]. Moreover, children with psychiatric conditions may be particularly vulnerable to the development of obesity and comorbid conditions [65], and this risk is exacerbated by the use of antipsychotic medications, many of which have the side effect of weight gain [66]; see also Chap. 37 by Drs. Reeves and Sikich. Notably, children with psychiatric conditions are twice as likely to develop obesity-related conditions such as diabetes or hypertension than children in the general population [67]. In many of these children, the use of antipsychotics cannot be discontinued as they are necessary to stabilize the psychiatric disorder, and thus obesity treatment is necessary to mitigate weight gain. Behavioral weight loss treatments among this high-risk population have been promising in adults, with more participants in the treatment group achieving clinically significant weight loss (i.e., ≥5% initial body weight) than participants in the control group [68]. While this is a nascent area in childhood obesity treatment research, a pilot FBT trial with three children with overweight or obesity taking antipsychotic medications was promising, showing that FBT is feasible among this population [69]. Additional research with larger samples is needed to confirm this finding.

Conclusions

Evidence supports early intervention for obesity during childhood as robust, and sustainable changes can be made at this time. FBT for childhood obesity, a multicomponent treatment that intervenes across several socioenvironmental contexts, has demonstrated effectiveness in reducing weight and

improving physiological and psychosocial outcomes in children and their parents. Given its reach beyond the target child, FBT may be a very cost-effective way to treat obesity across multiple generations [70].

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Editor's Comments and Questions

1. Effective management of pediatric obesity requires considerable commitment on the part of the child, family, and health-care providers; successful counseling programs generally involve frequent and often prolonged (26 to >75 h) contact[a]. You note that streamlined approaches integrated with primary care could be effective in selected circumstances.
   (a) Do you believe in "preventive" counseling in young children at high risk (e.g., those with obese parents)?
   (b) What essential elements of counseling might be conveyed in an "abbreviated" form of family-based behavioral weight loss treatment (FBT) administered in a primary care clinic?
   (c) How might the use of short-term FBT be applied to adolescents, who in general are far more resistant than young children to weight loss interventions?
   (d) Do you consider group counseling an effective tool for prevention or treatment of childhood obesity?
2. Studies in adults suggest that monetary rewards may be useful in promoting weight loss in adults. Women, singles, and the unemployed appear most likely to respond. The amount of the award can spell success or failure. It is currently unclear if the effects of the incentives are sustained after termination of the program[b]. Financial incentives seem inappropriate for children but are commonly used by parents to support behavior change in their wayward teens.

   Do you believe that parents should pay, or provide gifts to, their overweight children or teenagers to reward them for losing weight?

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Authors' Responses

1. Given that the most reliable risk factor for childhood obesity is having a parent with obesity,[a] and since two-thirds of adults have overweight or obesity,[b] the majority of children may be considered at high risk for obesity. Moreover, the risk for developing obesity increases as a child's BMI percentile increases (e.g., children with a BMI percentile >75th have a 40–50% change of developing overweight over time[c]); therefore, even children at BMI percentiles below the cutoffs for overweight or obesity are at risk. Thus health professionals should not wait until a child meets criteria for

overweight (i.e., BMI ≥ 85th percentile) but should consider having conversations regarding healthy behaviors with all children. These conversations should emphasize messages that target healthful eating, physical activity, and parental modeling of these behaviors (e.g., Let's Go! message of 5–2–1-0,[d] or 5+ servings of fruits/vegetables per day, ≤ 2 h screen time per day, 1 + _ h of physical activity per day, and 0 sugar-sweetened beverages per day).

2. An abbreviated form of FBT delivered in a primary care clinic still should contain the core components of FBT, which are modification of energy balance behaviors (i.e., increase in energy expenditure, decrease in energy intake), use of behavior change strategies (e.g., goal setting, self-monitoring), and active parental/caregiver involvement. For example, the effective abbreviated form of FBT that was delivered in primary care clinics among 2–5-year-old children and their parents included modification of energy balance behaviors, behavior change strategies, and active involvement of a parent.[e] Of note, treatment was abbreviated by reducing the number of sessions to 10 (4 weekly, 2 bimonthly, and 4 monthly), all delivered in a group-based format.
3. The central components of FBT (modification of energy balance behaviors, behavior change strategies, and parental involvement) are still critical for FBT with adolescent populations; however, unlike with younger children, the role of the parent is primarily to support their child and less to act as an agent of change.[f] For example, parents may attend separate sessions from their child in which they learn how they can best support their child and implement behavior change strategies such as stimulus control. If an incentive system is used as part of FBT, the lists of rewards will be different than those used with children to be consistent with the interests of adolescents (e.g., having car privileges).
4. Potential benefits of group-based childhood obesity treatments are that they may treat more people with fewer resources (e.g., staffing, time) and promote social support among individuals. However, a review of the effectiveness of group-based childhood obesity treatment found mixed results.[g] Mixed-format approaches (i.e., some individual sessions, some group sessions) were found to be preferable because they retain the benefits of group-based treatments while still achieving medium to large weight loss effects similar to those seen with the individual family format.
5. Incentive or point systems are a behavior change tool frequently used in FBT for childhood obesity. Points are used to incentivize the attainment of behavior goals (e.g., ≤ 15 servings of high energy-dense foods/week). Families are typically given a list of suggested rewards, with several examples listed for each of the following categories: (1) sporting events and activities, (2) time with mom or dad, (3) privileges, and (4) specific places to go. Parents and children work together to choose the rewards for which children can exchange their points, with the ideal rewards being ones that reinforce the targeted behaviors (e.g., physically active outings such as getting to go to the baseball batting cages).

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(c) Let's Go! http://www.letsgo.org/

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Exercise and Childhood Obesity

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Aerobic and Anaerobic Physical Fitness in Childhood Obesity

Aerobic Fitness in Overweight and Obese Youth

Poor cardiorespiratory fitness is recognized as an independent risk factor for cardiovascular and metabolic diseases [1] and mortality [2]. Even before the development of such diseases in adults, good aerobic fitness has been shown to attenuate significantly the severity of insulin resistance and other components of the metabolic syndrome in children and adolescents who are overweight or obese [3, 4]. Thus there is growing clinical and public health interest in assessing aerobic fitness for the diagnosis, treatment, and monitoring of functional and metabolic health in youth with obesity.

Assessing Aerobic Fitness in Obese Youth

The gold standard for assessing aerobic fitness is the measurement of maximal oxygen uptake (VO_{2max}) during exhaustive laboratory exercise tests [5–8]. These tests are most often conducted on a cycle ergometer with a step increase in workload (watts) to induce a proportional increase of oxygen uptake until a maximal value (VO_{2max}) is reached. Alternatively, incremental tests to exhaustion can be conducted on a motorized treadmill with increased speed or slope in place of increase in workload. In both cases, the initial workload is set to reach exhaustion within 10–12 min to avoid exhaustion caused by exercise duration rather than by exercise intensity. Criteria specific to children and adolescents are used to determine if VO_{2max} has truly been achieved. In addition to subjective exhaustion, these include heart rate above 195 beats.min^{-1} and/or respiratory exchange ratio (RER, calculated as the ratio between VCO_2 and VO_2) above 1.02 and/or a plateau of VO_2 [9].

Interpreting aerobic or anaerobic performance in obese youth is most often based on the comparison with performance of lean youth. The simplest expression of performance is in absolute terms: metrics include watts for power output measurements and newtons for strength

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measurement. These metrics are often expressed relative to body size (i.e., performance value divided by body mass). However, the use of body mass to quantify performance is problematic as it does not differentiate between metabolically active tissues responsible for the variation in metabolic rate (e.g., working muscle) and more redundant tissue that may limit movement efficiency (e.g., subcutaneous adipose tissue). In contrast to skeletal muscle, adipose tissue oxygen uptake does not increase during exercise and is considered as being almost inert in terms of metabolic rate, with less than 5% of contribution to daily energy expenditure [10]. Thus, as the proportion of body adipose tissue increases, VO_{2max} normalized to body mass decreases and more poorly reflects muscle oxidative capacity. This is illustrated by the strong negative correlation between VO_{2max} expressed relative to body mass ($ml.kg^{-1}\ min^{-1}$) and percentage body fat observed in girls ($r = -0.742$) and boys ($r = -0.843$) [11]. Yet, VO_{2max} normalized to body mass ($mL\ kg^{-1}\ min^{-1}$) remains the standard parameter used to reflect aerobic fitness, and reference values for VO_{2max} in youth with obesity are lacking.

When possible, muscle mass should be assessed and used to normalize performance variables. Medical imaging techniques, such as DXA or MRI, are not freely available, and as such, simpler estimates of body composition are used, separating the body composition into two compartments, with fat mass and fat-free mass (FFM) or lean body mass (LBM). FFM or LBM are commonly used as markers of muscle mass to normalize performance variables. It should, however, be remembered that human muscle mass accounts for less than 50% of fat-free mass in adult men and that the contribution of high metabolic rate organs (brain, kidney, liver, heart) to FFM undergoes important changes from childhood to adulthood [10]. Hence, even normalizing performance variables to FFM provides only an approximate picture of metabolic or contractile skeletal muscle properties. Throughout this chapter we will thus present VO_2 data in absolute terms and relative to body mass (because despite the important limitations, these are the most widely used methods) and fat-free mass or lean body mass when such experimental data are available (see Fig. 33.1a, b).

VO_{2max} relative to FFM has been shown to be reduced in some studies conducted in adults with obesity [12], whereas others have shown no significant differences. The view is commonly held that once expressed relative to fat-free mass, there is no detrimental effect of childhood obesity on VO_{2max} ($mL\ kgFFM^{-1}\ min^{-1}$). One of the most cited studies by Goran and colleagues [13] assessed VO_{2max} in 129 children (9.6 ± 1.3 years old): although VO_{2max} in absolute terms ($mL\ min^{-1}$) was higher in obese children, the difference disappeared once expressed relative to FFM. However, a recent meta-analysis of studies where VO_{2max} was assessed in obese and normal weight 12–18-year-old adolescents reported a trend for lower VO_{2max} adjusted to FFM [14], suggestive of potential reduced muscle oxidative capacity or altered cardiopulmonary responses to exercise. The difference of findings between adolescents and children regarding VO_{2max} highlights potential detrimental effects of long-term obesity: oxidative capacity remaining unaffected when children are prepubertal (obesity of short duration) [13], but as exposure to obesity increases, aerobic fitness could become progressively impaired [14].

Further, gender also appears as a parameter interacting with obesity and affecting aerobic fitness. Absolute maximal oxygen uptake (VO_{2max}, $mL\ min^{-1}$) is, for example, higher in boys with obesity compared to leaner peers and is related to differences in fat-free mass; however, the same has not been observed in girls [11].

The criteria used to assess the achievement of VO_{2max} need to be considered cautiously, especially regarding perceived exertion. To illustrate this point, it was shown that less than 1/3 of obese children who performed a maximal cardiorespiratory fitness (CRF) test were able to achieve VO_{2max} based on recommended criteria [15]. Those with obesity report a significantly higher perceived exertion during incremental testing compared to their healthy-weight peers [16], with pain and fatigue considered as the main causes. However, these criteria are rarely reached with children who are well acquainted

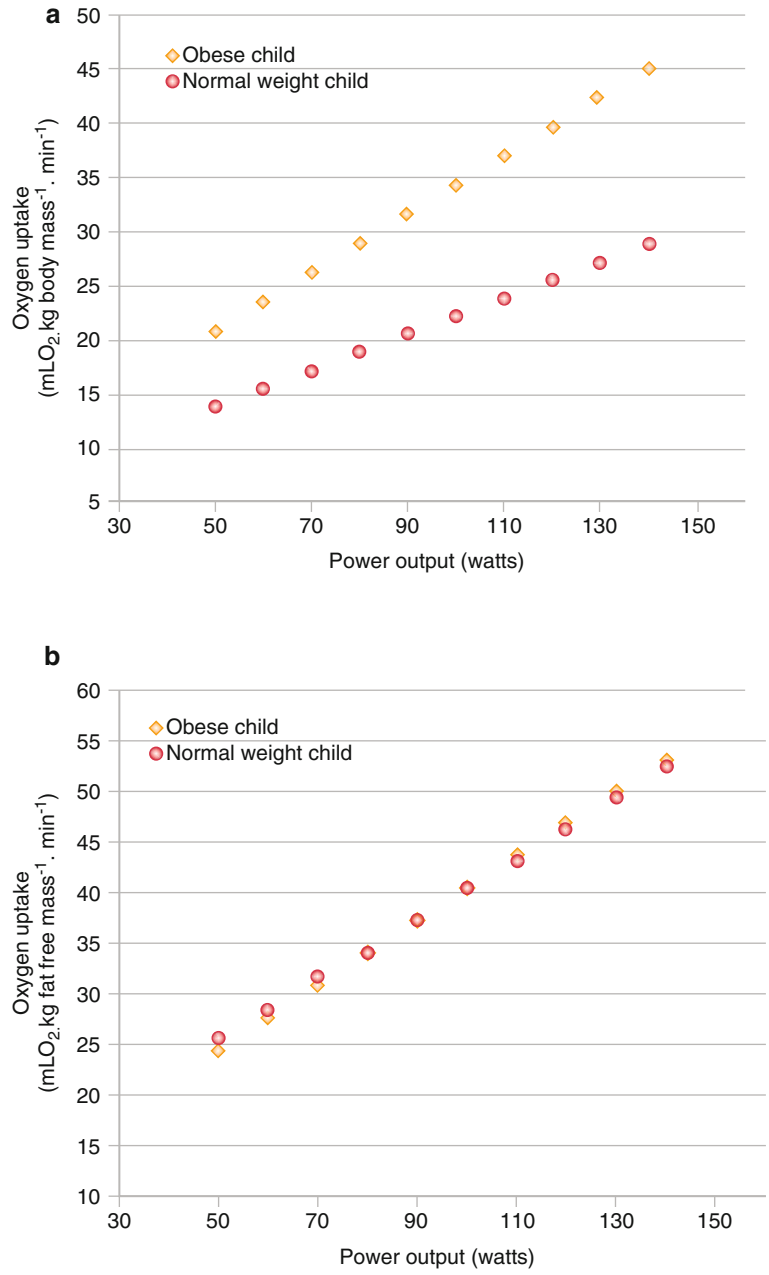

Fig. 33.1 (**a**, **b**) VO_2 differences between normal weight and obese youth when expressed relative to body mass (**a**) or fat-free mass (**b**)

with high-intensity exercise, and the maximal oxygen uptake measured during the test to exhaustion is termed VO_{2peak} rather than a "true" VO_{2max} [17]. Perceived exertion is a complex phenomenon that results from the interaction of multiple factors, such as exercise duration, modality, or the environment where exercise is performed rather than being mainly determined by exercise intensity. High-intensity exercise appears, for example, better tolerated during non-weight bearing physical activity, such as cycling, than during weight bearing physical activity, such as running [18]. Another possibility to decrease perceived exertion could be through frequent change in exercise intensity such as during short intermittent exercise, as it

has been shown that children with obesity have higher perceived exertion for the same exercise intensity when stage duration of an incremental test lasted 4 min rather than 2 min [15].

Central and Peripheral Factors Determining VO_{2max}

Even if VO_{2max} seems unaffected, there is evidence that the physiological factors determining oxygen delivery or oxygen utilization by working muscle are affected by obesity. For example, reports include a reduced arteriovenous O_2-difference or left ventricle ejection fraction, which are compensated for by increased cardiac output and stroke volume [19]. According to the Fick equation, whole body VO_2 is determined as the product of cardiac output, which determines O_2 delivery to the working muscle, and arteriovenous difference in O_2 content, which reflects the ability of the working muscle to extract and utilize O_2 through aerobic processes. Although we have previously described minor or no impairment of VO_{2max} in obese children and adolescents, studies have observed functional cardiovascular adaptations specific to obesity in response to exercise.

Muscle Oxidative Capacity

The impaired muscle mitochondrial function in obese and insulin-resistant children, but not in obese and insulin-sensitive children, supports the fact that it is not obesity per se that impairs aerobic fitness [20]. Rather, the insulin resistance that often occurs during the pubertal period is linked with changes in mitochondrial function [20, 21], which could translate to decreases in aerobic fitness.

Myocardial Function and Structure

Pediatric obesity affects cardiac morphology and function with increased resting stroke volume, cardiac output, and left ventricle mass or larger end-diastolic and end-systolic left ventricle diameter [9, 22]. Thus, obesity in childhood is associated with myocardial structural and functional alterations that may contribute to impaired cardiovascular response and VO_{2max} later in life. Morphological changes are at least in part related to eccentric ventricular hypertrophy as a consequence of hypervolemia [9]. Early insulin resistance is thought to be involved in hypervolemia in youth with obesity by increasing salt and water retention; hyperinsulinemia might also contribute to heart enlargement by acting as a myocardial growth factor [23]. These changes are already seen during the prepubertal period and are related to the degree of severity of obesity.

The extent of alteration in resting left ventricle longitudinal and circumferential strain is significantly and positively related to the reduction in exercise capacity [23]. Despite this association between resting cardiac function and aerobic fitness, there is no evidence that cardiac function directly limits exercise capacity in obese youth. In fact, stroke volume and cardiac output already elevated under resting conditions remain significantly higher in children with obesity compared to lean peers during submaximal and maximal exercise, but these differences disappear when normalized to body surface area [9, 22]. Left ventricle shortening fraction assessed by echocardiography levels off when reaching the high-intensity exercise domain (>85%VO_{2max}) in children with severe obesity, whereas it increases until a maximal effort is reached in lean children and those with mild obesity. Similarly, in a small study conducted with 13–16-year-old adolescents, Ingul and colleagues [24] observed that left ventricle function was impaired during submaximal cycling exercise. In light of these findings, it has been proposed that adaptive cardiac morphological and functional changes, characterized by increased myocardial diastolic and systolic velocities, could occur with mild or short-term obesity, but that with more severe obesity these changes become maladaptive and myocardial function is impaired [22].

Maximal Heart Rate

Based on a meta-analysis of data from exercise tolerance tests in obese adolescents, maximal heart rate does not appear to be altered by obesity in adolescents over 12 years old [14]. Similarly in younger children (although data are more limited), maximal heart rate during exercise is not affected by obesity, regardless of severity [22].

Though the meta-analytic procedure did not show a significant effect of obesity on maximal heart rate, three included studies independently reported a significantly lower maximal heart rate in obese relative to lean children and adolescents [14], which could be related to an altered response of the autonomic nervous system to exercise.

Anaerobic Fitness in Obese Youth

Muscle Strength

It has long been known that daily carrying overload can exert a hypertrophic stimulus on muscle mass [25]. It is hypothesized that excessive body fat could constitute such an overload with potential hypertrophic effect on muscle mass.

Garcia-Vicencio and colleagues [26] observed hypertrophy of lower limb muscles, with cross-sectional area of muscles such as vastus lateralis or vastus medialis more than 30% higher in adolescent girls who were obese compared to lean. More remarkably, adaptations of the muscle architecture usually characteristic of resistance training were also seen in those with obesity [26]. They showed, for example, that muscle thickness and the pennation angle of muscle fascicle (the angle of muscle fibers relative to the axis of force generation) were both increased in girls with obesity. The functional muscle cross-sectional area is thereby increased and results in improved capacity to generate muscle force.

As for aerobic fitness, it is important to keep in mind that anaerobic performances should be expressed in absolute terms, relative to body mass, fat-free mass, or specific muscle size, such as muscle cross-sectional area or limb muscle mass. The latter has seldom been used but probably allows the most accurate reflection of muscle function. Most often also, muscle contractile properties are studied during knee extensor exercise and only occasionally during upper body exercise such as elbow flexion [27].

There is a trend for higher absolute strength values in youth with obesity [26, 28–30], although this is not systematic [27, 31]. Once expressed relative to FFM, or muscle cross-sectional area, this difference disappears in most studies, which would suggest that muscle function is unaffected by obesity during childhood and adolescence [27, 29–31]. However, there are several reports that torque expressed relative to limb muscle mass in the case of plantar flexor muscle or knee extensor remained significantly higher in adolescent girls and boys, respectively, relative to lean control subjects [26].

The issue of potential neural drive impairment has been debated, with some studies indicating lower voluntary muscle activation in boys with obesity [31], while others report better agonist or synergetic muscle activation as a possible cause of higher MVC torque expressed relative to thigh muscle mass in obese adolescent boys [30]. Differences for muscle activation are also observed between boys and girls with obesity, with apparently enhanced voluntary activation in girls [26], whereas this is less evident in boys [30, 31]. It is important to remember that enhanced muscle strength in obese youth is conceived as an adaptive mechanism counteracting the effect of excess body load. Once puberty is initiated, boys have increased androgen levels that contribute to important gains in muscle mass and subsequent muscle strength, whereas muscle hypertrophy is much smaller in girls who compensate by increased voluntary muscle activation [26].

Maximal Anaerobic Power

Whereas VO_{2max} is unequivocally recognized as the gold standard to assess aerobic fitness, there is no equivalent standard to reflect anaerobic fitness. Various methods have thus been used over a variety of exercise durations (ranging from ~1 to 30 s) and exercise modalities (vertical jumping, sprint running, and cycling). In contrast with aerobic exercise, these methods provide values of peak mechanical power output, height, or velocity, but no direct measurement of metabolic rate.

Adaptations of maximal anaerobic power to obesity appear to occur early, as absolute peak power during cycling or measured with a sledge dynamometer is already shown to be higher in prepubertal children who are obese relative to leaner children [32, 33]. Likewise, strength performance (e.g., cycling peak power expressed relative to fat-free mass) has been shown to be

similar in youth with and without obesity, suggesting that muscle intrinsic contractile properties are not impaired by obesity [33, 34]. Power reflects the product of muscle shortening velocity and force generated by the muscle, and therefore power measurements provide additional information to the measurement of strength. Although data remain limited, lower velocity associated with cycling peak power in obese adolescents has been reported [34], whereas this was not apparent in prepubertal children [32, 33]. This suggests that power may deteriorate if obesity persists from childhood through adolescence.

Muscle Fatigue

Researchers who are interested in the effect of obesity on muscle neural drive have also investigated specificities of neuromuscular fatigue, which could contribute to an overall rapid increase in general fatigue in response to exercise, and ultimately low physical activity level. They have indeed shown a significantly faster decrease in maximal torque of knee extensor muscles during maximal voluntary contraction, which was attributed to impairment of the coupling between muscle excitation and contraction [28]. Increased peripheral fatigue could be explained by the greater proportion of type 2 muscle fibers in adolescents with obesity, which are more powerful but also more fatigable than type 1 muscle fibers, or higher occlusion of muscle blood flow during contraction associated with limitation of O_2 and substrate delivery.

Notably different findings have been observed in boys with obesity, with no differences relative to non-obese adolescents in the rate of fatigue development during knee extensor exercise [29], and it is therefore not possible to rule out unidentified factors related to sexual differences that may interact with obesity.

Physical Activity in the Treatment of Childhood Obesity

Physical activity and active play throughout childhood is vital to ensure healthy growth and development and is a cornerstone for weight management. The previous sections detailed how obesity leads to adaptations to the metabolic and cardiovascular systems and thus, obesity can be perceived as a barrier to physical activity. Obesity can restrict locomotor ability through impairments in cardiorespiratory fitness, biomechanical efficiency, and in some cases the presence of pain. Such barriers to physical activity can lead to low engagement and, in turn, reductions in fitness. Similarly, there is good evidence to suggest that lack of sufficient health-enhancing physical activity contributes to the development of obesity. As such, it is imperative that a thorough assessment of children with obesity is undertaken prior to intervention in order to estimate the barriers that may be limiting movement and thus fitness level.

Activity level is influenced by genetics, familial factors, neighborhood safety, time spent in sedentary pursuits, individual motivation, age, gender, and physical impairments that can act as barriers to movement [35, 36]. There is some evidence that genetic factors (e.g., PAPSS2 [3-phosphoadenosine 5-phosphosulfate synthase], Drd1 [dopamine receptor 1], and Nhlh2 [nescient helix loop helix 2]) contribute to differences in physical activity level between individuals and that both sedentary and physical activity behaviors are inherited [37, 38]. Similarly, there is evidence of a modulatory role for physical activity on the effect of genes associated with obesity (e.g., FTO gene) [39].

Measuring physical activity accurately in childhood is challenging as levels of play vary on a day-to-day basis and children engage in intermittent spontaneous bursts of movement [40] that can be difficult to recall. Physical activity can be measured using subjective tools such as activity questionnaires and objectively by motion sensors such as pedometers and accelerometers. Regardless of the method chosen, it is essential that the outcome measure is age-appropriate and has established psychometric properties. In youth with obesity, self-reported physical activity level is often overestimated and the use of objective accelerometry measures has enabled characterization of activity levels and patterns associated with a lower risk of body fat accumulation [41].

It has, for example, been shown that low adiposity is specifically associated with the amount of vigorous physical activity rather than the total amount of physical activity [39, 42].

Given the positive effects on physiological, mental, and physical health and the potential epigenetic effect of physical activity, it is essential for optimal obesity management that children are assessed for physical fitness, activity level, and important influential factors. Thereafter, identified barriers can be addressed during treatment planning and fun age-appropriate activity can be prescribed, monitored, and adapted as necessary during the behavior change process. Social support from friends and family and perceived levels of fun are key to influencing change in childhood activity and play level [43–47]. Social influence is of particular importance for children with obesity, as social rejection, isolation, and stigma from peers are commonly experienced and can contribute to disinterest in active play [48–50]

Current recommendations for health-enhancing physical activity in children are outlined in Table 33.1, and the first goal of any obesity intervention is for the child to reach these age-based recommendations [51–54]. Reaching the recommendations can be challenging, however, and success will be determined by problem-solving around individual and environmental barriers. Shared goals should be identified in order to optimize success, and thereafter in many cases the level and/or intensity of activity will need to be increased for ongoing maintenance.

When attempting to increase activity level, self-efficacy should be addressed through physical practice and experience in order to assist the child in coping with obstacles to moving and to develop confidence [51, 52]. There is huge value in the child being taught a new activity (e.g., core stability exercises) through modeling and practice rather than education or advice alone. Similarly, tailoring an activity to the child's ability, providing positive feedback, and developing realistic expectations (e.g., fatigue or delayed onset muscle soreness after starting a new activity) will assist motivation and potentially habit formation.

Treatment aims should be to have fun, to preserve fat-free mass, to improve fitness parameters, and to reduce adiposity [53]. When prescribing activity for children who are obese, the following principles should be followed:

- Use FITT guidelines to advise the child and family about the frequency, intensity, type, and time of activity that is needed.
- Tailor the prescribed activity to the ability, age, gender, and preferences of the child.
- Consider socioeconomic factors (e.g., safety of the child's environment, financial constraints).
- Use SMART goal setting to plan specific, measurable, achievable, realistic, and timed activity goals.
- Promote activity and training with other children to encourage activity as a social norm.
- Use "gain-framed" messages to highlight the effect of increasing activity and fitness (e.g., being able to keep up with peers in school, gaining independence, being able to manage weight, being picked for sports teams).
- Use a problem-solving approach to overcome the child's barriers to engaging in activity.
- Provide appropriate educational information to the parent/child on the importance of activity for child development and weight management.
- Encourage parents to move with their children and to integrate activity into the weekly routine.

Type of Physical Activity

Children who are obese will likely need to perform shorter age-appropriate bouts of activity depending on their baseline level of fitness; this is a primary consideration, particularly when intervention is first initiated. The types of activity that will assist improvements in cardiometabolic, cardiovascular, and musculoskeletal health are outlined below:

1. Facilitating basic motor skill and balance is an important target for improving confidence in movement, for reducing the risk of falls, and for promoting self-efficacy. As such, motor

Table 33.1 Health-enhancing physical activity guidelines for infants, children, and adolescents

Age	Type	Frequency	Benefit
<12 months	Supervised floor-based play in safe environments (e.g., tummy time, games with parents and siblings to encourage reaching, grasping, pulling, and pushing	*Daily* for 5–15 min play sessions	• Supports brain development • Builds strong bones and muscles • Improves movement and coordination skills • Promotes social skills through interactions with people
1–5 years	Supervised games with parents and other children which promote reaching, stretching, crawling, running, kicking, throwing, and catching	Daily for *at least 3 h* (short bouts of 10–20 min spread throughout the day)	• Builds strong hearts, bones, and muscles • Improves balance and coordination skills • Helps achieve and maintain a healthy weight • Encourages self-confidence and independence in preparation for school
5–12 years	Moderate to vigorous intensity physical activity[a] including high-impact activities to promote bone health (e.g., skipping, jumping, running & dancing)	*At least 60 min per day* On at least 3 days per week, children should engage in high-impact activity	• Supports concentration and learning • Builds strong bones and muscles • Improves balance and coordination skills • Helps achieve and maintain a healthy weight. • Encourage self-confidence and independence • Helps the child to make new friends and to develop social skills
13–17 years	Moderate to vigorous intensity physical activity[a] including high-impact activities to promote bone health (e.g., skipping, jumping, running, and dancing); active transportation, organized and non-organized sports, games, physical education, and other activities at home, school, work, and in the community	*At least 60 min per day* On at least 3 days per week, children should engage in high-impact activity	• Supports concentration and learning • Builds strong bones and muscles • Improves balance and coordination skills • Helps achieve and maintain a healthy weight • Encourages self-confidence and independence • Helps the child to make new friends and to develop social skills • Improves cardiometabolic health • Enhances mental health and wellbeing • Supports cardiorespiratory fitness

Data from Reference [54]

[a]Activities that cause the child to get warm, go red, and start to sweat

skill components (e.g., games in single-leg stance and ball skills training) should be integrated to promote motor skill capacity [55, 56] from the outset of treatment.

2. Aerobic games and exercise programs with sessions 3–5 times a week, of moderate intensity up to 60 min, are effective in inducing improvements in body mass index, fat mass, visceral adipose tissue, insulin sensitivity, ectopic fat stores, blood pressure, and lipid profile [57–59]. Activities such as walking, cycling, participation in ball and field games, jogging, and swimming should be encouraged. Research suggests that adolescents who are obese exhibited maximal fat oxidation rates at 41% VO_{2max}, which corresponded to 58% HR max [60]. Exercise in this low to moderate intensity will maximize fat oxidation while reducing fat mass with good results gained from 90 min of activity set at the Lipox max on 4 days a week [61, 62]. Non-weight bearing activities such as recumbent cycling, stationary cycling, rowing

ergometry, and swimming can be most useful to begin with in order to get buy-in, to avoid pain, and to reach higher activity intensities [18]. Consideration should be given, however, to the weight limits of any exercise equipment and to the accessibility and safety of public swimming pools. Active gaming via computer consoles may be useful to reduce sedentary time; however, given the lack of data regarding the effect of such tools on health-enhancing physical activity levels, they should not be used as a replacement for offline play, activity, and aerobic training [63].

3. Games and activities based around resistance training can safely be completed by children and adolescents [64, 65] and offer a less aerobically taxing option compared to endurance activities. As such, they may be more acceptable to those with obesity and can be performed successfully given the higher levels of muscle mass in youth with obesity. As such, good adherence can be achieved with programs of resistance exercise with favorable effects observed on adiposity, musculoskeletal health, self-confidence, self-esteem, lipid profile, blood pressure, and insulin sensitivity [66, 67]. Resistance activities should involve the whole body, be performed over at least 8 weeks at moderate submaximal intensities with 2–3 sets of 8–20 repetitions, and could include yoga, supervised weight lifting, or games involving the body's own weight as the resistance.
4. High-impact games and activities such as skipping, jumping, dancing, and martial arts are important for maximizing bone health which may be decreased in some sedentary children with obesity [68, 69]. Bone building play should be performed at least three times per week for 10 min, and any reports of discomfort or pain should be heeded due to high lower limb loading forces in those with obesity [70].
5. High-intensity interval training (e.g., sprint interval training) is useful for improving aerobic power, which may not be achievable by long-duration continuous low to moderate intensity exercise. Games, relays, or races consisting of "all-out" sprints of 30–60 s at 100% VO2peak or 100% heart rate favor improvements in aerobic power; interspersed with passive or active recovery periods of equal duration, this can improve aerobic capacities, blood pressure, insulin sensitivity, and percentage body fat in obese youth while not significantly reducing body weight significantly [71, 72]. The vigorous nature of interval training may have a particularly positive impact on mental health in childhood (levels of depression, self-worth, anger expression, and perceived physical appearance) [73, 74].

As weight begins to decline, it will be necessary for the child to maintain or even increase his/her level of activity due to concomitant reductions in bodily energy expenditure. It is likely that children would need more than 60 min of moderate-vigorous activity per day to prevent weight regain [75, 76]. Gradual increases in activity time should be promoted, and age-appropriate daily activity goal charts using stickers or rewards may be useful to support motivation. Similarly, pedometers, accelerometers, or smartphone applications may be useful aids for encouraging self-monitoring of active play and physical activity. As the child becomes more accustomed to moving, it is useful to advise that he/she try a variety of games, sports, and activities. Children should be encouraged to keep trying new games as it is usual to find new activities difficult when first undertaken. In addition, the whole family should be encouraged to move more, to commute actively where possible, and to spend family time doing fun activities. Particular attention and problem-solving will be needed for children who are wheelchair users or have limited mobility (e.g., following surgical procedures or due to comorbid conditions) such that activity and games may need to be modified accordingly.

Compensatory Responses to Physical Activity in Children with Obesity

The prevention and treatment of overweight and obesity mainly rest on the control and modification of energy balance using dietary restrictions and physical activity interventions to reduce the

energy ingested in the first instance and increase energy expenditure in the second instance. Although physical activity combined with energy restriction is widely used and recognized to induce weight loss, the effect of physical activity alone is often debated. Possible indirect relationships and compensatory mechanisms underlying the interaction between physical activity and energy intake are widely discussed by the scientific community as crucial determinants of energy balance and the impact on weight control [77–79]. Similarly, physical activity programs might lead to compensatory reductions in spontaneous physical activity outside of prescribed sessions, which could then annul or even reverse effects on energy expenditure and hence contribute to the lack of weight loss usually observed in response to physical training alone.

Nutritional Adaptations to Exercise and Physical Activity

Effect of Acute Exercise on Energy Intake and Appetite-Regulating Hormones

Despite the large number of studies that have been conducted in adults, the question of how exercise may affect energy intake (EI) and appetite control remains controversial and less explored in youth [80]. In 2004, Moore and collaborators were the first to question such effects in children and identified no detectable increase in EI after acute exercise in 10-year-old lean girls [81]. Similarly, Bozinovski and collaborators failed to find any effect of either short (15 min) or long (45 min) treadmill exercises set at the ventilatory threshold in lean 12-year-old (12.6 ± 0.3 year) boys [82]. One study compared immediate post-exercise energy intake responses between lean and overweight/obese youth [83]; it found that EI was decreased after 1 h of resistance training and remained unchanged after 1 h of aerobic exercises or swimming in lean prepubertal children; in contrast, the swimming session led to an increased food consumption in children with overweight/obesity [83]. In 2011, a study conducted among adolescents with obesity reported that an acute bout of cycling set at 70% of maximal capacity led to a spontaneous reduction in daily energy intake without altering appetite [84]. Subsequently, the authors explored the role of exercise intensity (comparing two isoenergetic cycling exercises set at 40 and 75% VO_2max) and showed that this transient "exercise-induced anorexia" was only observed in response to intensive exercise [85]. Interestingly this post-exercise reduction of energy ingested was only observed in adolescents with obesity and not in their lean peers, suggesting a weight status effect [86].

Although the studies conducted so far use different methods and designs, a recent systematic review and meta-analysis clearly found that indeed, an acute bout of exercise does alter energy intake at the following meal in lean children and adolescents while it leads to a significant reduction of daily food consumption in those who are overweight/obese when performed at high intensity [87].

While studies conducted so far in youth rest on energetic and behavioral observations, data are sparse regarding the potential physiological pathways and actors involved in these post-exercise nutritional responses. In adults, the literature provides some evidence regarding the implication of some of the main appetite-regulating peptides to explain the post-exercise energy intake modifications. As nicely reviewed by Stensel, bouts of running or resistance exercise effectively favor a transient suppression of acylated ghrelin (an appetite-stimulating peptide), lasting for an hour or so after exercise. Similarly, several studies have reported that plasma PYY (Peptide YY; an anorexigenic gastrointestinal peptide) concentrations are increased during aerobic exercise both in adults who are lean or obese. Other anorexigenic factors such as GLP-1 (glucagon-like peptide 1) and PP (pancreatic polypeptide) have been found increased during and for at least 30–60 min after aerobic exercise [88]. The post-exercise hormonal responses in young adults who are lean or obese are summarized in a 2009 paper [89, 90]. According to their results, PYY and GLP-1 were both increased after a 60-min cycling exercise

set at 50% of their VO_{2max}; this was accompanied by a reduction in subsequent energy intake [90]. Interestingly, the post-exercise $PYY_{3–36}$ response (the PYY isoform mainly involved in appetite control), was sensitive to the intensity of the exercise. Indeed, when performed at 75% VO_{2max}, post-exercise $PYY_{3–36}$ concentrations are higher compared to a moderate intensity exercise (50% VO_{2max}) and is accompanied by a greater reduction of subsequent energy intake in lean men [89].

In children, few data are available regarding the effects of acute exercise on appetite-regulating hormones. In 2011, Sauseng and colleagues asked school-aged children (12.6 ± 0.4 years old) to perform a continuous, progressive bicycle exercise test to exhaustion and, in contrast to studies in adults, reported a significant increase in acylated ghrelin after the controlled short-time exercise (mean duration 10.58 ± 0.38 min). According to the authors, the increase in acylated ghrelin concentration after exercise represents a physiological response to ensure a sufficient caloric intake to compensate for the induced energy depletion, but they did not assess energy consumption [91]. More recently, Prado and collaborators conducted the first study that questioned the effect of acute exercise on appetite-related hormones in youth with obesity [92]. In this work, nine adolescent girls with obesity (13–18 years old) were asked to run 30 min on a treadmill at their determined ventilatory threshold. Pre- and post-exercise leptin, $PYY_{3–36}$, and hunger were assessed. According to their results, while leptin concentration, 24-h energy intake (self-reported), and hunger did not vary, there was an acute increase in $PYY_{3–36,}$ which agrees with the previous reports of decreased post-exercise energy intake [92].

Although this cross-talk between peripheral actors (such as gastrointestinal peptides or adipokines) and the hypothalamus may explain differences in post-exercise food consumption [93], recent data suggest that post-exercise energy intake modifications can also be explained by other neural networks involved in the cognitive processing of food-related cues [94, 95]. Using functional magnetic resonance imaging (fMRI), Evero and colleagues showed that a 60-min cycling exercise (set at 83% of maximal heart rate) reduced the neural response to food vs. control images in several brain areas involved in motivation, attention, and visual processing, while simultaneously reducing self-perceptions of hunger and prospective food consumption in lean young men and women [94]. This suggests that the attentional response to food-related cues could be altered with exercise, which could contribute to the indirect effects of physical activity on food consumption. Whether this reduced neural activation was associated with an effective suppression of energy intake was, however, not assessed. Lately, Hanlon and colleagues also questioned the impact of acute exercise on the attentional response to food cues and energy intake in lean and obese women (by measuring event-related potentials, ERPs, using electroencephalography—EEG) [95]. According to their results, a moderate-to-vigorous 45-min treadmill exercise (relative to rest) leads to a reduction in the late positive potential (LPP) response to visual food cues in both obese and lean women [95]. This was interpreted as a neurologically determined measure of food motivation and attentional processing of food stimuli. Unfortunately the study was limited by the use of 24-h self-report questionnaires for assessing energy intake. A recent similar study conducted in adolescent boys with obesity reported that the neurocognitive response to food stimuli is significantly reduced compared to non-food stimuli after a 45-min cycling exercise set at 65% VO_2max. Importantly, this reduced neural activation coincides with a significant decrease in energy intake at the following meal compared to a resting condition [96]. These results are important since they clearly indicate that exercise can affect energy intake by modifying both its peripheral and neurocognitive control.

Are There Any Effects of Physical Training on Obese Youth's Energy Intake?

King and collaborators ran to our knowledge the first experiment that questioned the effect of longer term physical activity on appetite in youth

and observed that 6 weeks of physical activity led to an increase in the feeling of hunger and to a decrease in satiety in adolescents with obesity; this suggested a potential orexigenic effect of regular exercise in this population [97]. Gueugnon and colleagues conducted a well-designed 9-month interventional study among adolescents with obesity and reported increased ghrelin and unchanged PYY concentrations in response to their physical activity intervention, also suggesting a possible post-intervention drive to increased food intake [98]. However, others observed an increase in fasting total PYY after 8 months of physical training in a similar population, accompanied by unchanged active ghrelin and leptin concentrations (with decreased body weight and body fat mass), which should favor reduced food consumption [99]. Although these studies provide potentially important results, they remain contradictory and none effectively assessed energy intake.

Recently, a study of a 10-week physical activity program composed of 60 min of moderate intensity cycling exercise, twice a week, reported a decrease in daily food intake by about 10% in youth with obesity (mainly attributed to a decrease in fat intake) [100]. Carnier and coworkers also observed a decreased daily energy intake in adolescents with obesity in response to both aerobic training alone or aerobic plus resistance training programs (1 year) and explained this by a significantly increased α-MSH concentration (an anorexigenic factor) despite a concomitant increase in AGRP concentrations (orexigenic) in the aerobic + resistance group [101]. Recently, Prado and coworkers compared the effect of a 12-week physical activity intervention performed at low (20% below ventilatory threshold) versus high intensity (ventilatory threshold) on energy intake in adolescents with obesity. Both interventions were calibrated to induce the same energy expenditure, 350 kcal per session; results described a significant decrease in energy intake after the intensive program which was accompanied by decreased leptin and total ghrelin and increased PYY concentrations [102] (see Fig. 33.2a–d).

A recent systematic review and meta-analysis assessed pre- and post-physical activity energy intake in children and adolescents with obesity and concluded that medium- to long-term interventions significantly decrease daily energy consumption, with a significant decrease of each macronutrients [103]. However, this review stresses that all the included studies used self-reported methods to evaluate EI, which are quite limited particularly in youth with obesity [104]. Moreover, most of the included studies assessed energy intake as a secondary or tertiary outcome and may have been inappropriately powered and/or designed to provide accurate and reliable results [103].

While it seems then that both acute exercise and chronic physical activity has the ability to indirectly affect daily energy intake in obese youth, it seems necessary to also consider their potential effects on spontaneous-physical activity.

Are Their Post-exercise Energy Expenditure Compensatory Responses?

In 1998, Rowland proposed that physical activity is controlled centrally according to a set point of energy expenditure, predicting that more activity at one time point is compensated for by less activity at another to preserve an individual's set point [105]. Several studies conducted in school children have illustrated this compensatory trend in physical activity by examining children's physical activity levels (using accelerometers) as they were involved in different physical education timetables between schools [106–109]. Fremeaux and colleagues assessed the physical activity level of 8- to 10-year-old children in different schools and showed that this compensatory regulation of physical activity was reliable [106]. This explains why the physical education time offered at school cannot be associated with the overall physical activity level of children [110].

However, results from other work do not support the activitystat theory [111–113]. Using an observational design, Baggett and coworkers measured the physical activity level of 6916

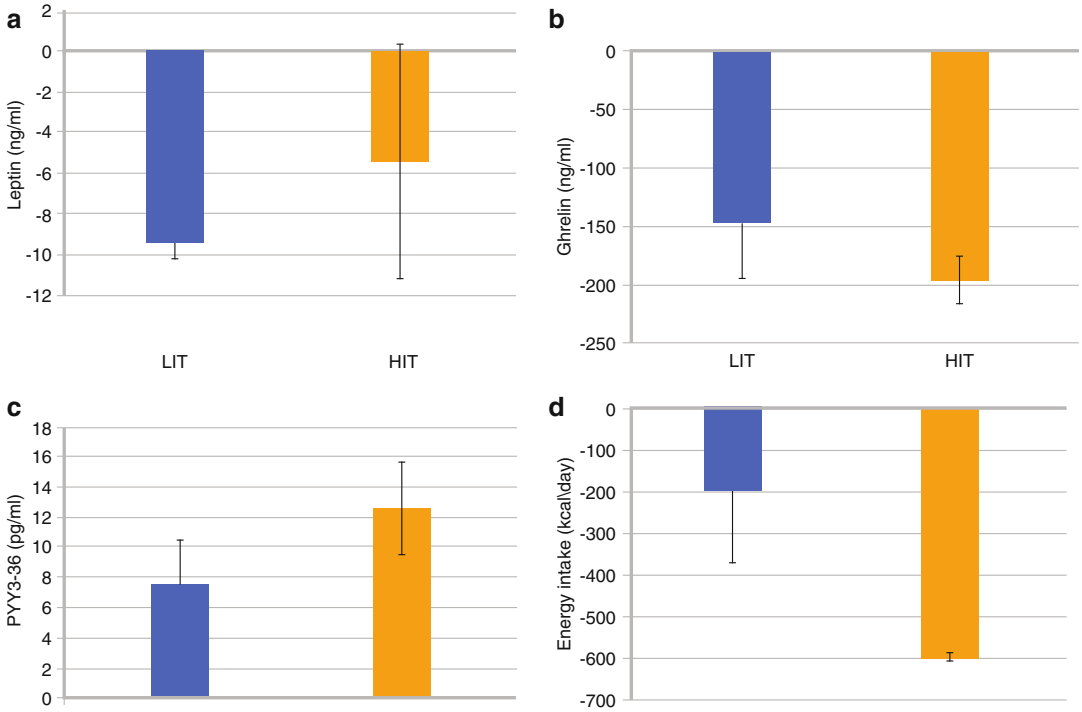

Fig. 33.2 (**a**–**d**). Leptin (ng/mL) (**a**), ghrelin (ng/mL) (**b**), PYY_{3-36} (pg/mL) (**c**), and daily energy intake (kcal/day) (**d**) variation from baseline to the end of the 12-week low-intensity (LIT) and high-intensity training (HIT) in obese adolescents (Data from Reference [102])

American girls and did not find any evidence of compensation that would be predicted by the activitystat theory within the same day or over a 2-day period [111]. Previously, Dale and collaborators voluntary decreased the opportunities for physical activity during the school day for primary school children (by suppressing physical education classes and restricting children to spend recesses inside in front of computers) and did not observe any compensatory response in children to preserve a possible set point of physical activity, measured by accelerometer [112].

Regarding the literature detailed so far, some have suggested that the existence of an activitystat mechanism is far from being established and is not highly probable [114, 115]. Some short-term explorations must, however, be discussed as they may have used more objective methods to assess energy expenditure and/or physical activity than longitudinal studies and because they also examined the impact of the children's adiposity status, which seems to be a key determinant of outcome.

Wang and Nicklas previously observed that postmenopausal women significantly decrease their spontaneous physical activity after an imposed exercise session compared to a control condition [116]. Interestingly, this decrease in spontaneous activity was more pronounced following high-intensity exercise compared to moderate exercise [116]. The same observation has been made in obese adolescents, who decrease their energy expenditure on the day of a moderate intensity exercise by 3% and by 6% on the day of an intensive exercise session and during the two following days [117]. In other recent studies, obese adolescents were asked on separate occasions to complete isoenergetic exercises at 40% and 75% of their maximal aerobic capacities (VO_2max) in metabolic chambers. The results highlighted a compensatory decrease in energy expenditure for the rest of the day (exercise set by the end of the morning) after the

high-intensity exercise, leading to unchanged 24-h energy balance compared to a control session [85, 118]. Although the same results have been replicated in similar groups of obese adolescents (using ActiHearts and armbands to track energy expenditure) [84, 118], lean adolescents do not seem to experience such a compensatory reduction in spontaneous activity post-exercise (measured using armband) [118].

Conclusion

Although the literature remains quite limited on this question, it seems that the application of the activitystat theory clearly depends on weight status in both adults and children, as does the previously described effect of physical exercise on energy intake. Altogether, these results must lead practitioners and scientists to consider the modification of both sides of energy balance when studying the effects of acute exercise and physical activity in children and adolescents and particularly for the prevention and treatment of pediatric overweight and obesity.

Editor's Comments and Question

1. Winston Churchill once attributed his success in life to "conservation of energy: never stand up when you can sit down, and never sit down when you can lie down." Nevertheless, exercise reduces visceral fat mass and increases lean body mass, thereby augmenting resting energy expenditure. Aerobic training increases insulin sensitivity, reduces fasting and post-prandial glucose, free fatty acid, and TG concentrations, and increases plasma HDL levels. Muscle oxidative enzyme activity is induced, possibly via increases in mitochondrial size; the resulting induction of AMP-activated protein kinase (AMPK) promotes Glut-4-dependent glucose uptake. In the aggregate, these effects improve fitness, which in adults is related inversely to cardiovascular mortality[a–c].

2. Many papers in the literature suggest that "sedentary behavior" is associated with childhood weight gain, while vigorous physical activity promotes weight stabilization or weight loss. Yet there is considerable controversy about the role of physical activity as a *determinant* of childhood obesity. In part, this is because we lack accurate and systematic longitudinal data regarding physical activity in large populations of adolescents and, especially, young children. But there are other important limitations. First, sedentary children and their families may eat very differently than those who have active lifestyles, so comparisons between sedentary and active children may reflect differences in diet as well as activity. Second, it can be difficult to exclude reverse causation; that is, children who become obese may be less likely, for all the reasons you cite, to participate in vigorous physical pursuits. And third, and perhaps most important, physical activity energy expenditure represents a minority of the total energy expended during the day; 50–70% of total energy expenditure reflects resting metabolic rate, which as you note depends on the mass of skeletal muscle and other metabolically active organs including the brain, kidney, liver, and heart. To determine if childhood physical activity determines subsequent risk of obesity, or if lifestyle interventions can reduce fat mass by increasing energy expenditure, it would seem most appropriate to assess their effects on total energy expenditure, as measured, for example, with doubly labeled water. Such studies would be quite challenging to undertake in large and diverse cohorts.

How can we accurately assess energy expenditure in children in real-life settings?

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Authors' Responses

Assessing energy expenditure has been one of the main methodological challenges for the last couple of decades in the field of exercise and health sciences. While objective measures such as calorimeters or doubly labeled water remain expensive, daily trackers such as accelerometers have been developed and validated to assess body motion and activity and provide great proxies and estimations of daily energy expenditure. Further studies are definitely needed to develop new tools and methods to estimate or measure energy expenditure but also quantify physical motion and activity, especially in children. It seems today that the best way to assess accurately physical activity level and energy expenditure in kids rests upon the combination of observations and trackers.

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School- and Community-Based Interventions for Childhood Obesity

34

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Introduction

For decades, school-based programs have constituted the primary approach for addressing the childhood obesity epidemic at the population level. School programs have the potential to reach many children and affect many factors in the causal path to obesity (i.e., diet, physical activity, knowledge, and other psychosocial factors); in theory, they have great promise for long-term sustainability through institutionalization of intervention components [1, 2].

On the other hand, the effectiveness of school-based interventions has for the most part been disappointing. Most school programs have been associated with only modest impacts on childhood behavior and weight gain [3, 4]. Some success has been observed in school intervention trials that have had strong program champions, but the beneficial effects in children are often reversed if staff members who championed the program leave the school [5, 6]. These findings have led us and other investigators to question the school-centered approach to child obesity prevention [7–9]. One of the primary critiques has been that school-centered programs are unlikely to be successful if not heavily reinforced by strong interventions in the community.

Children are influenced by the wide range of choices and factors that constitute the food and physical activity environments outside of schools; these include the presence and proximity of retail food stores, the availability of prepared and "fast" foods, the variety and quantity of foods available and served within the home, and the accessibility of parks and recreation centers. Parents and other caregivers have great control over the foods consumed by their children, particularly at a young age [10]. In recent years, a growing number of school-based intervention trials have sought to expand beyond the confines of the school to engage the broader community. We term these interventions "school–community programs." In addition to school-based interventions, they may include community and family components that invoke community involvement, nutrition environment intervention near schools, and family education and participation. Here we review the literature

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on "school–community" intervention trials to answer three questions:

1. What types of "school–community intervention trials" are found in the literature? How do these programs vary in terms of program components, emphasis on school versus community, strategies, study size, etc.?
2. How successful have "school–community" programs been? What components appear to be most successful overall?
3. What are future directions for school-based and school–community programs to prevent childhood obesity?

To identify the relevant literature for school–community programs, we conducted a literature search for the years from January 1990 to December 2016 using Medline, PubMed, PsycINFO, and the Cochrane Database of Systematic Reviews. The following inclusion criteria were used to select articles for the review: (1) selected studies should have both school-based intervention programs and substantial components outside the school aimed at preventing childhood obesity; (2) the overall goal of studies should be preventing unhealthy weight gain or obesity among children through increased physical activity, better nutrition, and/or environmental policy changes in schools and communities; (3) evaluation outcomes must include obesity, physical activity, and/or energy intake to be included in this review. We excluded studies that sent home materials and/or had activities within the school for family members as their primary form of community engagement (e.g., Pathways [11], CATCH [12]). In addition, recent review articles (2000–2016) on school-based and community-based childhood obesity prevention program were manually checked to be sure that any studies mentioned in the reviews would meet the inclusion criteria for this study. A total of 15 intervention studies were found matching these criteria. Additional searches were performed to identify the relevant literature for school–community-based diabetes prevention studies. Two additional studies were reviewed and included in the tables.

Therefore, a total of 17 intervention studies were reviewed. In addition to reference to published articles, we contacted the lead authors when information was missing and included the information provided by the authors to provide a more complete description of the studies.

Summary of the Literature

Summary of Articles of School–Community Programs for Obesity Prevention

Tables 34.1 and 34.2 summarize our findings from the review of the literature. Table 34.1 describes the background, target population, and intervention approach of each program. Table 34.2 outlines the methods of evaluation used and the primary results and recommendations.

General Description of the Intervention Trials

Of the 17 studies reviewed, eight were implemented in the USA, three in Australia, one in Canada, one in New Zealand, one in France, one in Tonga, and one in Fiji. One study was a multicountry study and summarized the results from eight European countries, including Sweden, Germany, Hungary, Italy, Cyprus, Spain, Belgium, and Estonia. The intervention periods ranged from 1 to 3 years, with two exceptions [5, 13]. All interventions were controlled trials with comparison groups; four of the studies (Aventuras [14], TAAG [6], SNPI [15], Switch [16]) randomly assigned schools to intervention and control status.

Some studies took a slightly different approach than others included in this review. One study conducted in France, titled Fleurbaix-Laventie Ville Santé (FLVS [17], was initiated in 1992 as a school-based nutrition education intervention and evolved into a school–community intervention beginning in 1999. The program was still ongoing in 2007 when the evaluation paper was

Table 34.1 Theory and intervention strategies used in the ten school–community intervention trials

Study title, duration	Theory used	Preparatory work	Main intervention components	
			School based	Outside of school
The APPLE Project (A Pilot Programme for Lifestyle and Exercise) [38, 44, 51, 60, 61]	"ANGELO" (Analysis Grid for Environments Linked to Obesity)	Community activity coordinators (ACs); interviews with community stakeholders and school personnel	*Curriculum*: science/health lessons and an interactive card game on nutrition *Policy/Env*: non-curricular activity at recess, lunchtimes, and after school; teachers to facilitate short bursts of activity in class and after school	*Family*: increased parental involvement *Community Links*: physical activity classes; community-based healthy eating resource and free fruit for 6 months
The Aventuras Para Ninos Study (Aventura) [14]	Ecological model of behavior change, social cognitive theory, health belief model	Not reported	*Curriculum*: improving PE classes	*Family*: *promotora* home visits and booster phone calls
			Policy/Env: training for teachers and food service workers; improving school playgrounds and salad bars; teachers' discipline and classroom practices (water bottles in classrooms, using nonfood rewards); physical education equipment	*Community links:* improving community parks; healthy child menus in restaurants; frequent produce buyer cards in grocery stores; culturally appropriate media messages
Be Active Eat Well (BAEW) [29, 52]	Capacity-building approach	Community involvement in planning activities	*Curriculum*: a 2-week curriculum for reducing screen time	*Family*: healthy families program
			Policy/Env: school dietitian and nutrition policies; after-school activities	*Community links*: community garden; fruit shop displays; activity programs
				Policy: municipal public health plan
The Travis County Coordinated Approach To Child Health Project (CATCH BPC) [20]	Social–ecological model and social cognitive theory	Community participatory methods in program development	*Curriculum*: nutrition and PE program (CATCH)	*Family*: family fun night events and activities
			Policy/Env: nutrition service component; teacher training; social marketing efforts; PA equipment	*Community links:* formation of community action team; community workshops
Eat Well Be Active (EWBA) [26, 46, 62, 63]	Social–ecological model	Community-based, capacity-building approach; local action groups	*Curriculum*: school curriculum for nutrition and physical activity	*Family*: training parents
			Policy/Env: healthy policies in schools and child care; physical environment improvements to outdoor play spaces; water fountain in schools and public areas	*Community links:* workforce development and peer education, policy, infrastructure improvements, promotion/local marketing, community development in various community settings

(continued)

Table 34.1 (continued)

Study title, duration	Theory used	Preparatory work	Main intervention components	
			School based	Outside of school
Fleurbaix-Laventie Ville Santé (FLVS) study [17]	Not reported	Not reported	*Curriculum*: nutrition education program for all grades	*Family*: health checkup and clinical examination, targeted counseling
			Activities in schools: cooking classes, visits to farms, family breakfast in schools	*Community links*: dietitians and sport educators; town councils for sporting activities/ facilities
			Policy/Env: school cafeterias to increase affordable and diversified food	
Healthy Youth Healthy Communities study, Fiji (HYHC) (OPIC) [21, 40]	"ANGELO" (Analysis Grid for Environments Linked to Obesity)	Community capacity-building approach	*Curriculum*: curriculum development with home economics and agricultural science	*Family*: awareness programs to parents; pamphlets and school assembly morning talks on healthy eating
			Policy/Env: nutrition policies for school canteen (supporting breakfast, water, fruit, vegetable); social marketing for healthy eating at school events; improving road safety; school policy on PE classes and PA equipment	*Community links:* programs within churches, mosques, and temples (vegetable gardening, morning walk); awareness programs within the community
Identification and prevention of Dietary- and lifestyle-induced health EFfects In Children and infantS (IDEFICS) [18, 19, 55, 64, 65]	Social–ecological model	Not reported	*Curriculum*: "Healthy Weeks" activity on diet and PA; distribution of educational game posters and card games; PE curriculum and training for teachers	*Family*: providing educational folders and videos
			Policy/Env: formation of working group within schools and kindergartens; staff training; environmental school policy changes on PA and nutrition (water, F&V consumption)	*Community links:* community stakeholder group invited and given responsible for campaigns and the communication strategy; cooking competition in the community; community environmental and policy interventions (community playgrounds, quality checks of tap water)
It's Your Move! Australia (IYM) (OPIC) [47]	"ANGELO" (Analysis Grid for Environments Linked to Obesity)	Community capacity-building approach	*Curriculum*: education strategies on healthy body image; nutrition education; PA sessions	*Family*: parent education and information (support, role models)
			Policy/Env: capacity building among school officers and student ambassadors; increasing awareness of project messages; water accessibility; breakfast programs; school food policy; professional development for PE teachers	*Community links:* partnerships and collaborations with government and regional organizations

(continued)

Table 34.1 (continued)

Study title, duration	Theory used	Preparatory work	Main intervention components	
			School based	Outside of school
Jumpin' Jaguars: Community-driven obesity prevention and intervention in an elementary school [28]	Universal, targeted	Academic, community partners, school teachers	*Curriculum*: behavior modification to all children in the school	*Family*: evening classes on healthy cooking and lifestyle changes
			Policy/Env: not reported	*Community links*: free healthy snacks by local NGO; scholarship incentives
			After-school: targeting activity and counseling	
Kahnawake School Diabetes Prevention Project (KSDPP) [13, 25, 35, 66–68]	Social learning theory, behavior change theory, native learning styles, health promotion	Community advisory board	*Curriculum*: structured school health education program	*Family*: healthy breakfasts
			Policy/Env: healthy nutrition policy; teacher training	*Community links*: community advisory board; research ethics code; conferences
Ma'alahi Youth Project, Tonga (MYP) (OPIC) [27, 37]	"ANGELO" (Analysis Grid for Environments Linked to Obesity)	Community capacity-building approach	*Policy/Env*: school food policy; school vegetable gardens; PA equipment provision; aerobic classes; capacity-building programs for students and teachers	*Family*: program leaflet distributed in one village
				Community links: partnerships and collaborations with government and regional organizations; capacity-building and leadership workshop with key personnels in the community; social marketing approaches; community vegetable garden and fruit tree planting; weekend soccer and volleyball tournament; aerobic sessions at village level
School Nutrition Policy Initiative (SNPI) [15]	Social learning theory	Community-based organization; nutrition advisory group	*Curriculum*: nutrition education	*Family*: parent meetings and weekly nutrition workshops
			Policy/Env: staff training to change in-school nutrition environment	*Community links*: community-based organization with family resource network coordinators and parent–teacher organizations
Shape up Somerville: Eat Smart, Play Hard (SUS) [34, 41, 42, 69, 70]	Social–ecological approach	Meetings, focus groups, interviews, advisory councils	*Curriculum*: classroom curriculum	*Family*: parent outreach and education; family events; nutrition forums; "health report card"
			Policy/Env: breakfast program; walk to school; staff development; school food service; enhanced recess after-school curriculum	*Community links*: community advisory council; ethnic minority group collaborations; pedestrian training; wellness campaign; farmers markets; physician and clinic staff training

(continued)

Table 34.1 (continued)

Study title, duration	Theory used	Preparatory work	Main intervention components	
			School based	Outside of school
Switch What You Do, View, and Chew (Switch) [16, 30]	Social–ecological model	Community events	*Curriculum*: monthly teacher's packet	*Family*: materials on physical activity, nutrition and screen time
			Policy/Env: school-wide kickoff	*Community links*: a community-wide event; public service advertising campaign
Trial for Activity for Adolescent Girls (TAAG) [6, 31–33, 43, 71–74]	Social–ecological theory, operant learning theory, social cognitive theory, social marketing, organizational change theory	Formative research with adolescent girls, parents, school personnel, and community members	*Curriculum*: physical education, health education *Policy/Env*: teacher workshop and materials; school champions	*Community links*: collaboration between schools, community agencies, and university staff; after-school programs; social marketing efforts
Zuni Diabetes Prevention Program (ZDPP) [5]	Social cognitive theory	Focus group, interviews, dietary survey	*Curriculum*: diabetes education in school curricula	*Family*: meetings with parent–teacher organizations (PTOs)
			Policy/Env: workshop with school administrators, teachers, employees; modification of food supply; wellness facility	*Community links*: supportive social networks; teen task force

published; the reviewed paper summarized the intervention effect through 2004. The Identification and prevention of Dietary- and lifestyle-induced health EFfects In Children and infantS (IDEFICS) study was designed as a longitudinal population-based multicenter cohort study with an embedded quasi-experimental intervention trial implemented for 2 years from 2008 to 2010 [18, 19]. The Travis County Coordinated Approach To Child Health Project (abbreviated in this chapter as CATCH BPC) implemented an evidence-based coordinated school health program (Coordinated Approach To Child Health BasicPlus, CATCH BP) in both intervention and comparison schools and added community-based components in the intervention schools (CATCH BasicPlus and Community, CATCH BPC) in order to test whether adding community-focused components would be more effective in controlling childhood obesity [20].

Three studies included in this review (Healthy Youth Healthy Communities study (HYHC) [21], It's Your Move! (IYM), and Ma'alahi Youth Project (MYP)) were part of a larger project, the Pacific Obesity Prevention in Communities (OPIC) project, which targeted adolescents in four countries (Fiji, Tonga, New Zealand, and Australia) from 2004 to 2009 [22–24]. These studies share similar intervention strategies and evaluation methods.

Target Populations

Most of the studies reviewed targeted elementary school students, most of whom ranged from 4 to 12 years of age. SNPI study targeted fourth through sixth graders, whereas SUS mainly focused on first through third graders. Five of the reviewed studies targeted older students; TAAG worked mainly with middle school girls, ZDPP targeted high school students, and the HYHC, IYM, and MYP studies worked with both middle and high school students.

The trials in this review included children from a wide range of ethnic groups. Many of the studies focused on low-income populations; for example, the two studies designed to reduce

Table 34.2 Study design, results, and main conclusions of the ten school–community intervention trials

Study title	Study design; evaluation methods used	Results	Main conclusions/ recommendations
The APPLE project	*Treatment*: semirural community in Otago, New Zealand. Elementary schools ($n = 4$, 5–12 years; 381 children)	*Process evaluation*: not reported	Increased activity and slowed unhealthy weight gain in primary school children
	Control: one community in same area. Elementary schools ($n = 3$, 5–12 years; 346 children)	*Behaviors*: higher activity level with intervention; lower consumption of carbonated beverages and more fruit	*Sustainability*: after the discontinuation benefits in BMI remained apparent in intervention children
	Ethnicity: mostly white, middle-class (17.3% Maori, 0.9% Pacific Island)	*Health*: *year 1*, BMI *z*-score − 0.11 ($p < 0.05$). No difference in the risk of being overweight or obese, waist circumference, blood pressure, or pulse rate	
		Year 2: BMI *z*-score − 0.26 ($p < 0.05$). WC −1 cm ($p < 0.05$)	
		Follow-up after ~ 2 years: BMI *z*-score − 0.17 ($p < 0.05$) and less likely to be overweight	
Aventuras	*Treatment*: elementary schools in the South Bay region of San Diego County ($n = 9$, K-2 grades). Family-only ($n = 3$; 198 students); community-only ($n = 3$; 218 students), family + community intervention ($n = 3$; 165 students)	*Process evaluation*: 71% of participants received home visits; mean of 1.9 booster calls received; all schools improved their playgrounds; 34% of classrooms had visible water bottles; all schools placed posters on healthy eating; 90% of teachers distributed newsletters to students; 7800 buyer cards distributed and 287 returned completed	Health promoter(*promotora*)-based intervention was effective in changing child obesity-related health behaviors among family-only intervention group, but no overall intervention effects on children's BMI z-score
	Control: elementary schools in same area as T ($n = 4$; 227 students)	*Behaviors:* significantly increased in parent-reported child PA, reduced child frequency of watching TV, increased F&V intake, increased behavioral strategies for fat in family-only intervention group	More community involvement in developing strategies may help program adherence
	Ethnicity: schools with >70% of Latino enrollment	*Health:* All participants increased their overall mean BMI z-score; no significant intervention effects on children's BMI z-score and percentile	
BAEW	*Treatment*: Colac, Australia (pop 11,000). All preschools ($n = 4$, 4 years) and primary schools ($n = 6$, 5–12 years)	*Process evaluation*: 6789 person-hours	Effective at slowing rate of weight gain
	Control: random samples from the region of Victoria (pop 323,000)	*Psychosocial*: no harm in body image	
	Ethnicity: mostly white	*Health*: intervention group gained less weight (−0.92 kg), smaller increases in waist circumference (−3.14 cm), BMI *z*-score (−0.11), and waist/height ratio (−0.02, all $p < 0.05$); no difference in prevalence and incidence of overweight and obesity	

(continued)

Table 34.2 (continued)

Study title	Study design; evaluation methods used	Results	Main conclusions/ recommendations
CATCH BPC	*Treatment*: four districts in Texas; school and community program (n = 15, fourth graders)	*Process evaluation*: better implementation data on some classroom activity measures and community engagement measures with treatment	School program with community-enhancing components can be more effective than school-only program
	Control: school-only program in same districts as T (n = 44, fourth graders); for evaluation, 15 schools were selected based on ethnicity and percent economic disadvantaged matched with T	*Behaviors:* more positive impact on breakfast eating and screen time with treatment	
	Ethnicity/SES: low-income schools (≥60% of low-SES students enrollment); 61% of Hispanic/ Latino children of the total sample	*Health:* decrease in prevalence of overweight and obesity by 1.3% point (p = 0.33) in control schools and 8.8% points (p < 0.005) in treatment schools	
EWBA	*Treatment*: Morphett Vale, South Australia (outer metropolitan suburb, pop 23,000) and Murray Bridge (rural city, pop 18,000); targeted 0–18 years and their families; 4–5 years and 10–12 years selected for evaluation (n = 39 schools in 2006, n = 35 schools in 2009)	*Process evaluation*: not reported	Moderate impact in weight status among children at 3-year follow-up of multicomponent school–community interventions
	Control: sea and vines for metropolitan comparison site and Port Pirie region for regional comparison site; matched by pop size and SES	*Psychosocial:* improved attitude and knowledge of healthy eating and physical activity	
	Ethnicity/SES: low SES, higher proportions of Aboriginal and Indigenous people	*Behaviors:* increased some nutrition behaviors in both T and C	
		Health: [4–5 years] decrease in mean BMI z-score in both T and C (changes not significant between T and C); larger reduction in overweight and obesity prevalence in T	
		[10–12 years] no changes in BMI z-score	
FLVS study	*Treatment*: two communities in northern France, elementary school children 5–12 years; analysis sample 633 children in 2004	*Process evaluation*: not reported	Low SES population may benefit from nutritional and health-related interventions
	Control: two communities in same area with similar SES as T	*Behaviors*: not reported	
	Ethnicity: not reported	*Health*: decrease in prevalence of overweight between 2000 and 2004: boys from 10.2 to 7.4% and girls from 18.6 to 10.4% (2000–2004). Adjusted OR for overweight was 0.72 (boys) and 0.52 (girls). Lower prevalence of overweight with treatment 8.8% vs. 17.8%	

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Table 34.2 (continued)

Study title	Study design; evaluation methods used	Results	Main conclusions/ recommendations
HYHC	*Treatment*: Nasinu, Fiji (peri-urban area, pop 100,000); 13–18 years in seven schools for evaluation; analysis sample 879 students	*Process evaluation*: not reported	Need additional "top-down" or other innovative approaches to reduce adolescent obesity in the Pacific
	Control: three areas in Fiji; 11 schools matched on the ethnic profiles of the T schools; analysis sample 2069 students	*Psychosocial:* lower increase in quality of life in T	
	Ethnicity: 32% of indigenous Fijian; 62% of Indo-Fijian	*Behaviors:* mixed results in behavioral changes	
		Health: lowered percentage of body fat in T; no changes in BMI z-score	
IDEFICS	*Treatment*: one region in eight participating European countries (16,545 students invited, 5727 analyzed); Sweden, Germany, Hungary, Italy, Cyprus, Spain, Belgium, and Estonia	*Process evaluation*: 50% or less intervention components delivered	Smaller efficacy trials should be implemented before large investments made
	Control: one region matched to T (14,998 students invited, 5314 analyzed)	*Behaviors:* no impact on energy balance-related behaviors, physical activity, and sleep after 2 years of intervention; better outcome in water and sugar consumption in T after 5 years	
	Ethnicity/SES: not reported	*Health:* no impact on adiposity; protective effect on initially overweight and obese children in T (OR: 0.76, CI = 0.58–0.98)	
It's Your Move! Australia	*Treatment*: Victoria, Australia; secondary schools ($n = 5$; 3505 students targeted, 1276 analyzed)	*Process evaluation*: majority of the interventions were implemented in schools, focusing on capacity-building and healthy eating strategies	First study to show that the community-based interventions can be effective preventing unhealthy weight gain among adolescents
	Control: different area in Victoria, Australia; secondary schools ($n = 7$, 778 analyzed)	*Behaviors:* mixed results with no pattern of positive intervention outcomes	
	Ethnicity/SES: not reported	*Health:* weight reduction (−0.74 kg, $p < 0.04$); BMI *z*-score (−0.07, $p < 0.03$); no significant reduction in prevalence of overweight and obesity and BMI	
Jumpin' Jaguars	*Treatment*: elementary school in Kentucky ($n = 1$; 166 children for universal school program, 40 children for the targeted after-school program)	*Process evaluation*: 27/40 participated in 80% or more of sessions; parental participation low	Easily implemented at reasonably low cost
	Control: elementary school with similar demographics selected upon completion in the project school's first year (184 children)	*Health*: BMI percentile lower ($T = 68.57 \pm 31.62$, $C = 75.49 \pm 26.11$, $p = 0.027$)	
	Ethnicity/SES: 57% of annual household incomes <$10,000; 80% of participants AA or Hispanic	No significant differences in mean BMI percentile for after-school participants	

(continued)

Table 34.2 (continued)

Study title	Study design; evaluation methods used	Results	Main conclusions/ recommendations
KSDPP	*Treatment*: Kahnawake (Mohawk), Canada; 458 students in grades 1–6	*Behaviors*: no significant differences in mean intake of energy, fat, and sucrose after 4 years of intervention; significant decrease in the frequency of consumption of high-fat foods ($p < 0.05$) and fruits ($p < 0.001$); significant increase in energy contribution of white sugar ($p < 0.05$). Consumption of high-fat and high-sugar foods and fruits and vegetables decreased after 8 years of intervention. Activity and TV watching favorable trends 1994–1999; not sustained in 2002	Early results showed some successes; benefits not maintained over 8 years
	Control: Tyendinaga; 199 students in grades 1–6	*Health*: increases in skinfold thickness and BMI from repeated cross-sectional measures. Fitness showed favorable trends from 1994 to 1999 that were not sustained in 2002	
	Ethnicity/SES: first nations		
Ma'alahi Youth Project, Tonga	*Treatment*: Tongatapu, Tonga; secondary schools ($n = 7$; 815 students analyzed)	*Process evaluation*: dose and frequency of activities were insufficient and not sustained; the intervention dose to adolescents was diluted due to many community-level activities	Community-based interventions among adolescents with high obesity prevalence may require more intensive or longer interventions
	Control: Vava'u, Tonga; secondary schools ($n = 6$ schools; 897 students analyzed)	*Psychosocial:* lower quality of life in T	
	Ethnicity/SES: not reported	*Behaviors:* intervention had few positive effects on diet and PA	
		Health: both T and C showed large increases in overweight and obesity prevalence; small relative decrease in % body fat in T (−1.46%, $p < 0.0001$)	
SNPI	*Treatment and control*: elementary school in Pennsylvania ($n = 10$; 1349 children in 4–6 grades)	*Process evaluation*: teachers and support staff averaged 10.4 and 8.4 h of training, respectively, and devoted 48.0 and 44.0 h to each year of intervention	A multicomponent school-based intervention can be effective in children in grades 4–6, but stronger or additional interventions are needed
	Ethnicity/SES: ≥50% of children eligible for free or reduced lunch; 44% African-American, 17% Asian, 22% Hispanic	*Behaviors*: no difference in dietary intake, activity change before and after the program but less sedentary behavior	
		Psychosocial: no harm in body image	
		Health: predicted odds of overweight ~33% lower for T. No difference in incidence of obesity	
		Effect strongest for black students (OR: 0.59)	

(continued)

Table 34.2 (continued)

Study title	Study design; evaluation methods used	Results	Main conclusions/ recommendations
SUS	*Treatment*: Somerville, MA, public elementary schools (n = 10, grades 1–3; 631 children)	*Health*: BMI z-score decreased −0.1005 (p = 0.001); expected to decrease weight gain by 1 pound for a child at the 75th percentile BMI z-score and 50th percentile for height	It is possible to address childhood obesity through a multifaceted environmental change approach that involves the community, schools, families, and students
	Control: two communities that matched by SES (n = 20 schools; 1065 children)		
	Ethnicity: mixed (7.5% AA, 18.2% Hispanic, 9.1% Asian)		
SWITCH	*Treatment*: two communities from Lakeville, MN, and cedar rapids, IA, USA (n = 5 schools, grades 3–5; 685 children)	*Behaviors*: decreased screen time (1.38 h/week at 6-month post-intervention); increased fruit and veg consumption (1 serving/week); no difference in activity	Positive effect on child-reported screen time was greatest for obese children
	Control: two nearby communities (n = 5 schools, grades 3–5; 674 children)	*Psychosocial*: positive perceptions on target behaviors	
	Ethnicity/SES: 90% white	*Health*: no difference in mean BMI	
TAAG	*Treatment*: 18 schools in six US areas	*Behaviors*: no differences in adjusted MET-weighted minutes of moderate-to-vigorous physical activity	Modestly improved physical activity in girls
	Control: 18 schools sixth graders in 2003 (n = 1721), eighth graders in 2005 (n = 3504), and eighth graders in 2006 (n = 3502); girls the focus of intervention; however, both boys and girls received health and physical education classes	Girls in intervention schools were more physically active (mean difference 10.9 MET-weighted minutes of MVPA, 95% CI = 0.52–21.2).	
	Ethnicity: mixed	*Health*: no differences in fitness or % body fat	
ZDPP	*Treatment*: Zuni Indian reservation (western New Mexico)	*Behaviors*: decreased consumption of sugared beverages	Cross-sectional analysis limits conclusions
	High school (n = 2, 119 students in year 1, 9–12 grades)	*Health*: increase in glucose/insulin ratios	
	Control: Anglo females and males of same age in Tucson area	No comparison group and statistical analysis was done between 1 and 3 years	
	Ethnicity/SES: Native American		

diabetes risk factors were conducted with American Indian and First Nation children [5, 25]. Two US studies conducted in California and Texas targeted schools with higher proportion of Hispanic children [14, 20]. In addition, one study from South Australia focused on schools with high proportions of Aboriginal and Indigenous students [26], and two studies from Fiji and Tonga worked with population with high prevalence of overweight and obesity living in low-resource communities [21, 27].

Of the remaining studies, two specifically targeted populations with relatively lower socioeconomic status. Jumpin' Jaguars worked with one elementary school in a community in which 57% of households earned less than $10,000 annually; among participating children, 80% were either African-American or Hispanic [28]. Similarly, more than 50% of the SNPI participants were eligible for federally subsidized, free, or reduced-price meals. The majority were ethnic minorities: 44% African-American, 17% Asian, and 22% Hispanic [15]. On the other hand, the BAEW study population (Australia) and the Switch population were mostly white [29, 30].

Theoretical and Participatory Approaches

Not surprisingly, all studies reviewed mentioned community engagement as a key component of the formative phase of the intervention. The TAAG study obtained detailed information on formative research with community and school members as well as youth and family members [31–33]. SUS and SNPI formed advisory councils to assist in assessing community needs and designing the program [15, 34]. The community-based intervention components in the FLVS study were proposed by community members and organizations that had previously participated in an earlier school-based nutrition education intervention in the community. The communities themselves suggested and organized events for increasing physical activity levels targeting whole communities [17]. The Pacific OPIC study groups (HYHC, IYM, and MYP) emphasized using a community capacity-building approach in designing intervention strategies and conducting community workshops using Analysis Grid for Environments Linked to Obesity (ANGELO) approaches. Lastly, all the diabetes prevention studies in native communities emphasized partnership between research teams and community leaders for a successful intervention; this is well documented in the KSDPP study [13, 35, 36].

Intervention Components Inside and Outside Schools

All the studies included in this review have both school-based and out-of-school components (Table 34.3). While studies that solely emphasized family materials/workshops were not considered sufficient for inclusion, most studies included parent outreach programs and events (except TAAG [6] and MYP [37]). The MYP study in Tonga did not have specific intervention components targeting families or parents, even though most of the intervention activities targeted the whole community, such as planting fruit trees and making vegetable gardens [37]. Most of the studies (13/17) included policy and environmental changes as components of school-based programs. For example, the SNPI study [15] used a coalition of community-based organizations to focus on changing the food and nutrition environment within schools. After-school programs were incorporated to increase physical activity levels (BAEW [29], SUS [34], TAAG [6], and APPLE [38]) and to target overweight or obese children by collaborating with other local agencies (Jumpin' Jaguars [28]).

The types and intensity of community-based intervention activities varied considerably (Table 34.3). However, more than half of the studies (12/17) endeavored to change the food environments in their communities. For example, the SUS study devoted a substantial part of the intervention to developing community gardens and farmers' markets and recruiting SUS-"approved" restaurants in the city [34]. SNPI and Aventuras also worked with local restaurants or food stores to help customers choose healthier food options by providing children's menus and point of purchase information [14, 15]. More than half of the studies (11/17) focused on environmental factors that encourage physical activity in communities. With the support of the town councils, the FLVS study led to the construction of new sporting facilities; new sport educators were employed as a part of the intervention [17]. The KSDPP study held various promotional events on increasing physical activities targeting the whole community [13]. The SUS study worked closely with the city government to increase walkability and bikeability in the community [34].

Most of the interventions (16/17) worked closely with local stakeholders. The TAAG study implemented intervention components for increasing physical activity among girls both on and off school properties, working with small advisory groups of school staff and community organizations and members. Community organizations, such as the YMCA or YWCA, local health clubs, and community recreation centers, were identified in intervention schools and invited to plan and implement programs and events. Moreover, the study recruited and trained program champions from intervention schools and communities to take ownership of the program for the purpose of sustainability after researchers from outside the community leave

Table 34.3 Types of intervention strategies used in the studies included in this review

	APPLE	Aventuras	BAEW	CATCH BPC	EWBA	FLVS	HYHC	IDEFICS	IYM	JJ	KSDPP	MYP	SNPI	SUS	SWITCH	TAAG	ZDPP
Classroom curriculum	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x
School policy development[a]	x	x	x	x	x		x	x	x		x	x	x	x			x
Before school program[b]			x		x	x	x	x	x			x	x	x		x	
After-school program	x		x	x			x	x	x	x		x		x		x	
Parent outreach	x	x	x	x	x	x	x	x	x	x	x		x	x	x		x
Community components																	
Participatory research	x		x	x	x		x		x	x	x	x	x	x		x	x
Advisory council formed				x	x		x	x	x		x	x	x	x			
Changing food environments[c]	x	x	x		x	x	x	x	x		x	x	x	x			
Changing PA environments		x	x		x	x	x	x	x		x	x		x		x	
Working with various local stakeholders[d]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Collaboration with local health offices			x		x	x	x	x	x			x		x			
Community events	x		x		x	x	x	x	x		x	x		x	x		
Mass media campaigns	x	x	x		x	x	x	x	x		x	x		x	x		

[a]Including a wide variety of school policies with regard to better nutrition and higher physical activities (school food service, vending machines, cooled water filters, improvement of school physical activity facilities, etc.)
[b]Including breakfast program, walk to school campaign
[c]Including farmers market, community gardening, working with local food stores and restaurants
[d]Including local physician, clinic staff, and city employers training and involvement of other community-based organizations

the study [6]. The Jumpin' Jaguars study enlisted the support of various local community-based organizations (e.g., YMCA, Community Trust Bank, and God's Pantry) for their after-school program [28]. The SUS trained local physicians and clinic staff to increase awareness of childhood obesity and formed collaborations with ethnic minority group in the community [34]. The Zuni Diabetes Prevention Program (ZDPP) developed supportive social networks by forming a Teen Task Force, which helped to recruit youth participants into the study and served as peer mentors for other students [5]. The HYHC study involved members of faith-based organizations in promoting healthy eating and physical activities in their communities [21]. The MYP study also collaborated with various local organizations, including churches, youth group, and women's group [37]. Lastly, the SNPI, SUS, and Aventuras studies worked with local food stores and restaurants to promote intake of healthy foods [14, 15, 34]. Eight of seventeen studies included collaboration with local health offices or support from government organizations. For example, the BAEW strategies were incorporated into the municipal public health plan and integrated health promotion plan [29], and the MYP study had meetings and workshops with five government ministries including ministries of health, finance and planning, and education [37]. Most studies (12/17) reported that the intervention attempted to reach the whole community in order to increase awareness of the programs through mass media campaigns.

Process Evaluation

Most of the studies (15/17) collected process evaluation data (except [17, 28]), with great variation in methods and forms of documentation. Process evaluation measures included changes in schools' and in communities' environments as well as dose, reach, and fidelities of intervention activities [13, 34, 37, 39, 40]. Two papers from the SUS study presented the results of food environment modification efforts in the community, focusing on food service at schools and local restaurants [41, 42].

Psychosocial Measures and Behavioral Impacts

We compared the forms of evaluation used by the different trials. Psychosocial factors were measured in more than half of the studies reviewed. The BAEW [29] and the SNPI [15] studies administered body dissatisfaction questionnaires to monitor adverse effects of the interventions. The EWBA [26], KSDPP [13], Switch [30], TAAG [43], and ZDPP [5] studies measured psychosocial factors such as self-efficacy, outcome expectations, knowledge, perceptions, and/or attitudes. The HYHC and MYP studies measured quality of life among participants [21, 27].

Most studies assessed change in both dietary intake and physical activity. The TAAG study measured only physical activity levels among participating girls using accelerometers and observations [6]. FLVS and Jumpin' Jaguars did not include behavioral assessments [17, 28]. Most of the studies of physical activity level and dietary intake used self-reported questionnaires. Some specific behaviors, such as intake of fruits and vegetables or screen time, were reported separately in some studies (KSDPP [25], Switch [30], and ZDPP [5]).

Health Outcomes

BMI and BMI z-scores were the most common health outcomes measured. In addition, some studies included other anthropometric measures such as waist circumference, waist–hip ratio, percent body fat, and physiological measures such as blood pressure and heart rate. Overweight or obesity prevalence and incidence were also reported in some studies (CATCH BPC [20], FLVS [17], MYP [27], SNPI [15]).

Community Measures

Impacts at the community level were assessed in some trials. One study measured sustainability of the program effect after 2 years of program

completion by interviewing school principals (APPLE [44]). Other studies [13, 14, 41, 45, 46] mentioned environmental and policy changes as a measure of the impact of intervention. The Switch study performed community surveys before and after the intervention to measure the changes on community awareness of the study's target healthy behaviors [16]. The SUS study team described efforts to change food environments in restaurants and schools. The compliance rate of restaurants that followed approval criteria was not high (~50%); however, school food environments improved after implementation, with increased availability of fruits, vegetables, whole grains, and low-fat dairy products [41, 42]. As part of process evaluation, the MYP study documented changes in community infrastructure and equipment related to diet. These measures included documenting the number of vegetable gardens and greenhouses constructed in the community [37].

Study Results

Impact on Psychosocial Factors and Behavior

Seven studies assessed the psychosocial impacts of intervention: two studies found no increase in body dissatisfaction or eating disorders among participants (BAEW [29], SNPI [15]), one study reported that participants perceived positive changes in their behaviors [30], and one study showed improved attitude and knowledge of healthy eating and physical activity [46]. Three studies measured quality of life among adolescent participants and two showed negative impact [21, 27], and one showed no impact on quality of life [47].

Among 12 studies that reported nutrition-related behavioral changes, six had positive results [5, 18, 20, 26, 30, 38], while four found no changes in dietary intake [15, 25, 27]. Two studies showed both positive and negative results in various nutrition-related behaviors with no clear patterns [21, 47]. Specifically, the APPLE project documented lower consumption of carbonated beverages and higher consumption of fruit among intervention children, and the ZDPP noted lower consumption of sugared beverages. Lastly, the parents of children from the Switch intervention communities reported higher consumption of fruits and vegetables [30]. Only one study reported dietary results at the nutrient level (KSDPP); no significant impacts were observed.

Among 12 studies that reported effects on physical activity or sedentary lifestyle, five had a positive impact. The CATCH BPC, SNPI, and Switch reduced sedentary behavior [15, 20, 30], and the APPLE and TAAG study increased the activity levels of participants [6, 38]. The KSDPP study showed increases in physical activity during the initial study period (1994–1999); however, these changes were not sustained in a 3-year follow-up [25]. The IDEFICS study showed no changes in physical activity measures, yet country-specific analyses found some positive intervention effects among Swedish boys, Spanish boys, and Belgian girls [48].

Impact on BMI and Anthropometric Measures

Eight of the seventeen studies demonstrated positive albeit small impacts on BMI and related anthropometric measures (Table 34.4). Children undergoing the BAEW intervention gained less weight and had smaller increases in waist circumference, BMI *z*-score, and waist–hip ratio than children in the comparison group. Even though the program did not analyze changes in the prevalence and incidence of overweight and obesity between intervention and comparison groups, the changes in BMI and other anthropometric measures are encouraging [29]. The SUS [34] and the APPLE project also showed promising outcomes [38, 44]; mean BMI *z*-scores were reduced. Moreover, BMI *z*-scores and the prevalence of overweight remained lower in the APPLE intervention group for 2 years. The SNPI program [15], which focuses on changing nutrition environment at schools, showed that the predicted odds of incidence and prevalence of overweight were lower for the intervention group.

Table 34.4 Study impact and target age summary

Study	Age (years)	Effect on BMI z or rates of overweight/obesity
APPLE	5–12	−0.11 to −0.26
Aventuras	5–7 (K-2nd graders)	None
BAEW	4–12	−0.11
CATCH BPC	9–10 (4th graders)	−7% point decrease in overweight and obesity prevalence in T ($p = 0.051$)
EWBA	4–5 years	Mean BMI z lowered for both T and C/ larger reduction in
	10–12 years	overweight and obesity prevalence in T (−6.3% vs. -3.7%) None in BMI z
FLVS	5–12	Odds ratio overweight: 0.72 boys, 0.52 girls
HYHC	13–18 years	None in BMI z; lower % body fat in T
IDEFICS	2–9.9 years	None
IYM	12–18 years	−0.07
Jumpin' Jaguars	Elementary school	Mean BMI percentile lowered in T
KSDPP	6–12 (1st–6th graders)	None
MYP	11–19 years	None in BMI z; lower % body fat in T
SNPI	9–12 (4th–6th graders)	Odds ratio overweight 0.67/no effect on obesity
SUS	6–9 (1st–3rd graders)	−0.10
SWITCH	8–11 (3rd–5th graders)	None in BMI mean value
TAAG	11–14 (6th–8th grade girls)	None
ZDPP	14–18 (9th–12th graders)	None (lowered BMI post-intervention but NS)

The EWBA study targeted two different age groups, 4–5 years and 10–12 years. After 3 years of intervention, there was no change among older children. Among 4–5-year-old children, mean BMI z-score was significantly lower in both intervention and comparison groups, yet changes were not significantly different between the two groups. One positive outcome was larger reduction in overweight and obesity prevalence among the intervention group of 4–5-year-olds (−6.3% vs. −3.7%) [26]. The KSDPP showed some early positive effects on skinfold thickness but not on BMI or fitness [25]. Glucose/insulin ratios were increased in the ZDPP study; the significance of this finding is unclear without proper comparison groups and without controlling for other factors in the analysis [5].

Impact on Community

Most of the studies sought to work with community groups to reduce unhealthy weight gain or diabetes risk factors; however, little information on how the intervention changed communities was found in the papers. One follow-up study of APPLE explicitly addressed sustainability issues: whether the intervention components in schools and communities were still in place 2 years after program cessation [49]. The Aventuras study showed that 36 restaurants out of 61, which initially agreed to provide healthy child menu, still used the menu at 16 months [14]. The EWBA study documented the detailed changes in the school environments related to nutrition and physical activity [46]. Some studies mentioned that they followed environmental and policy changes in communities as part of process evaluation, but results were not documented (e.g., KSDPP [13], TAAG [45]).

Discussion

Our review of the literature identified 17 school-based obesity prevention programs that had a substantial community component. It is noteworthy that we observed a great increase in the number of studies between 2010 and 2016, since the first version of this review. During the first 19 years (from 1990 to 2009), there were ten studies published that met our inclusion criteria. From 2010 to 2016, seven studies were added to our list.

Since the early 2000s, more trials have incorporated community involvement in childhood obesity programs. Frequently based on the social–ecological model, more recent obesity prevention studies have emphasized the

importance of implementing multilevel and multicomponent programs. These studies hoped to target various elements at home, school, and community to effectively influence children's behavior. During this time period (2010–2016), two large school–community multicenter projects were implemented in various countries. One was the IDEFICS, conducted in eight European countries targeting children from 2 to 9.9 years old, and the other was the Pacific OPIC study, conducted in Australia, Fiji, and Tonga targeting secondary school students. These two large projects showed that community-based strategies have been tested with various age groups in diversified regions. Earlier studies mostly targeted younger children and were conducted in the USA, Canada, and Australia.

The 17 studies included in this chapter showed mixed results on the effectiveness of school–community prevention studies. Eight trials have had a limited but significant impact in reducing BMI *z*-scores or obesity rates in children, and six trials have had no impact. The remaining three studies showed a marginal impact (CATCH BPC [20]) or mixed results depending on the different outcome indicators. Specifically, the HYHC [21] and MYP [27] studies did not have any impact on BMI z-scores, yet the intervention groups showed a small relative decrease in percentage body fat.

It should be noted that 12 of the 17 studies we reviewed were conducted targeting elementary school children, and among these, seven studies showed some positive impact. On the other hand, among five studies of teenagers, only one study showed a positive impact on BMI z-scores (IYM [47]). If we consider the percentage of body fat measures as an outcome measure, we could include two more studies (HYHC [21], MYP [27]) that showed some positive impact. However, if we look at the results more closely, the MYP study showed a large increase in the prevalence of overweight and obesity among both male and female participants (36.4–42.8% in male, 55.0–68.2% in female) after 2 years of intervention. Moreover, none of these studies targeting adolescents showed any clear evidences of behavioral improvements. These results underscore the difficulty in changing weight-related behaviors in obese adolescents [49, 50].

Changing the environment around schools and in communities is enormously challenging and requires a great deal of focused effort and community support and engagement. Community engagement and participatory approaches are central features of the successful "school–community" intervention trials reviewed in this chapter. No single approach appears to have been highly effective, and in fact the level of engagement ranged considerably.

Many of the programs reviewed stressed and incorporated policy changes both inside and outside schools [15, 29, 34, 38]. Policy changes may be viewed as another form of community engagement. Policy changes would lead to institutionalization of program activities in schools and community settings, which may lead to long-term sustainability.

Serious deficiencies exist for most of the intervention trials reviewed in terms of evaluation methodologies. While the studies included community intervention components, there is significant room for improvement in assessing change at the community and environmental levels pre- and post-intervention. More recent trials included the results from process evaluations, and these help to understand and interpret the results of impact evaluations. Yet, more detailed information on how the intervention strategies are implemented would help future researchers in planning and improving their school–community interventions. Furthermore, most of the studies did not provide data on the impact of their programs on dietary intake at the nutrient level. Behavioral outcomes like diet and physical activity are required to explain the mechanisms for change in weight status or lack thereof.

In addition, it is important to document and disseminate information regarding costs for future assessment of trials in this area. Only two studies conducted a cost analysis [51, 52], and one mentioned the total cost of intervention implementation [28]. We contacted the original authors of the studies to gather more information on cost, yet we are still missing much information (Table 34.5). In addition, due to the complex

Table 34.5 Intervention cost summary

Study	Total cost
APPLE	$239,518 for 2 years; $429/children/year
Aventuras	$450,000 per year
BAEW	$326,806 for 4 years; a net cost per DALY saved of AUD 29,798 (dominated; $0.26 M)
CATCH BPC	N/A
EWBA	N/A
FLVS	$2.84/person/year
HYHC	N/A
IDEFICS	N/A
IYM	N/A
Jumpin' Jaguars	$14,000–16,000/school/year
KSDPP	N/A
MYP	N/A
SNPI	$30,000/school/year
SUS	N/A
SWITCH	$1.2 Million for the whole program; $35–40/family
TAAG	N/A
ZDPP	N/A

nature of school–community-based interventions, including variation in study size, geographical differences, and evaluation methods, it was challenging to make any comprehensive comparisons using the data provided by the authors. The variation that we observed was substantial: costs of intervention ranged from 2 euro (~2.9 USD) to 429 USD per child per year. This can be explained by program differences. One was an intensive 2-year intervention beginning with building partnership with other stakeholders in the community to working with school cafeterias to alter food choices [51]; the other capitalized on an established collaboration with the community and did not require many external resources [17].

Two studies found no adverse effects on children's psychological health, yet two studies among adolescents showed lower quality of life among intervention groups (HYHC [21], MYP [27]). Stigmatization of children in school-based programs is a potential concern and led to the termination of one reportedly successful approach that targeted overweight children [53, 54]. Only 1 of the 17 studies reported here (Jumpin' Jaguars) included a specific intervention for overweight children. On the one hand, the inclusion of the entire school population (or even the entire community) represents a strength of school–community programs. On the other hand, the lack of targeting may limit the effectiveness of school-based obesity interventions for overweight or high-risk children.

For instance, the MYP study dealt with the communities with high prevalence of overweight and obesity among secondary school students [27]. Two years of extensive school–community interventions did not stop the increase in weight gain among both male and female students. The authors of this study discussed that community-based intervention strategies were the main foci of their program, and this may be one of the reasons for the weak outcome. The community-based strategies were "diluted" throughout the community members, and the target adolescents did not receive enough interventions. Given the limited evidence at this point, it is not clear how to divide the resources and budget between targeted programs (in schools or homes) and universal programs (for the entire community). More detailed investigation will be required to resolve this conundrum.

Most of the intervention studies reviewed in this chapter reported 2–3 years of intervention implementation. It would be challenging to conduct rigorous school–community interventions for an extended period of time for various logistical reasons. Yet, given the limited success of curbing childhood obesity globally, it would be necessary to come up with strategies to conduct scientifically sound intervention studies with proper evaluation measurements and longer follow-up periods. Along the same line, sustainability issues and capacity-building approaches within the communities would be key components in designing future interventions.

Due to the size of target population and the comprehensiveness of planned interventions, the IDEFICS study conducted in eight European countries looked promising. However, the results after 2 years of intervention implementation were disappointing. As the authors noted, there was no impact on weight status [19] and

no clear changes in observed behavior [48]. Weak implementation would be one explanation [55] based on the process evaluation results. However, it would be meaningful to examine whether the intervention strategies were tailored enough to each country and each community. In addition, we should reexamine the interrelationships with previously hypothesized environmental, behavioral, and biological factors [56].

An additional challenge lies in the area of study design. Many school-based studies, such as CATCH [12] and Pathways [11], took the unit of analysis and randomization as the school itself. This is not possible when extensive community engagement and changes become an additional focus of the intervention. This is why most of the included trials had quasi-experimental study design without community randomization. In this case, rigorous statistical analytical methods are needed to capture the unique aspects of community involvement and social engagement.

As noted, the reductions in mean BMI *z* observed in these studies were modest and variable, and the interventions are time-consuming and, in some cases, expensive. Should we then abandon our efforts with school and communities and focus on targeting families and children at the highest risk for obesity and its complications? Strong evidence indicates that these targeted efforts can be effective [57, 58]. We would argue, however, that the sheer size, scope, and progression of the obesity epidemic will not permit us to focus our efforts solely on the small number at greatest risk.

To conclude, the experience with *school-based interventions* has been discouraging, and an emerging body of literature reveals strong associations between the obesogenic environment and the prevalence of childhood obesity. Our findings suggest that *school–community interventions* provide one possible solution to the problem. Ongoing studies with strong design and evaluation plans will provide more information regarding the efficacy and costs of school–community programs for prevention (and management) of childhood obesity. In the meantime, the positive trends noted in our review provide support for continued and expanded research trials that intervene in both schools and the communities that surround them. Some large-scale interventions with extensive community involvement are underway: the EWBA [26] and BAEW studies [59]. We expect to see more evaluation results in a few years; this should provide more definitive information regarding the effectiveness of school–community intervention programs.

Editor's Comments and Question

Many case-controlled clinical investigations[a] have found that weight loss interventions are far more likely to reduce BMI z-scores in young children than in teenage girls and boys. It is perhaps not surprising, then, that school- and community-based interventions appear to be more effective in elementary than in secondary school students. It is also interesting that two studies involving teenagers (HYHC [21], MYP [27]) showed lower "quality of life" following intervention.

Do you think that the evidence inclines toward focusing community interventions (and funding) on young children?

Authors' Response

I think that a majority of clinical trials have focused on intervening on children and families/households. Younger children have less autonomy and are more likely to be influenced by the home food and physical activity environment. Teenagers are more autonomous, and make a lot of food and activity decisions on their own, with their own money, outside the home environment. If I had to target funding at young children, I would emphasize the home environment. If I had to target funding at older children, I would emphasize the community (outside the home) environment.

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Part IX

Pharmacotherapy and Bariatric Surgery for Obesity and Co-morbidities

35 Role of Pharmacotherapy in the Treatment of Pediatric Obesity and Its Comorbidities

Aaron S. Kelly and Claudia K. Fox

Biology of Obesity: The Rationale for Pharmacotherapy

The confluence of unacceptably high rates of pediatric obesity and unsatisfactory weight loss outcomes with clinical treatment has led many to wonder whether alternative strategies might be needed to effectively manage this complex and refractory disease. Adding to the urgency in regard to finding effective treatments is the fact that severe obesity is burgeoning in the pediatric population (approximately 6% prevalence in the United States), and the degree of adiposity of youth falling into this category makes clinical management even more difficult than those with milder forms of obesity [1, 2]. That obesity, even in childhood, is a recalcitrant disease should not come as a surprise considering the strong biological propensity for humans to store and maintain body fat. In fact, in light of our historically uncertain food supply, the human body has almost certainly adapted to survive prolonged periods of starvation, and the current gene pool is likely replete with individuals biologically adept at vigorously defending body weight.

Weight loss maintenance has proven to be a monumental challenge for the field of obesity. Although short-term weight reduction is achievable for many individuals with obesity, long-term maintenance is often elusive owing to a multitude of physiological adaptations that are triggered soon after the body senses a negative energy balance has been initiated (Fig. 35.1). These counterregulatory forces include neuroendocrine changes involving appetite and satiety and reduction of energy expenditure [3–5]. In the context of even modest weight loss, peripheral and central biological mechanisms respond in a way similar to starvation—sensing dwindling energy reserves and triggering a strong counterresponse to increase caloric intake [4]. Making matters worse for the individual trying to lose weight, metabolic rate often plummets, setting the stage for weight loss plateauing or weight regain [3]. Moreover, evidence suggests that many of these physiological adaptations may be hardwired into human biology since they persist for years after the initial weight is lost [5, 6]. Therefore, the individual trying to lose weight (and keep it off) faces strong and unrelenting biological forces favoring positive energy balance and the defense of the highest achieved body weight.

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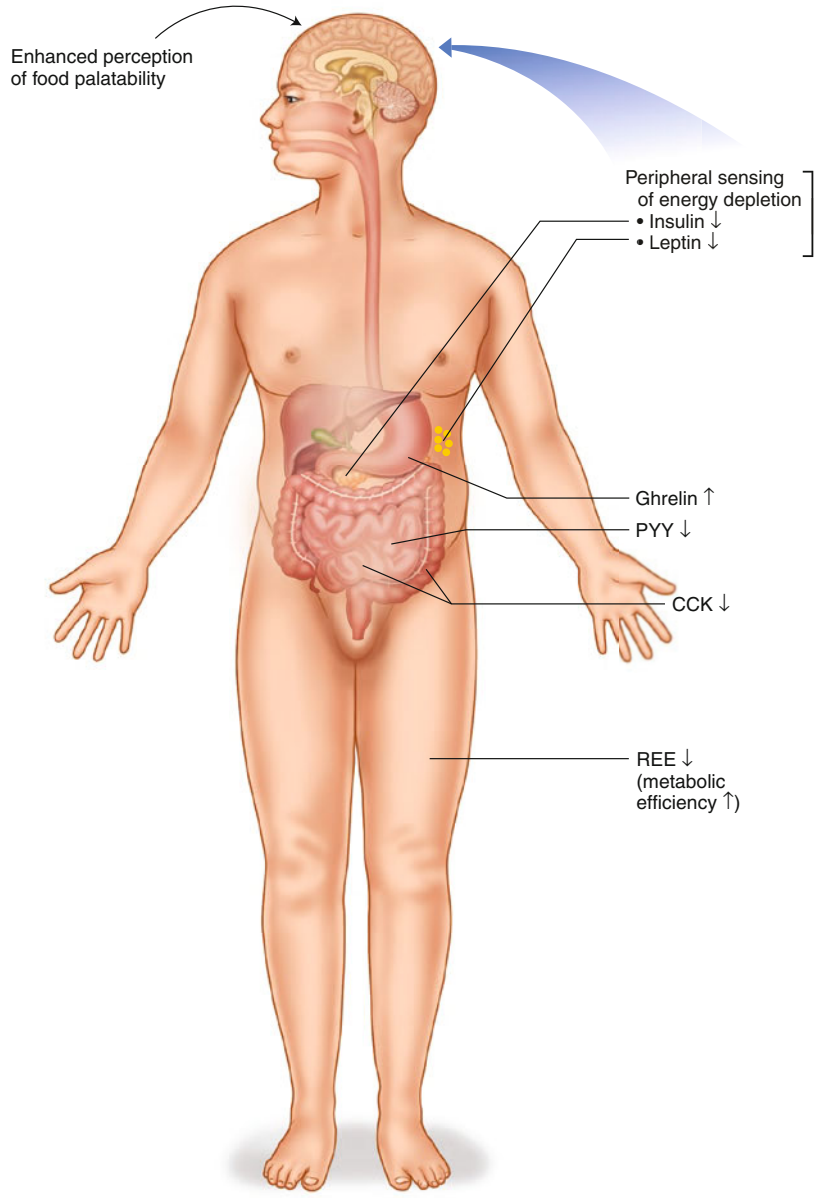

Fig. 35.1 Biological adaptations to weight loss. Depiction of changes in central and peripheral counter-regulatory mechanisms promoting weight regain. These changes occur in the brain, adipose tissue, gut (stomach, small intestines), and peripheral tissues involved in energy expenditure (e.g., skeletal muscle). *CCK* cholecystokinin, *PYY* peptide tyrosine tyrosine, *REE* resting energy expenditure

Based on this line of evidence, it is reasonable to conclude that offering treatments aimed at counteracting the body's attempts to defend its energy stores offers patients with obesity a better chance to lose and maintain weight over the long term. Pharmacotherapy, the focus of this chapter, is one example of a biologically based treatment that can be used in conjunction with lifestyle modification therapy to target the underlying biology of

obesity and potentially improve long-term weight loss outcomes. Ideal medications will not only reduce adiposity but also the number and severity of obesity-associated comorbidities and thereby ameliorate the risk for other chronic diseases such as type 2 diabetes and cardiovascular disease.

The field of obesity pharmacotherapy has unfortunately suffered from a challenging history checkered with serious safety issues surfacing during the development of various agents and, in some cases, even after initial approval by regulatory agencies. Most notably, fenfluramine and dexfenfluramine were found to cause cardiac valve degeneration and were subsequently removed from the US market less than 2 years after initial Food and Drug Administration (FDA) approval [7]. The backlash from the medical community and general public regarding this and related incidents is still being felt as evidenced by the slow rate (until recently) of development of new obesity medications by pharmaceutical companies and the low uptake of obesity pharmacotherapy by physicians and patients. Indeed, an extremely low percentage of patients who meet indications for obesity pharmacotherapy in the United States are using these medications (estimated at approximately 1% in a recent study) [8], and prescriptions for obesity medications have declined [9]. Nevertheless, since 2012, four new obesity medications (discussed later) have been approved in the United States (two of these were also approved in Europe) for long-term use in adults, offering new treatment options for physicians and patients. This resurgence offers hope that the pharmacotherapy toolbox will continue to expand, even for pediatrics [10], thereby providing biologically based treatments to patients that desperately need them.

Currently, there is lack of consensus regarding indications for the use of pharmacotherapy in children and adolescents [10]. Expert committee recommendations advise that medication be considered an option only after lifestyle modification therapy has failed [11]. There is also disagreement about the appropriate age at which to introduce pharmacotherapy and whether comorbidities should be present to justify the risk/benefit ratio of medication use [10]. In deliberating about the appropriate use of pharmacotherapy in a pediatric patient, the healthcare provider should seek to balance the potential risks of medication use against the lurking threats of persistent obesity and high likelihood of future development of comorbidities.

Although only one obesity medication, orlistat, is approved for pediatric use (adolescents ≥12 years of age) in the United States, others have been evaluated for safety and efficacy in the pediatric population. Importantly, the future appears to be bright in terms of new medications slated to be tested among children and adolescents with obesity. In this chapter we review the evidence from pediatric obesity clinical trials of approved (orlistat) and off-label (metformin, exenatide, topiramate, and others) medications, discuss the pediatric pipeline by briefly introducing the medications recently approved for adult use and plans for pediatric development, and offer a glimpse into the future directions for the field of pediatric obesity medicine.

Well-Studied Medications

Orlistat

Mechanism of Action

Orlistat is a reversible inhibitor of gastric and pancreatic lipases and as such inhibits the hydrolysis of dietary triglycerides into free fatty acids. As a result, at the recommended therapeutic dose (120 mg three times daily), approximately 30% of dietary fat is not absorbed. In theory this should limit energy intake without altering energy expenditure and thereby reduce body weight.

Effects on BMI and Body Fat

Maahs and colleagues, in a double-blind, randomized, placebo-controlled clinical trial, examined the efficacy of orlistat for change in BMI in 40 adolescents (ages 14–18 years old) with obesity (mean baseline BMI 40.0 kg/m^2) [12]. Study

participants received either orlistat 120 mg orally three times daily or placebo for 6 months. There was no statistically significant difference between study groups in BMI change over 6 months, though the decrease in BMI *within* each group was statistically significant (orlistat group, -1.3 ± 1.6 kg/m^2, P = 0.04; placebo group, -0.8 ± 3.0 kg/m^2, P = 0.02) [12]. In a much larger study, Chanoine and colleagues examined the effect of orlistat on BMI among 539 adolescents (ages 12–16 years old) with obesity (BMI ≥ 2 units above the 95th percentile for age and sex) in a double-blind, randomized, placebo-controlled clinical trial [13]. Participants received either orlistat 120 mg or placebo orally three times daily in addition to lifestyle modification therapy for 52 weeks. The placebo-subtracted change in BMI from orlistat at 52 weeks was -0.86 kg/m^2; 26.5% and 13.3% of the orlistat group decreased BMI by at least 5% and 10%, respectively [13]. Further, in the subset of participants who underwent body composition testing, those in the orlistat group lost significantly more fat mass (-2.40 kg) than the placebo group (-0.38 kg).[2] A pooled estimate of both studies demonstrated a mean change in BMI of -0.83 kg/m^2 with orlistat [14].

Effects on Comorbidities and Cardiometabolic Risk Factors

In pediatric trials, the effects of orlistat on cardiometabolic risk factors, including fasting lipids, glucose, and insulin, were negligible. The pooled estimates from the two randomized controlled studies showed no statistically significant differences in these parameters between the orlistat and placebo groups [14]. However, it should be noted that, in the large trial conducted by Chanoine and coworkers [13], the mean baseline levels of lipids, glucose, and insulin among participants were within normal ranges. In contrast, in a systematic review of 17 randomized controlled studies of the effect of orlistat on more than 10,000 adults with obesity, there were statistically significant improvements in total cholesterol, LDL cholesterol, and LDL/HDL cholesterol ratio favoring the orlistat group at 1 year [15]. This same review identified four studies that examined the change in glycated hemoglobin and fasting glucose in adult patients with diabetes and abnormal glycated hemoglobin at baseline. The pooled treatment effect for glycated hemoglobin in the orlistat compared to placebo group was -0.40% (95% CI: 0.52%, -0.27%; $P < 0.00001$); a similar improvement was reported for fasting glucose (-0.83 mmol/L, 95% CI: 1.19 to -0.47 mmol/L; $P > 0.00001$) [15]. The 4-year Xenical in the prevention of diabetes in obese subjects (XENDOS) study, which examined if orlistat in addition to lifestyle modification therapy could decrease the incidence of type 2 diabetes in adults with obesity, found a risk reduction of 37.3% (P = 0.0032) [16]. Similar pediatric data do not exist but would be valuable.

Safety and Commonly Observed Side Effects

The most common side effects of orlistat are related to its mechanism of action and include oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, and fecal incontinence [13]. These side effects are worse when the dietary fat exceeds 30% of daily calories. In post-marketing surveillance, there have been reports of rare cases of hepatic failure, with some resulting in liver transplant or death, and renal failure from oxalate nephropathy in adults. There have also been post-marketing reports of hypothyroidism in patients taking orlistat and levothyroxine concomitantly. Further, orlistat has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene.

Clinical Considerations

At the time of this publication, orlistat is the only FDA-approved medication for the treatment of obesity in the pediatric population (approved in 2003 for children ages ≥12 years old). However, orlistat does not have a pediatric indication in Europe. While the prescription strength is 120 mg three times daily, an over-the-counter formulation at half the prescription dose is available. Although attractive owing to its peripheral (vs. central) mechanism of action and relatively safe track record, tolerability issues limit its acceptability to some patients. Because orlistat may reduce the absorption of fat-soluble vitamins, it is

recommended that patients additionally take a multivitamin supplement containing vitamins A, D, E, K, and beta-carotene.

Metformin

Mechanisms of Action

Metformin, belonging to the biguanide class, is approved in the United States and in Europe for the treatment of type 2 diabetes in adults and children ≥10 years old. It is administered orally and available in a twice per day formulation and a once per day extended-release formulation (the latter is not FDA approved for pediatric use). Metformin is thought to improve glycemic control by suppressing hepatic gluconeogenesis, decreasing intestinal absorption of glucose, and increasing insulin sensitivity via enhancing peripheral glucose uptake and utilization [17, 18]. Although not approved for the treatment of obesity, initial studies in participants with type 2 diabetes and obesity have consistently demonstrated modest weight-reducing effects of metformin. Indeed, an anorectic effect of metformin has been reported in animal models of obesity as well as in humans with obesity [19, 20]. The weight loss mechanisms of action are not fully characterized but are thought to primarily involve activation of AMP-activated protein kinase, which is a key regulator of energy balance promoting catabolism [21]. Some evidence suggests that metformin inhibits ghrelin secretion via the AMP-activated protein kinase pathway [22]. Other proposed mechanisms include dipeptidyl peptidase IV inhibition and enhanced bioavailability of glucagon-like peptide-1 (GLP-1), which inhibits food intake through central actions in the hypothalamus [23–26].

Effects on BMI and Body Fat

In one of the larger adolescent weight loss studies, investigators from the Glaser Pediatric Research Network sought to determine the effect of 48 weeks of treatment with metformin extended release on BMI change in a multicenter, randomized, double-blind, placebo-controlled trial [27]. Following a 1-month placebo run-in period, 77 adolescents (13–17 years old) with BMI ≥95th percentile were randomly assigned to treatment with metformin 2000 mg once daily or placebo, with both groups also receiving concomitant lifestyle modification therapy. Compared to placebo, metformin reduced BMI by 1.1 kg/m^2 (approximately 3%), BMI z-score by 0.08, and total body fat mass (measured by dual-energy X-ray absorptiometry, DXA) by 2.4 kg. In a separate study, Yanovski and colleagues evaluated the effect of 6 months of treatment with metformin on BMI change in a randomized, double-blind, placebo-controlled trial [28]. One hundred children (6–12 years old) with BMI ≥95th percentile and fasting hyperinsulinemia were randomly assigned to treatment with metformin titrated to a maximum dose of 2000 mg twice daily or placebo followed by open-label treatment with metformin for a subsequent 6 months. Both groups received concomitant lifestyle modification therapy. Compared to placebo at 6 months, metformin reduced BMI by 1.1 kg/m^2 (approximately 3%), BMI z-score by 0.07, and total body fat mass (measured by DXA) by 1.4 kg. Much of the BMI lost during the placebo-controlled period (initial 6 months) was regained with continued open-label treatment out to 1 year. In another large study that included both children and adolescents (8–18 years old), Kendall and colleagues evaluated the effect of 6 months of treatment with metformin on BMI change in a randomized, double-blind, placebo-controlled trial [29]. One hundred and fifty-one youth with BMI ≥98th percentile (based on UK charts) and either fasting hyperinsulinemia, impaired fasting glucose, or impaired glucose tolerance were randomly assigned to treatment with metformin titrated to a maximum daily dose of 1500 mg (1000 mg morning and 500 mg night) or placebo with both groups also receiving concomitant lifestyle modification therapy. Compared to placebo at 6 months, metformin reduced BMI by 1.1 kg/m^2 (approximately 3%) and BMI z-score by 0.10. Body fat mass was not measured in this trial. Finally, results of systematic reviews utilizing pooled analysis have demonstrated BMI reductions of approximately 1.5 kg/m^2 or 3–4% with metformin treatment ranging from 6 to 12 months among children and adolescents with obesity [30–32].

Effects on Comorbidities and Cardiometabolic Risk Factors

The effects of metformin treatment on comorbidity and cardiometabolic risk factor improvements appear to be limited to a small number of factors, and the magnitude of change is rather modest. In the adolescent trial conducted by the Glaser Pediatric Research Network, no changes were observed in any of the oral glucose tolerance test measures, fasting homeostasis model assessment of insulin resistance (HOMA-IR), or lipid profile [27]. In the trial of younger children conducted by Yanovski and coworkers, reductions in fasting glucose, insulin, and HOMA-IR were observed [28]. However, the authors reported no improvements in first-phase insulin secretion or insulin sensitivity (measured by hyperglycemic clamp), lipid profile, blood pressure, or C-reactive protein levels. In the trial of children and adolescents performed by Kendall and coworkers, no changes were observed in any of the oral glucose tolerance test measures, fasting glucose, insulin, HOMA-IR, lipid profile, blood pressure, C-reactive protein, resistin, adiponectin, or leptin [29]. Results of systematic reviews generally support the findings of these three large trials noting modest improvements in fasting insulin and HOMA-IR but no changes in blood pressure [30–32]. Pooled analyses revealed modest reductions in total cholesterol [31, 32]. It is important to note that evidence from a large adult trial demonstrated a reduction in the incidence of type 2 diabetes with metformin treatment among individuals with prediabetes [33]. Although similar data do not exist for the pediatric population, it is not unreasonable to speculate that metformin may have benefits in this regard among youth with obesity at particularly high risk of developing type 2 diabetes.

Safety and Commonly Observed Side Effects

In general, metformin has a well-described safety profile and is widely viewed as having an acceptable benefit-to-risk ratio, even within the context of treatment for obesity and prediabetes. The most frequently reported side effect is gastrointestinal discomfort in the form of nausea, vomiting, and loose stools/diarrhea. The prevalence of gastrointestinal complaints in the large pediatric studies varied by trial but was most often 10–20% higher in those treated with metformin compared to placebo [27–29, 31, 32]. No concerns were noted regarding lactic acidosis or changes in liver enzyme levels. In the trial of younger children performed by Yanovski and coworkers, vitamin B12 levels were reduced in the metformin compared to placebo group [28]. However, despite the mean decrease in vitamin B12 levels, values remained in the normal range in all participants.

Clinical Considerations

In light of the relatively modest BMI reduction noted in clinical trials (approximately 3% with 6–12-month treatment), metformin is not an ideal medication if the explicit goal is weight loss. However, owing to its metabolic mechanisms of action and its ability to reduce the incidence of type 2 diabetes among adults, metformin may have a beneficial preventative role in children and adolescence at high risk of developing type 2 diabetes. The relatively strong safety profile provides some level of assurance that the benefits of treatment might outweigh the risks in certain situations.

Less Well-Studied Medications

A number of other medications have been less well studied (as compared to orlistat and metformin) in the pediatric population but are worthy of mention since a reasonable amount of evidence has been generated in regard to their safety and efficacy. A short discussion of two such medications (exenatide and topiramate), along with brief mention of a few others, is provided below.

Exenatide

Exenatide, a GLP-1 receptor agonist (GLP-1RA), is approved in the United States and in Europe for the treatment of type 2 diabetes in adults. Exenatide is administered subcutaneously and

available in two formulations, a shorter-acting twice per day version and a longer-acting once-weekly version. Although not approved for the treatment of obesity, adult studies have consistently demonstrated weight-reducing effects of exenatide [34–36]. The weight loss mechanisms of action are thought to include a reduction of appetite through activation of GLP-1RA receptors in the hypothalamus and enhancement of satiety by slowing gastric emptying and bolstering the vagal afferent signaling of gastric distension to the nucleus tractus solitarius portion of the hindbrain [37–39].

To date, only two small studies have investigated the weight loss effects of GLP-1RAs among youth with obesity. The first was a randomized, controlled trial of 12 adolescents with severe obesity who received either exenatide plus lifestyle modification therapy or lifestyle modification therapy alone for 3 months, followed by crossover to the other treatment arm [40]. Compared to the control phase, BMI was reduced by approximately 5% during exenatide treatment. The second study was a double-blind, randomized, placebo-controlled trial that assigned 26 adolescents with severe obesity to exenatide or matching placebo for 3 months [41]. This was followed by an open-label extension during which all of the participants were offered exenatide treatment. Compared to placebo, exenatide reduced BMI by approximately 3% at 3 months. Participants treated with exenatide for the entire 6 months of the trial (including the extension) experienced a cumulative BMI reduction of approximately 4%. Nausea, vomiting, headache, abdominal pain, and diarrhea were the most commonly reported adverse events in these trials [40, 41]. Improvements were observed in glucose tolerance, surrogate measures of insulin sensitivity and beta-cell function, and systolic blood pressure [40, 41].

Topiramate

Topiramate is approved in the United States and in Europe for the treatment of seizures (≥2 years of age) and for migraine prevention (≥10 years of age) and has been associated with weight loss. Clinical trials of adults with obesity have demonstrated placebo-subtracted weight loss on the order of approximately 5 kg [42]. Although the weight loss mechanism(s) of action of this orally administered medication is not entirely understood, modulation of the neurotransmitter gamma-aminobutyrate (GABA) is thought to be involved. A recent pilot trial in adolescents with severe obesity evaluated the effects of a short-term (1-month) low-calorie meal replacement period followed by topiramate (75 mg per day) or placebo for a subsequent 6 months [43]. A modest placebo-subtracted reduction in BMI of approximately 2% was observed, which did not reach statistical significance. Importantly, no adverse changes in cognitive function were detected with topiramate treatment as measured by the Cambridge Neuropsychological Test Automated Battery (a computerized test of motor speed, memory, and attention) and the Conners' Continuous Performance Test II (a computerized measure of attention and impulsivity).

Other Medications

Various other medications have been evaluated as weight loss agents in adults and, to a much lesser extent, children and adolescents. For some medications, the only safety and efficacy data available are from trials with relatively small sample sizes that were conducted decades ago. Other agents are either no longer available or not widely used at the present time owing to uncertainty regarding side effects. Examples include phentermine, diethylpropion, lisdexamfetamine, fenfluramine/dexfenfluramine, sibutramine, rimonabant, fluoxetine, and zonisamide. None of these agents are approved in the United States or in Europe for the treatment of pediatric obesity. Interested readers are referred to a comprehensive review of pediatric obesity pharmacotherapy trials published by Sherafat-Kazemzadeh and coworkers in 2013 that offers more detail about many of these medications [44].

New Options on the Horizon

The obesity medicine pipeline is strong and growing. Since 2012, four new obesity medications have been approved for use in adults in the United States: lorcaserin, the combination of phentermine and topiramate, the combination of naltrexone and bupropion, and high-dose liraglutide (note: only naltrexone/bupropion and high-dose liraglutide are approved in Europe). The efficacy varies by agent, with the placebo-subtracted weight loss at 1 year ranging from approximately 3 to 9% (for details about the safety and efficacy of these medications in adults, readers are referred to Yanovski and Yanovski) [45]. Pediatric trials are slated to begin within the next few years, offering hope that more pharmacotherapeutic options will soon be available to the pediatric medical community.

Lorcaserin

Lorcaserin, a selective serotonin receptor agonist, was approved by the FDA in 2012 for the treatment of obesity in adults. Lorcaserin is administered orally in a 10 mg dose, twice per day. Phase III clinical trials demonstrated placebo-subtracted weight loss of 3–4% following 1 year of treatment [46, 47]. The most commonly reported side effects in these trials were headache, dizziness, fatigue, nausea, dry mouth, and constipation. Modest improvements were observed in blood pressure, lipid profile, glucose, insulin, HOMA-IR, C-reactive protein, fibrinogen, and quality of life [46, 47].

Phentermine and Topiramate

The combination of phentermine (a norepinephrine reuptake inhibitor) and topiramate extended release (mechanism(s) not fully characterized but may involve GABA modulation) was approved by the FDA in 2012 for the treatment of obesity in adults. This orally administered medication is available in mid- (phentermine 7.5 mg + topiramate 46 mg) and high (phentermine 15 mg + topiramate 92 mg)-dose formulations, both taken once per day. Results from the largest of the phase III clinical trials demonstrated placebo-subtracted weight loss of approximately 7% and 9% following treatment for 1 year at the mid and high doses, respectively [48]. The 2-year extension trial demonstrated that the weight loss achieved in the first year was maintained, suggesting a durable effect [49]. A separate trial of adults with severe (class II or III) obesity reported similar efficacy with treatment for 1 year [50]. The most commonly reported side effects in these trials were paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth [48, 49]. Improvements were observed in blood pressure, lipid profile, glucose, insulin, HOMA-IR, C-reactive protein, and adiponectin [48–50].

Naltrexone and Bupropion

The extended-release combination of naltrexone (an opioid receptor antagonist) and bupropion (a dopamine reuptake inhibitor) was approved by the FDA in 2014 for the treatment of obesity in adults. Naltrexone + bupropion is administered orally twice per day (daily doses of 32 mg naltrexone and 360 mg bupropion). Phase III clinical trials demonstrated placebo-subtracted weight loss of approximately 5% following treatment for 1 year [51, 52]. The most commonly reported side effects in these trials were nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea. Improvements were observed in lipid profile, glucose, insulin, HOMA-IR, C-reactive protein, and quality of life [51, 52]. However, despite superior weight loss with naltrexone + bupropion treatment, no reductions in either systolic or diastolic blood pressure were observed, which was in contrast to the improvements noted in the placebo group.

Liraglutide

Originally approved as a treatment for type 2 diabetes, liraglutide (belonging to the GLP-1RA class) was approved by the FDA in 2014 for the

treatment of obesity in adults. Liraglutide is administered subcutaneously in a 3 mg dose (note this dose is higher than the 1.8 mg dose approved for the treatment of type 2 diabetes), once per day. Results from the largest of the phase III clinical trials demonstrated placebo-subtracted weight loss of approximately 5% following 1 year of treatment [53]. The most commonly reported side effects in the phase III trials were nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain, and increased lipase level. Improvements were noted in blood pressure, lipid profile, glucose, insulin, glycosylated hemoglobin, glucose tolerance, C-reactive protein, plasminogen activator inhibitor-1, adiponectin, and quality of life [53]. In addition, participants treated with liraglutide were less likely to develop prediabetes and type 2 diabetes compared to those receiving placebo.

Pharmacotherapy: The Next Frontier in Pediatric Obesity Medicine

Pediatric obesity, particularly severe obesity in the adolescent, is a recalcitrant disease [1]. Current evidence, though extremely limited, suggests that monotherapy with currently available obesity medications results in only modest BMI reduction in youth [10, 44]. This should not come as a surprise given the complex biological processes that contribute to the development and maintenance of obesity and suggests that the most effective pharmacological strategies are likely to be combinations of medications targeting multiple pathways involved in the physiological regulation of energy balance (Fig. 35.2). This is analogous to other chronic conditions such as hypertension and type 2 diabetes for which multiple medications are employed to achieve long-term disease control. Ideally, these combinations would act synergistically, address counter-regulatory mechanisms known to hinder sustained weight loss, and minimize side effects by employing lower doses of the individual agents than might be needed otherwise if used in isolation. One such example is phentermine plus extended-release topiramate, which elicits approximately 10% weight reduction at its highest dose [48–50] and represents the most effective obesity medication currently on the market [54].

The strategic use of pharmacotherapy along with other intensive lifestyle modification treatment approaches offers the potential to meaningfully enhance weight loss outcomes, thereby bridging the large gap between behavioral weight management and bariatric surgery. For example, meal replacements, consisting of shakes and preportioned meals of fixed caloric content, have been shown to be effective for weight reduction in the adolescent population. Berkowitz and coworkers randomized 113 adolescents to either 1300–1500 kcal/day of meal replacements or conventional diet of equal calories and reported a mean BMI reduction of 6.3% for the meal replacement group and 3.8% for the conventional diet group [55]. However, at 1 year, participants in the meal replacement group regained much of their weight. Using pharmacotherapy during or at the end of the meal replacement phase to dampen the counter-regulatory mechanisms which promote weight regain is a rational approach and may lead to improved outcomes with enhanced durability. Similarly, pharmacotherapy could help "seal" the weight loss achieved in residential obesity treatment programs (immersion therapy in a hospital, camp, or boarding school-type setting) [56].

Pharmacotherapy may also serve to augment the weight loss achieved by devices, another emerging therapeutic option for pediatric obesity. In 2015, two different types of intragastric balloons were approved by the FDA for treatment of obesity in adults. These balloons are inserted endoscopically and remain in the stomach for up to 6 months. Because the intragastric balloon is at present considered a temporary treatment and the weight loss from these devices is relatively modest (<5% weight loss) [57], utilizing pharmacotherapy during or after device therapy may be a useful strategy for pediatric patients in whom bariatric surgery is not desired. Finally, although

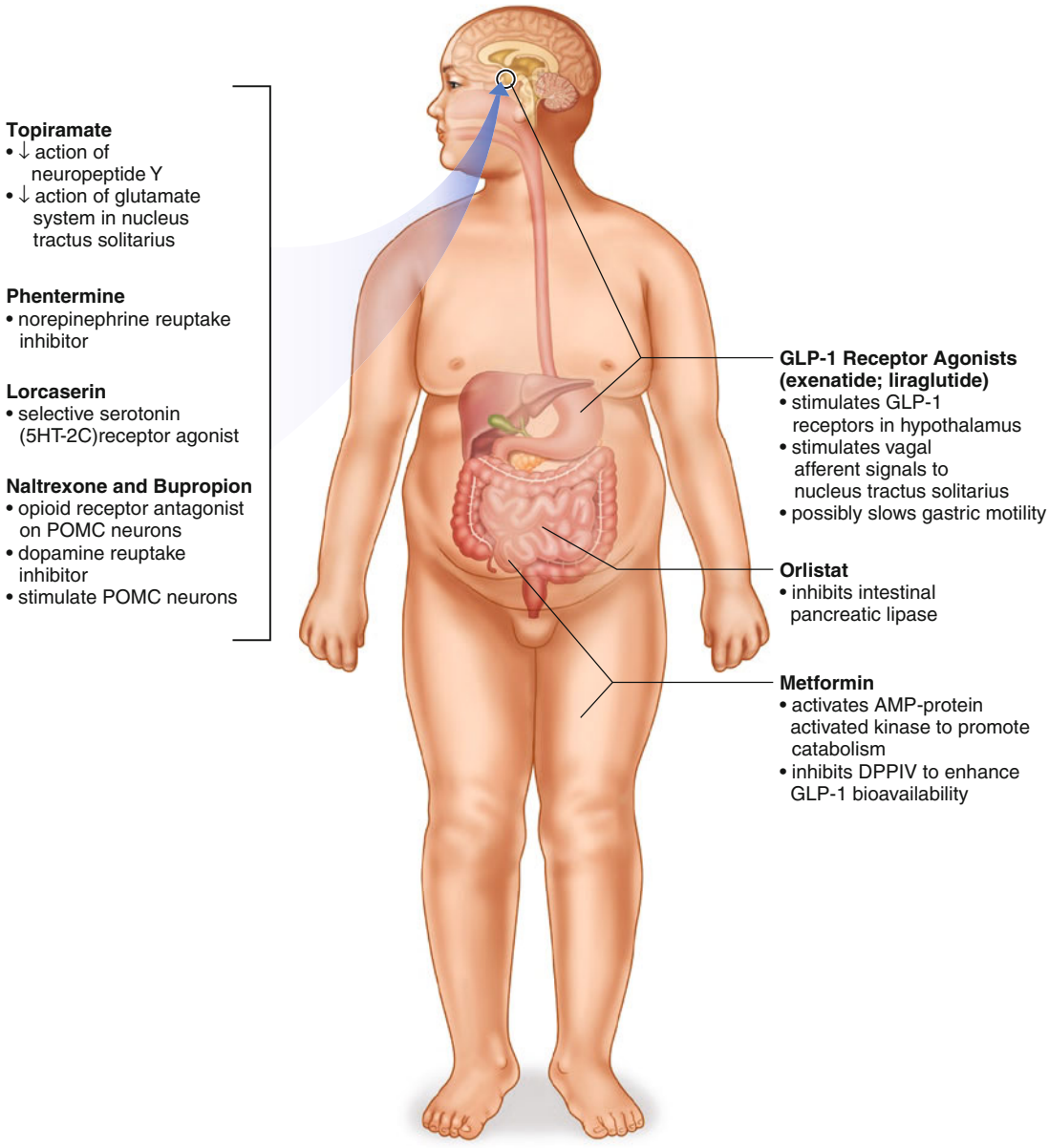

Fig. 35.2 Proposed mechanisms of action of various obesity medications. Depiction of how various obesity medications are thought to alter central and peripheral pathways to elicit negative energy balance. These medications act on different pathways including the brain, gut (stomach, small intestines), and peripheral tissues involved in energy expenditure (e.g., skeletal muscle). *GLP-1* glucagon-like peptide-1, *AMP* adenosine monophosphate, *DPP IV* dipeptidyl peptidase IV, *POMC* pro-opiomelanocortin

bariatric surgery is the most effective weight loss treatment for severe obesity in adolescents, some individuals experience partial weight regain. Though the exact incidence of "failure" after bariatric surgery in the adolescent population is unknown, pharmacotherapy may have a role in helping to limit weight regain in bariatric surgery patients experiencing weight rebound.

The future of pediatric obesity pharmacotherapy will also see the development of tailored or personalized therapies. The contributors to obesity are multifaceted, and not every patient has

the same constellation of weight-promoting factors. As such, not all patients respond to the same extent to a given medication. Characterizing discrete measurable predictors of medication response may enhance outcomes and minimize the incidence of side effects. The use of precision medicine in the context of obesity treatment will be especially important for pediatric patients, most of whom will require the use of weight management medications for life.

Editor's Comments and Question

You reason, persuasively, that pharmacologic agents can be employed to counteract the biological drive toward weight recovery in those who have succeeded in achieving weight loss through other means. Clinicians, however, are often asked to manage obese children who, for whatever reason, have been unable to achieve even modest weight loss with standard lifestyle recommendations. In this setting, should the provider and family begin a pharmacologic agent?

I have argued that pharmacotherapy should be *considered* when *obesity and comorbidities persist or worsen* despite formal counseling and a good faith effort at diet and exercise. Given the critical need to prevent type 2 diabetes mellitus in those at high risk, I would consider obese children with the following conditions to be potential candidates for drug treatment:

- Prediabetes (impaired fasting glucose, impaired glucose tolerance, HbA1c $\geq 5.7\%$)
- Metabolic syndrome
- Ovarian hyperandrogenism/PCOS
- Hypothalamic dysfunction
- Long-term atypical antipsychotics, glucocorticoids, and other drugs known to cause weight gain

In all of these cases, I would be more likely to recommend drug therapy if the child had a strong family history of type 2 diabetes and/or early cardiovascular disease.

What criteria would you use to begin pharmacotherapy in an obese child or teenager?

Authors' Response

For the clinician, decision-making regarding the use of pharmacotherapy is rarely straightforward and necessarily involves the synthesis of many factors. The complexities and unique considerations of each child require a tailored approach to the management of obesity, and clinical judgment must be applied accordingly. At the core of the decision to utilize pharmacotherapy for pediatric obesity is assigning weight to the relative risks and potential benefits. Risks of pharmacotherapy are real and depend on the type/class of medication. These may include adverse effects on the cardiovascular or neurocognitive systems, for example. With short-term use, the clinician may be able to select medications strategically to minimize some of the expected side effects. For example, the clinician should avoid prescribing phentermine in a patient who has a cardiac arrhythmia. Nevertheless, the effects of long-term use of most of these medications are simply unknown. In the case of phentermine, what is the effect of chronic use on the cardiovascular system? Even if blood pressure remains within a normal range, what subclinical effects might this have that may eventually become clinically relevant over time? In considering the long-term risks, it is important to acknowledge that the toll of failing to effectively treat obesity in the pediatric patient is substantial.

Inherent in the risk calculation are factors such as the severity of obesity, age of the patient, presence of weight-related comorbidities, response to lifestyle modification therapy, and several practical considerations. Current evidence clearly demonstrates that lifestyle modification

therapy is much more effective in reducing BMI when implemented in younger childhood (generally less than 12 years old) compared to adolescence and in patients with moderate (class I) vs. severe (class II or III) obesity. Furthermore, evidence indicates that nearly all adolescents with severe obesity become adults with at least class II obesity; yet, the risk of persistent obesity for the younger child is less clear. Therefore, in younger children with uncomplicated obesity, initiating treatment with lifestyle modification therapy, without the use of adjunctive pharmacotherapy, is a well-reasoned approach. Conversely, in adolescents with severe obesity, lifestyle modification plus pharmacotherapy may be indicated from the outset. For pediatric patients who already have obesity-related comorbidities, there is a heightened urgency to reduce weight. For instance, if the school-aged boy who has nonalcoholic steatohepatitis with bridging fibrosis on liver biopsy cannot reduce his weight via lifestyle modification therapy alone, it may be prudent to intensify the treatment plan by adding pharmacotherapy. Of course, not all comorbid conditions carry the same gravitas. The clinician must determine the degree to which the comorbidity is affecting the patient's morbidity, including quality of life, and mortality risk.

Some argue that pediatric patients should first "fail" a course of lifestyle modification therapy before they are given the option of using pharmacotherapy. This notion suggests that patients must "earn" this treatment strategy, which further reinforces a sense that obesity is the fault of the patient rather than a biological disease with psychosocial contributors. The adult research literature suggests that early weight loss success predicts favorable long-term outcomes. While this has not yet been demonstrated convincingly in the pediatric population, it seems plausible that it would hold true for adolescents. For this reason, withholding pharmacotherapy to treat obesity in adolescents until they have demonstrated lack of success with lifestyle modification therapy alone does not seem like an optimal strategy.

Finally, practical considerations such as cost also drive decisions to use pharmacotherapy. Many insurance companies do not cover obesity medications for adults or children. Some medications are relatively inexpensive, but others have prohibitive costs.

In sum, younger patients (<12 years) should probably begin weight management therapy with lifestyle modification therapy alone. However, adolescent patients with severe obesity and/or serious comorbid conditions will likely require lifestyle modification therapy with adjunctive pharmacotherapy to have a reasonable chance at experiencing a favorable outcome.

Additional Comments by Editor

The mechanisms by which metformin limits weight gain[a] are poorly understood. Reductions in hepatic glucose production reduce circulating insulin levels and thereby limit lipogenesis and fat storage, while inhibition of DPP-4 may increase the levels of GLP-1, which acts locally (at the level of the vagus nerve) and centrally to reduce food intake. A recent study suggests that the drug increases fasting but not postprandial GLP-1 levels[b]; perhaps it attenuates the drive to eat. Metformin also modulates the gut microbiome[c] and concentrates in the ileum, the site of GLP-1 production. Modulation of gut flora might alter nutrient extraction and/or utilization and thereby limit both weight gain and glucose excursion.

In some ways the GLP-1 receptor agonists would seem ideally suited to treatment of obesity and prevention of type 2 diabetes, as they increase glucose-stimulated insulin secretion while reducing food intake and body fat mass. However, their use may be associated with serious adverse effects. In the largest study[d] of liraglutide in obese adults, 2.5% of treated subjects had gall bladder

events and 1 in 59 required a cholecystectomy. In contrast, only 1 of every 208 placebo-treated controls required gall bladder surgery. Pancreatitis developed in 10 of 2481 liraglutide-treated patients and 1 of 1244 control patients. Withdrawal rates among the rest of the liraglutide-treated patients were high, in part because nausea and vomiting can be quite troublesome after initiation of therapy.

The magnitude of weight loss with higher-dose combinations of phentermine and Topamax exceeds that achieved with liraglutide and other pharmacologic agents. It should be noted, however, that high doses of Topamax (in my experience >25–50 mg) can cause paresthesias and difficulties with concentration, attention, and memory.

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Pathogenesis and Management of Adiposity and Insulin Resistance in Polycystic Ovary Syndrome (PCOS)

Thomas M. Barber, Jalini Joharatnam, and Stephen Franks

Introduction: Polycystic Ovary Syndrome (PCOS)

PCOS is the most common female endocrine disorder, affecting 5–10% of reproductive-aged women [1]. It typically manifests in a heterogeneous manner, often during adolescence. The cardinal features of PCOS encompass both reproductive and hyperandrogenic expressions, manifesting clinically as oligo-amenorrhoea, and hirsutism, acne, and alopecia, respectively [1]. The most frequent biochemical abnormality in PCOS is hyperandrogenaemia, defined typically as elevated total serum testosterone levels as well as increases in androstenedione and free androgen index [1]. An elevated ratio of LH-FSH, although not a diagnostic feature, also often occurs in PCOS [1]. Importantly, PCOS is also associated with metabolic abnormalities, notably insulin resistance and hyperinsulinaemia, which are associated with high risk for development of type 2 diabetes mellitus (T2D) [1]. Onset of obesity can worsen metabolic dysfunction through its association with insulin resistance. One serious consequence of the current obesity epidemic (that affects both adults and children) will be a further increase in numbers of adolescent girls diagnosed with PCOS with an associated escalation in metabolic dysfunction [1].

The diagnostic criteria for PCOS are somewhat controversial. The 1990 NIH multidisciplinary "consensus" conference recommended that the diagnosis of PCOS be based on both oligo-anovulation and hyperandrogenism [2]. Recognition that regular ovulatory cycles can sometimes be maintained in women with hyperandrogenaemia and polycystic ovaries prompted revision of the diagnostic criteria for PCOS at the 2003 consensus conference (sponsored jointly by the American Society for Reproductive Medicine [ASRM] and the European Society of Human Reproduction and Embryology [ESHRE]). The "Rotterdam" diagnostic criteria for PCOS require at least two of the following three criteria: (a) clinical and/or biochemical hyperandrogenism,

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(b) polycystic ovaries on ultrasonography, and (c) menstrual irregularities [3]. One advantage of these revised diagnostic criteria is that they promote awareness of the heterogeneous presentation of PCOS. However, the "Rotterdam" diagnostic criteria have been controversial, primarily because of inclusion within the diagnostic realm of PCOS of women with polycystic ovaries and anovulation with no evidence of androgen excess. Whilst there is evidence to support inclusion of this subset within the diagnostic criteria for PCOS [4], it is also clear that metabolic dysfunction (including insulin resistance) is associated mainly with those subgroups of PCOS manifesting both anovulation and hyperandrogenism [5–7]. To counter the contention associated with the normoandrogenaemic subgroup of PCOS defined by the Rotterdam diagnostic criteria, the Androgen Excess Society (AES) released a further set of diagnostic criteria for PCOS based on a prerequisite for androgen excess [8]. However, the results from recent genetic studies (see below) support the view that despite the variable phenotype, the etiological basis is similar amongst the clinical subtypes.

Developmental Origin of PCOS and Its Evolution During Childhood

There is ample evidence that the aetiology of PCOS implicates a major genetic component (see below) but that environmental factors, particularly diet, play an important role [9]. The frequent presentation of PCOS during adolescence suggests that its origins stem from childhood or perhaps even from fetal development. Animal models of PCOS support this hypothesis. Female rhesus monkeys exposed to high concentrations of testosterone *in utero* develop many features that typify human PCOS as adults, including high serum levels of LH, ovarian hyperandrogenism, and anovulation associated with increased body weight and insulin resistance [10, 11]. Similar observations pertain to the prenatally androgenised sheep model of PCOS [12, 13]. Rodents exposed to excess androgen during early development also show a characteristic metabolic phenotype [14, 15]. These observations suggest that the PCOS phenotype manifesting during adolescence and adulthood may originate directly from fetal androgen exposure. Such *in utero* exposure to androgens may "programme" the fetal hypothalamic-pituitary-ovarian (HPO) axis (with resultant elevations of serum LH) and fat deposition [16]. "Androgen programming" may also disrupt the negative feedback of progesterone and oestrogen on gonadotropins [17], abnormalities that can be reversed by treatment with the anti-androgen flutamide. This observation highlights an effect of hyperandrogenaemia in reducing hypothalamic sensitivity to feedback inhibition [18].

In the case of the rhesus monkey model of PCOS, it is important to note that the maternal doses of androgen that were used were high enough to exceed two efficient physiological barriers: firstly, placental aromatase (which converts excess androgen to oestrogens) and, secondly, high circulating sex hormone-binding globulin (SHBG, which binds testosterone in the maternal circulation and prevents placental transfer). Therefore, "vertical transmission" of PCOS from mother to fetus via *transplacental delivery* of excess androgen may not occur [19]. Rather, the source of excess fetal androgen that predisposes to later development of PCOS may be the fetal ovary and/or adrenal. Possible mechanisms include active secretion of excess androgen *in utero* from the fetal ovary and/or adrenal or, perhaps more plausibly, genetic predisposition to ovarian overproduction of androgens during activation of the HPO axis in infancy or at puberty [16]. An adrenal contribution to androgen excess in PCOS manifests as premature and/or augmented adrenal androgen "burst" secretion during adrenarche, with existing evidence to support links between premature adrenarche, premature pubarche, and the manifestation of PCOS during adolescence [20].

Normal pubertal development is characterized by activation of the HPO axis and is associated with a physiological reduction in insulin sensitivity. In girls with an underlying genetic predisposition to PCOS, these normal physiological changes are exaggerated by elevated serum lev-

els of LH and hyperinsulinaemia resulting from physiological insulin resistance, amplified by weight gain and obesity. For these reasons, PCOS often becomes manifest during adolescence [20].

Candidate Gene Studies and PCOS

Heritability studies on women with PCOS reveal a strong genetic susceptibility [9, 21]. Familial clustering has been noted [22, 23], and greater concordance of clinical and biochemical features of PCOS has been observed between monozygotic and dizygotic twins [24]. Genetic studies in PCOS are challenging due to the heterogeneity and complexity of this disorder [25]. Several genes are likely to be implicated in the aetiology of PCOS, but despite a plethora of reported candidate gene (mostly case-control) studies, few loci have been shown convincingly to be associated with the condition. Methodological problems have contributed to this confusion since many of the published studies have been underpowered and are based on ethnically heterogeneous populations.

Based on evidence from the reported candidate gene studies in PCOS, variants within the fat mass and obesity-associated (*FTO*) gene are likely implicated in disease susceptibility. Common variants in a 47 kb region of the first intron of *FTO* are known to contribute towards susceptibility to the development of Type 2 Diabetes Mellitus (T2D), via effects on BMI and fat mass [26]. Barber and colleagues showed a significant association between *FTO* variants and PCOS status in a UK-based case control analysis [27]. The association was most evident in obese women with PCOS, suggesting that such genetic susceptibility from *FTO* variants is mediated, at least in part, via effects on fat mass.

Using linkage analysis, an association has also been demonstrated between PCOS and a dinucleotide repeat marker D19S884 (close to, but not in linkage disequilibrium with, the insulin receptor gene) on chromosome 19p13.2 [28]. Fine mapping locates this polymorphism in the region of intron 55 of the fibrillin 3 gene (*FBN3*) [25]. This locus is associated with metabolic features of PCOS in reproductive-age women and their brothers [21]. Although the precise function of *FBN3* is unclear, fibrillins are known to be binding proteins for transforming growth factor beta (TGFβ). Growth factors in the TGFβ family have been implicated in early follicle development and theca formation in the ovary [29]. Therefore, D19S884 may contribute towards the reproductive features that characterize PCOS.

The poor yield of well-characterized and plausible susceptibility loci using the candidate gene approach has been disappointing. However, some of the problems associated with the candidate gene approach have been surmounted through application of genome-wide association studies (GWAS), similar to those used for identification of susceptibility variants for development of T2D [30]. A summary of data from reported GWAS in PCOS is outlined later in this chapter.

Metabolic Dysfunction in PCOS

Insulin resistance and its associated secondary hyperinsulinaemia are central defects that underlie metabolic dysfunction in women with PCOS [31]. Obese women with PCOS have a metabolic "double whammy" given that insulin sensitivity is known to worsen with increasing weight gain and is also further reduced in women with PCOS in comparison with weight-matched control women [31]. Insulin resistance promotes glucose intolerance in obese women with PCOS [32] and increases by three- to fourfold the risk of developing T2D [33–35]. Dyslipidaemia is also more common in women with PCOS and likely contributes to cardiovascular risk [36]. Due to the lack of long-term prospective studies in PCOS, however, there is no clear evidence that the cardiovascular risk factors associated with PCOS actually translate into increased number of cardiovascular *events*. Insulin resistance in PCOS may also limit post-prandial thermogenesis [37], which in turn may beget further weight gain.

It is important to emphasize that metabolic dysfunction in PCOS is a feature of women who have both anovulation and androgen excess. Weight-matched and equally hyperandrogenaemic women

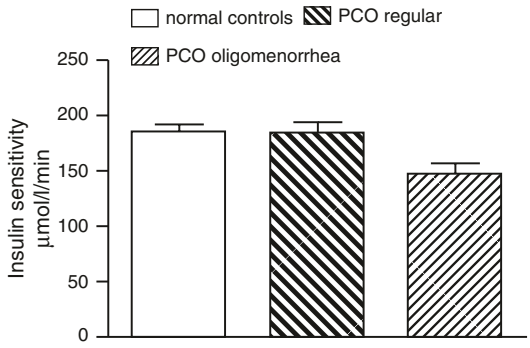

Fig. 36.1 Insulin sensitivity in BMI-matched groups of women with oligomenorrhoea and PCOS (n = 53) or in hirsute women with polycystic ovaries and regular cycles (n = 19), compared with values in BMI-matched normal controls (n = 31). The two groups of women with PCOS were equally hyperandrogenaemic. Only the groups with PCOS and oligomenorrhoea were insulin resistant ($p < 0.01$ compared with controls). Values shown are means + SEM (Data from Ref. 32)

with polycystic ovaries, but who have regular menses, have normal insulin sensitivity and serum insulin concentrations [32] (Fig. 36.1). This observation has implications for identification and targeting of PCOS women with higher risk of long-term metabolic sequelae [7]. The association between anovulation and metabolic dysfunction in hyperandrogenaemic women with PCOS also implies that insulin resistance and hyperinsulinaemia are implicated in the mechanism of anovulation, with *in vitro* data supporting a role of hyperinsulinaemia in the arrest of follicle development [38]. Furthermore, therapies that reduce insulin levels (weight loss and use of insulin-sensitizing drugs) significantly improve menstrual cyclicity, fertility, and hyperandrogenism [39–41].

Mechanism of Insulin Resistance in PCOS

The cause(s) of reduced insulin sensitivity in PCOS remains unclear. Abnormalities of the insulin receptor itself are rare in women with PCOS, with a majority of evidence favouring a post-receptor defect in insulin-signalling pathways [31, 42, 43, 44]. It is likely that the insulin-signalling defect in PCOS is located proximally in the pathway, involving serine phosphorylation of the insulin receptor [31, 43]. In one study, about 50% of women with PCOS who had insulin resistance (documented by euglycaemic clamp studies) appeared to have constitutive activation of serine phosphorylation of the insulin receptor in skin fibroblasts. Serine phosphorylation in turn inhibited insulin-stimulated tyrosine phosphorylation and thereby impaired insulin signalling [44].

In cultures of skeletal muscle obtained from obese women with PCOS, insulin receptor substrate 1 (IRS-1) protein abundance was found to be significantly increased, but there was decreased activity of phosphatidylinositol 3-kinase (PI3K) [43]. Phosphorylation of IRS-1 Ser^{312} (equivalent to Ser^{307} in rat) was increased in PCOS, yet cultured myotubules showed normal insulin responsiveness. No differences in insulin receptor tyrosine phosphorylation were seen between women with PCOS and controls. Thus, in contrast to skin fibroblasts, there are no apparent defects in the insulin-signalling pathway in skeletal muscle based on data from culture studies. These observations suggest that the *in vivo* environment is an important determinant of muscle insulin resistance in PCOS.

In contrast to skeletal muscle, insulin signalling in adipocytes may be impaired in PCOS [45]. Expression of the insulin-dependent glucose transporter GLUT4 is abnormally low in adipocytes of women with PCOS [46]. Reduced expression of GLUT4 has also been observed within skeletal muscle from non-PCOS patients with T2D [47].

As in skin and adipose tissue, the mechanism of insulin resistance in the ovary in PCOS appears to involve a selective post-receptor insulin-signalling defect. Importantly, the effect of insulin on glucose metabolism in granulosa-lutein cells from women with anovulatory PCOS is attenuated, whilst the steroidogenic response to insulin is preserved [48]. The selective defect of post-insulin receptor signalling in PCOS explains the apparent paradox of insulin resistance and secondary hyperinsulinaemia in the pathogenesis of this condition: the former

underlies metabolic dysfunction, and the latter, hyperandrogenism and reproductive abnormalities. In the special case of the ovary, glucose metabolism is needed for efficient oocyte maturation and function [49]. Therefore, ovarian insulin resistance (in addition to direct effects of hyperinsulinaemia on follicle development) may contribute towards infertility in women with PCOS.

Adiposity in PCOS

The relationship between adiposity and PCOS is complex. Whilst exacerbation of insulin resistance by weight gain and obesity is incontrovertible, less clear are possible effects of PCOS status and hyperandrogenaemia on further weight gain and the pattern of such weight gain (including proclivity for visceral fat deposition and adiposity). There is some evidence to support the notion that adolescents or adults with PCOS are predisposed to weight gain because of reductions in post-prandial thermogenesis: in one study, there was a difference of 42 kJ in post-prandial thermogenesis between obese women with and without PCOS. Such a difference in post-prandial energy expenditure, if maintained over a whole year, would equate to >735, 000 kJ or 1.9 kg of fat for the same calorie intake [37]. Such differences in post-prandial energy expenditure, however, are likely to be less important than dietary factors in the development and manifestation of PCOS. Hyperinsulinaemia-dependent lipogenesis likely plays a central role.

With regard to fat distribution, established dogma had suggested that women with PCOS have preferential accumulation of visceral fat. However, data from recent studies have cast doubt on this "accepted" view. Barber and colleagues used systematic axial magnetic resonance imaging (MRI) to quantify visceral and subcutaneous fat accumulation in women with an established diagnosis of PCOS versus fat mass-matched control women [50]. In this study, visceral fat depot areas taken from axial MRI images increased proportionately with increasing total body fat in both women with PCOS and fat mass-matched control women (Fig. 36.2). Areas of visceral fat depots were similar between PCOS cases and fat mass-matched control women despite clear differences between the groups in androgenicity and insulin sensitivity. These observations suggest that insulin resistance in PCOS cannot be attributed simply to altered body fat distribution but rather that other mechanisms are likely contributory.

Evidence that exposure to excess androgen increases adiposity derives from studies of prenatally androgenized animals, as discussed above. In women with PCOS, there is an association between serum androgen concentrations and body fat mass (or truncal fat). The directionality of this relationship, however, cannot be inferred. Weight gain and increased fat deposition are clearly associated with a worsening of clinical and biochemical features of PCOS [51, 52]. Thus, women who are overweight or obese are more likely to develop anovulatory cycles or amenorrhoea and more severe hirsutism. The association between free testosterone index (testosterone/SHBG ×100) and fat mass in women with PCOS likely reflects the impact of obesity on suppression of SHBG. Serum levels of SHBG are inversely related to BMI and fasting insulin concentrations, and there is evidence for a direct inhibitory effect of insulin on hepatic production of SHBG [53, 54].

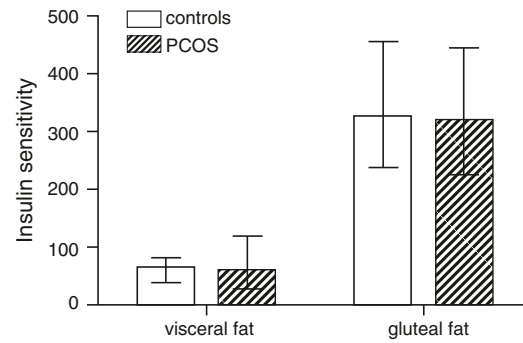

Fig. 36.2 Area of visceral and gluteal subcutaneous fat (cm^2) (geometric mean and SD) as measured by MRI in 44 BMI-matched obese women with PCOS (n = 22) or controls (n = 22). Note similar relationship of visceral to subcutaneous fat in both groups (Data from Ref. 50)

Metabolic Syndrome in Adolescents with PCOS

Metabolic syndrome comprises increases in waist circumference, blood pressure, glucose, and lipids and is associated with higher cardiovascular risk. The prevalence of metabolic syndrome in obese adults with PCOS has been reported to range from 30 to 45% [7, 55–58]. There are relatively few studies on prevalence of metabolic syndrome in adolescent girls. One study by Rossi and colleagues reported the prevalence of metabolic syndrome in a group of 43 obese girls with PCOS (mean age 15.6 years) compared with that in a group of 31 control girls with similar BMI [59]. Using adult criteria for diagnosis of metabolic syndrome, 26% of the PCOS group and 29% of controls had metabolic syndrome. The authors concluded that obesity, rather than PCOS *per se* was a major determinant of metabolic syndrome in adolescents.

Diagnostic Investigation

The diagnosis of PCOS is mainly based on clinical features. In adolescents with symptoms of hyperandrogenism, measurements of total and free testosterone and adrenal androgens may help to exclude other causes of androgen excess. Serum 17-hydroxyprogesterone levels can help to differentiate patients with non-virilizing 21-hydroxylase deficiency from those with PCOS. In those with oligo- or amenorrhoea, measurements of LH, FSH, and prolactin should be undertaken to exclude hypothalamic amenorrhoea and hyperprolactinaemia as underlying causes of menstrual disturbance. A transabdominal ultrasound is useful in some cases, with typical polycystic ovarian morphology showing at least 12 follicles 2–9 mm in diameter and/or an ovarian volume greater than 10 cm^3. However, some specialists argue that a scan is not essential for assessment and management [3] because girls with both hyperandrogenism and menstrual disturbance are likely to have PCOS. In patients with BMI exceeding 30 kg/m^2, an oral glucose tolerance test or simply an HbA1C measurement should be performed to exclude dysglycaemia and T2D.

Management of Adolescents with PCOS

The principles of management of adolescents with PCOS include control of reproductive and hyperandrogenic symptoms (anovulation, hirsutism, and acne) and reduction of longer-term risks of T2D and cardiovascular disease. Early diagnosis of PCOS is paramount to ensure that girls are provided with appropriate lifestyle and dietary advice that may include facilitation of weight loss and avoidance of further weight gain. In this way, the likelihood of worsening clinical features of PCOS (hyperandrogenism, anovulation, and metabolic dysfunction) will be reduced.

Management of PCOS is tailored to the needs of the patient. Hirsutism, acne, and weight gain often cause deep distress in adolescent girls. Treatment of cutaneous problems should therefore be instituted without delay. Treatment of infertility is rarely an issue in this age group, although many girls will wish to be reassured about their future prospects of childbirth. The preferred and most effective method of treatment for obese adolescent girls with PCOS is lifestyle modification. In overweight and obese patients, education about beneficial effects of weight loss on the menstrual cycle and future long-term health should be emphasized with provision of practical advice regarding diet and exercise. Such a treatment strategy often improves all features of PCOS [39, 60]. Although this treatment approach is safe and non-pharmacological, weight loss programmes in children are notoriously unsuccessful [61].

Treatment of menstrual irregularities in adolescents focuses on re-establishing a predictable cycle of menstruation. This can be attained with the combined oral contraceptive pill (COCP), which is considered a first-line therapy for adolescent PCOS by most paediatric endocrinologists [62].

In addition to regulating the menstrual cycle and reducing risk of future complications resulting from endometrial hyperplasia, the COCP has an anti-androgenic effect mediated through elevation of SHBG levels and reduction of LH-driven ovarian androgen production.

Symptoms of androgen excess are best treated with a combination of cosmetic management and, if necessary, anti-androgen therapy [63]. Cosmetic management includes shaving (efficient but not popular), waxing, and epilation by electrolysis or laser. The most commonly used anti-androgen in the UK is cyproterone acetate, often used in combination with ethinylestradiol (as in co-cyprindiol, ethinylestradiol 35μg + cyproterone acetate 2 mg, often prescribed as Dianette in the UK). If necessary, additional cyproterone acetate (25–50 mg daily) can be combined with co-cyprindiol.

Cyproterone acetate is not available in the USA, where the pharmacologically similar spironolactone is preferred. Spironolactone is an equally effective anti-androgen; doses as low as 50 mg daily have produced efficient reduction in hyperandrogenism in adolescents [64]. Flutamide is a potent, nonsteroidal anti-androgen that is not routinely used in the UK but is effective in the treatment of hyperandrogenism in adolescents [65, 66]. Its high cost and potential hepatotoxicity preclude its widespread use. Although there is little evidence for liver damage from use of flutamide at chronic low doses, it is probably best avoided [67]. Acne can be treated with topical and oral antibiotics. Those with more severe disease often respond to anti-androgen therapy. In resistant cases, treatment with retinoic acid derivatives under dermatology supervision is recommended.

Although treatments with the COCP and/or antiandrogens can improve hyperandrogenism and menstrual irregularities, these agents have little effect on insulin resistance and its metabolic sequelae, and some may even exacerbate hypertriglyceridaemia. In addition to lifestyle modification, drug therapies may assist in the management of metabolic dysfunction. Metformin has been shown to increase insulin sensitivity, reduce free testosterone levels, and improve menstrual cyclicity in PCOS [68–70]. The recommended starting dose is 500 mg daily, increasing to a maximum of 2 g daily in divided doses. However, there are only a few reported adequately powered short-term studies regarding the efficacy of metformin in PCOS and a serious lack of data on the longer-term effects of metformin on metabolic complications of PCOS. There are even fewer such studies in adolescents. Recently, a large and well-conducted randomized controlled trial comparing metformin and clomiphene (either alone or in combination) showed no benefit of metformin for ovulation induction [71]; although not usually relevant in adolescents, this highlights the importance of large randomized trials in clarifying potential benefits of metformin. Thiazolidinediones, although successful in adults in improving androgen levels, insulin resistance, and lipid profiles, are not likely to overtake metformin in their use in adolescents due to their side effects, which may include weight gain, fluid retention, heart failure, and osteopenia [72, 73].

Genome-Wide Association Study (GWAS) in PCOS

As outlined earlier, PCOS develops in the context of underlying genetic predisposition [21–24, 74]. Yet PCOS is a difficult condition to study genetically due to its underlying heterogeneity and complexity, associated subfertility, and retrospective diagnosis in postmenopausal women [75]. In recent years, the GWAS has superseded the candidate gene approach for genetic studies in PCOS. The main advantage of GWAS is that it does not rely upon an *a priori* hypothesis promoting candidacy for a particular gene, but rather provides data for the entire genome [75]. The main limitation of GWAS, however, is that such studies require many thousands of subjects to provide sufficient power, usually necessitating multinational collaboration.

Reported studies utilizing GWAS in PCOS have included populations with both Chinese [76, 77] and European ancestries [78–81]. From these studies, there have been 16 significant replicated loci demonstrated to have genome-wide significant association with PCOS development, each with a small effect size [81]. The remaining heritability for PCOS may involve epigenetic or structural variants [81].

In one reported GWAS, Hayes and colleagues (including our own group) published data based on >980 women with PCOS and >2900 population controls with European ancestry [81]. Three loci were associated with PCOS at a genome-wide significant threshold: 11p14.1 (*FSHB/ARL14EP* locus), 8p32.1 (*GATA4/NEIL2* locus), and 9q22.32 (*c9orf3/FANCC* locus). Of these, two were novel (11p14.1 and 8p32.1). The 9q22.32 locus had previously been demonstrated to be associated with PCOS in a GWAS based on a population of Chinese ancestry [77]. The lead SNP within the 11p14.1 (*FSHB/ARL14EP*) locus associated strongly with LH levels [81]. Therefore, association of PCOS with variants within *FSHB* (encoding the specific beta subunit of FSH) [82] is likely mediated via effects on LH [81]. The 8p32.1 (*GATA4/NEIL2*) locus is thought to regulate transcription of genes involved in steroidogenesis and gonadal development [81, 83].

Most recently a GWAS on women with PCOS of European ancestry demonstrated six signals at genome-wide statistical significance [84], including the gene *ERBB4/HER4*, which encodes an epidermal growth factor receptor [84]. Previously, GWAS from Chinese populations showed association of 11 SNPs with susceptibility for development of PCOS (including 2p16.3, 2p21, and 9q33.3) [76, 77], seven of which (including the gonadotrophin receptor genes *LH/CGR* and *FSHR*) showed nominal replication in data reported by Hayes and colleagues [81].

To summarize, GWAS reported from European [78–81] and Chinese [76, 77] ancestry populations suggests important roles for gonadotropin secretion (*FSHB*) and action (*LHCGR* and *FSHR*) in the development of PCOS [81]. It is likely that variants within *FSHB* contribute to anovulation and hyperandrogenism in women with PCOS via effects on LH secretion [81]. It is important that additional GWAS be performed in women with PCOS from different population groups to gain further insights into underlying pathogenesis, and to provide essential genetic data on which to base future development of novel screening tests and therapeutic strategies.

Summary

PCOS is a common condition in women of reproductive age and typically becomes clinically and biochemically manifest during adolescence, a phase associated with physiological insulin resistance, activation of the HPO axis, and weight gain. PCOS is an important cause of hirsutism and menstrual disturbance but is also associated with the development of metabolic abnormalities, including insulin resistance. Insulin resistance and hyperinsulinaemia are more prevalent in adolescent girls with PCOS than in age- and weight-matched control girls, and these metabolic abnormalities are amplified by weight gain and obesity. The association of PCOS with insulin resistance underlies the heightened risk of developing T2D and other features of the metabolic syndrome in women with this disorder, particularly in the context of weight gain and obesity. Prevention and effective treatment of metabolic aberrations in PCOS are optimally managed through modification of diet and lifestyle, a challenge in many teenagers. Although insulin-sensitizing therapies may play a future role in the management of metabolic dysfunction in PCOS, there have been few large-scale controlled trials in this field to guide clinical practice. Weight loss remains the most important preventive and management strategy. With the current global obesity epidemic affecting both adults and children, it is incumbent upon all of us to promote a healthy lifestyle amongst our children, to avoid excessive weight gain and the obesity-related morbidities that can ensue, including PCOS.

Editor's Comments and Questions

1. As you imply in your review, precocious adrenarche may be the initial manifestation of PCOS or a marker of risk for development of PCOS in puberty or young adulthood. As a clinician, I find the family history to be particularly informative, noting the occurrence of menstrual irregularity, hirsutism, infertility, and/or ovarian cysts in first- or second-degree relatives. Many (but by no means all) children with precocious adrenarche are overweight or obese; in addition to lifestyle intervention, some investigators[a] suggest that metformin may reduce fat accumulation and increase insulin sensitivity even in peri-pubertal girls with adrenarche and might thereby prevent progression to PCOS. What is your opinion of such an approach?
2. Many obese adolescents and adults maintain normal menstrual cycles and have no clinical or biochemical evidence of hyperandrogenism. However, excess weight gain and insulin resistance can reproduce several of the features of PCOS through insulin induction of ovarian androgen production and suppression of hepatic SHBG. In such cases, it would appear the effects of obesity are superimposed upon a genetic predisposition to dysfunction of the hypothalamic-pituitary-ovarian axis. Interesting, then, is that a recent meta-analysis found that bariatric surgery reduced markedly the incidence of menstrual irregularity, hirsutism, and PCOS in adult women with severe obesity[b]. What is your view of the role of bariatric surgery in the management of PCOS in obese adolescents and adults?

References for Editor's Comments and Question Section

(a) Ibáñez L, López-Bermejo A, Díaz M, Marcos MV, de Zegher F. Early metformin therapy (age 8–12 years) in girls with precocious pubarche to reduce hirsutism, androgen excess, and oligomenorrhea in adolescence. J Clin Endocrinol Metab. 2011;96(8):E1262–7.

(b) Skubleny D, Switzer NJ, Gill RS, Dykstra M, Shi X, Sagle MA, de Gara C, Birch DW, Karmali S. The impact of Bariatric surgery on polycystic ovary syndrome: a systematic review and meta-analysis. Obes Surg. 2016;26(1):169–76.

Authors' Responses

1. Given the genetic predisposition necessary for development of PCOS and the evidence from twin studies to confirm the heritability of PCOS, we agree that a detailed family history is certainly useful and important to elicit in any woman or girl presenting with features suggestive of PCOS.

   Lifestyle changes through dietary modification can be difficult to achieve and especially to maintain over the longer term, particularly in adolescent girls. There is clearly a need for other therapies to complement lifestyle changes. The study by Ibáñez and colleagues provides useful evidence for the clinical benefits of early metformin therapy in adolescent girls with a history of low (normal) birth weight and precocious pubarche. There also appeared to be improvements in visceral and hepatic fat for those girls treated with early versus late metformin therapy. These data suggest that early use of metformin in such patients is a reasonable approach, and it is one that we also adopt. Although further data from other populations to validate the findings of Ibáñez and colleagues would be desirable, the study referred to represents some of our best evidence for early use of metformin therapy in adolescent girls with PCOS and precocious pubarche.

2. PCOS is essentially a condition that occurs in women and adolescent girls with an underlying genetic predisposition for its development. The clinical and biochemical manifestations of PCOS often develop during weight gain and heightened physiological insulin resistance, typified by the onset of puberty in girls who are genetically predisposed. Pubertal onset of PCOS is also promoted through activation of the hypothalamic-pituitary-ovarian axis and adrenarche, given the important role of increased androgenic production in the aetiology of this condition. It is also clear that weight loss (even amounting to just 5% of body weight) can result in significant improvements in both clinical and biochemical features of PCOS in obese women with this condition.

The role of bariatric surgery as a treatment option in women with PCOS is a very interesting question and one worthy of serious consideration. Weight loss (mainly through dietary means) represents a primary objective in the effective management of obese women and girls with PCOS. As alluded above, even modest weight loss can result in significant improvements. However, weight loss through lifestyle change, especially longer-term maintenance of weight loss, is challenging. This is particularly relevant to obese adolescent girls. Therefore, other means of facilitating weight loss and its maintenance would be desirable.

Bariatric surgery is an excellent means of achieving weight loss, and existing literature (e.g. the Swedish Obese Subjects study) suggests that this technique represents an effective longer-term strategy. Furthermore, weight-related conditions such as type 2 diabetes and obstructive sleep apnoea (OSA) often improve or even resolve following weight loss from bariatric surgery (one meta-analysis on bariatric surgery showed an 85% resolution rate of OSA). Given the central role of increased fat mass in the manifestation of PCOS, it is reasonable to hypothesize that weight loss following bariatric surgery would result in improvements in the features of PCOS. The meta-analysis by Skubleny and colleagues provides evidence to corroborate this hypothesis, with the incidence of PCOS reducing from a pre-bariatric surgery rate of 45.6% to 6.8% at 12-month follow-up. This improvement is certainly comparable to anecdotal experience of the authors.

Although bariatric surgery would appear to represent a highly effective treatment strategy for PCOS associated with obesity, there are important limitations that need to be considered. The first is that bariatric surgery could never represent a treatment option that is scalable to the population level. PCOS currently affects between 5 and 7% of reproductive-aged women, most of whom are also obese. The proportion of women in our population who are eligible for bariatric surgery on clinic grounds in our view will always far exceed the overall capacity for performing bariatric surgery. The situation is likely to get worse in future as the obesity epidemic ensues. Furthermore, PCOS is only one of a number of weight-related conditions that are amenable to improvements through bariatric surgery.

Secondly, age of patients needs to be considered. Bariatric surgery is generally only considered for adult patients, and it is rare to consider its usage in children under the age of 18 years, unless there is an exceptional clinical need. Our experience of bariatric surgery is very limited in adolescents, and the benefits versus risk assessment for bariatric surgery in this age group, even in the context of obesity-related PCOS, is far from clear on the basis of available evidence and cultural considerations. It is

difficult to envision that bariatric surgery will play a prominent role in the management of obesity-related conditions in adolescents in the near future.

Thirdly, implications for pregnancy need to be considered. Many women with PCOS have impaired fertility. Weight loss, including that through bariatric surgery, is likely to improve fertility. The weight loss-associated improvements in fertility need to be reconciled with the strict limitations on timing of pregnancy following bariatric surgery, which adds a further potential barrier to this form of weight loss in PCOS, particularly in those women who desire fertility.

To summarize, it is clear that weight loss through any means is usually an effective treatment strategy for obese women and girls with PCOS. Lifestyle change is challenging. Bariatric surgery can result in excellent outcomes but is limited for the reasons outlined above. It is hoped that bariatric surgery will play a more prominent role in the treatment of obese adult women with PCOS in the future given its utility. There is clearly a need for development of non-surgical effective weight loss strategies in obese PCOS, particularly in adolescent girls.

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37 Prevention and Treatment of Obesity and Metabolic Dysfunction in Children with Major Behavioral Disorders: Second-Generation Antipsychotics

Gloria Reeves and Linmarie Sikich

Introduction

Youth with serious mental illness are at increased risk of obesity compared to youth in the general pediatric population [1], partly due to metabolic side effects of second-generation antipsychotic (SGA) medication treatment. SGA are broadly prescribed to youth in both primary care and mental health treatment settings for management of psychotic and non-psychotic behavioral disorders. This chapter reviews metabolic adverse events associated with pediatric SGA treatment and possible mechanisms underlying SGA-induced obesity. Emerging pharmacologic and behavioral interventions to manage SGA-induced obesity are also discussed.

Historical Background

Chlorpromazine was the first antipsychotic medication marketed in the USA in the 1950s, and it was used as a "major tranquilizer" to target a variety of serious mental health conditions [2]. A dozen additional antipsychotic medications were introduced to the US market over the next 20 years [3]. This "first generation" of antipsychotic medications replaced damaging biologic treatments (e.g., frontal lobotomy surgery) and contributed toward the de-institutionalization of patients [4]. However, side effects of these first generation antipsychotics included painful and stigmatizing involuntary movements, including tremors, dystonic reactions, and dyskinesias. Conventional wisdom was that neurologic side effects were required in order for antipsychotic medications to be effective [5].

After a 15-year hiatus in new antipsychotic drug options, a truly novel antipsychotic medication called clozapine became available in the USA in 1990 [3]. Clozapine has a unique risk-to-benefit profile compared to first-generation antipsychotics because it does not cause extrapyramidal side effects and it has superior efficacy for treatment refractory psychosis [5]. Clozapine is referred to as an "atypical antipsychotic," and it ushered in an era of new antipsychotic medications referred to as "second-generation" antipsychotic (SGA) medications. Clozapine is not recommended for first-line treatment because of a potentially life-threatening immunologic side effect (agranulocytosis) but remains a recommended option for individuals with treatment refractory psychosis who are able to comply with frequent blood draws for safety monitoring.

Ongoing drug development sought to improve tolerability and therapeutic efficacy of antipsychotic medications. A first-generation

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Table 37.1 SGA with pediatric FDA-approved indications

Antipsychotic	Irritability due to autism	Bipolar I	Schizophrenia
Aripiprazole (Abilify®. Otsuka Pharmaceutical, Tokyo, Japan)[a]	X	X	X
Risperidone (Risperdal®, Janssen Pharmaceuticals, Beerse, Belgium)	X	X	X
Olanzapine (Zyprexa®, Eli Lily and Co, Indianapolis, IN, USA)[b]		X	X
Quetiapine (Seroquel®, AstraZeneca, Cambridge UK)		X	X
Asenapine (Saphris®, Merck, Kenilworth, NJ, USA)		X	
Paliperidone (Invega®, Janssen Pharmaceuticals, Beerse, Belgium)			X
Lurasidone (Latuda®, Sunovion Pharmaceuticals, Marlborough, MA, USA)			X

[a]Also has indication for treatment of Tourette's disorder
[b]Considered a second-line agent because of greater risk of metabolic side effects

antipsychotic medication called haloperidol served as the model for development of risperidone, and clozapine research led to development of olanzapine and quetiapine [3]. These three SGA were noted have much lower risks of involuntary movement side effects and did not cause agranulocytosis. Ongoing development of new SGA agents has continued.

Pediatric uptake of SGA medications was supported by advances in pediatric psychopharmacology research. The Food and Drug Administration (FDA) enacted regulations, including the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act, which served to increase pediatric research on medications with adult indications [6]. There are now SGA medications with pediatric approval for treatment of schizophrenia, manic/mixed episodes of bipolar I disorder, and irritability due to autism. Please refer to Table 37.1 for the list of pediatric approved SGA.

Pediatric SGA Treatment

Marked increases in SGA prescribing to youth started in the 1990s, influenced by availability of new agents, expanded FDA-approved indications, reduced risk of neurologic side effects compared to first-generation antipsychotics, and a general shift in child psychiatry treatment from psychoanalytic to a more medical approach. The National Ambulatory Medical Care Survey from 1993 to 2002 identified a sixfold increase in absolute number of outpatient visits that resulted in an antipsychotic prescription to youth [7]. A follow-up survey from 2005 to 2009 indicated that 31% of psychiatry appointments with youths involved an antipsychotic prescription, similar to adult psychiatry appointments [8]. Most pediatric antipsychotic treatment was for "off-label" treatment of severe aggression and irritability. Rapid increases in antipsychotic prescribing to Medicaid-insured youth plateaued in 2008 after increased scrutiny of high prescribing rates and strong evidence of metabolic adverse events associated with SGA treatment [9].

Summary Points

- SGA treatment of children and adolescents is common in community care and is primarily used to target non-psychotic conditions (aggression, irritability).
- SGA treatment of youth increased dramatically with availability of newer agents that were perceived to be safer because of lower risk of neurologic side effects.

Metabolic Side Effects of SGA Treatment

A 2004 consensus statement endorsed by the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity established that there were "clear-cut trends" regarding the relationship between SGAs and obesity/diabetes and made specific recommendations for universal metabolic monitoring for SGA-treated patients [10]. Baseline recommended assessments included personal/family history, weight/height, waist circumference, blood pressure, and fasting blood work (lipid profile, plasma glucose). The protocol recommended tracking BMI monthly for the first 3 months and then quarterly. Repeat fasting blood work and blood pressure were recommended at 3 months (glucose and lipids) and again annually (glucose), along with annual monitoring of waist circumference. The guidelines emphasized that more frequent monitoring may be required based on a patient's unique risk factors and initial safety monitoring data (e.g., presence of an abnormal lab result).

Pediatric SGA treatment trials reported that metabolic side effects began early in treatment and that risk varied among different SGA agents. The Treatment of Early Onset Schizophrenia Spectrum Disorders [11] was conducted from 2002 to 2006 as awareness of metabolic side effects was still emerging. Participants were randomized to double-blind treatment with olanzapine, risperidone, or molindone (a first-generation antipsychotic medication that is no longer available in the USA) for management of a schizophrenia spectrum disorder. After 8 weeks of treatment, olanzapine-treated youth gained an average of 6.1 kg (SD = 3.6) and 2.2 kg/m^2 increase in body mass index compared to risperidone-treated youth who gained 60% as much weight and molindone-treated youth who had no change in body mass index. Enrollment of olanzapine-treated youth was discontinued by the safety monitoring board after review of interim data, signaling a need for more pediatric research to study metabolic side effects of SGA treatment in growing children.

Weight Gain

Almandil and colleagues [12] completed a systematic review and meta-analysis of double-blind, placebo-controlled, randomized pediatric SGA trials that reported metabolic adverse effects. The authors identified 21 studies, with risperidone (14 trials) being the most widely investigated SGA. The three SGAs included in the review were associated with significant weight gain. Most studies assessed short-term weight gain over 6–8 weeks. Mean weight gain compared to placebo was 3.45 kg for olanzapine (95% CI 2.93–3.98), 1.77 kg for risperidone (95% CI 1.35–2.20), and 0.94 kg for aripiprazole (95% CI 0.65–1.24).

SGA-induced weight gain for specific pediatric clinical populations has been studied. A 2015 systematic review and meta-analysis of randomized trials for treatment of children, adolescents and young adults with psychotic disorders identified 19 antipsychotic medication trials [13]. These studies included 7 placebo-controlled and 12 head-to-head comparison studies with median treatment duration of 8 weeks. The median of mean study participant ages was 15.5 years old (11.0–24.5 years). Drugs studied in placebo-controlled trials included quetiapine, aripiprazole, risperidone, paliperidone, amisulpride, olanzapine, and haloperidol. In these studies, weight gain of >7% baseline weight was very common among antipsychotic-treated youth (RR = 3.62, 95% CI 1.29 to 10.17). Over all trials, antipsychotic-induced weight gain ranged from 0 to 4.3 kg over the first 6 weeks of treatment, with a median of mean weight change of 1.25 kg. The authors concluded that youth/young adults are more vulnerable to antipsychotic-induced weight gain than older adults.

A NIMH-funded study conducted by the Research Units on Pediatric Psychopharmacology (RUPP) network assessed short- and long-term weight gain after risperidone treatment of youth with autism. The study had three phases, including an 8-week placebo-controlled trial, 4-month open-label treatment for responders, and an 8-week double-blind, placebo-controlled, drug

discontinuation phase. The eligibility criteria restricted most co-treatment with other psychiatric medications (mood stabilizers were permitted if they were prescribed to treat a seizure disorder) so the design greatly minimized the potentially confounding effects of other psychotropic medication [14]. Weight gain at 1 month was predictive of weight gain at 6 months, and mean rate of weight gain of 1.4 kg/month over the acute trial decreased to 0.88 kg/month over the open-label treatment [15]. Of note, parent report of child excessive appetite was significantly higher among youth who continued on long-term treatment compared to those who discontinued the medication, suggesting that medication-induced satiety changes may persist beyond acute treatment [16].

Data on long-term weight outcomes with pediatric antipsychotic treatment are limited. Ronsely and colleagues [17] enrolled 130 antipsychotic-naïve youth who received non-randomized treatment (drug selection by prescriber) with either risperidone (54%) or quetiapine. A small subgroup of the original sample continued on their original medication and completed follow-up assessments at 6 months (22 quetiapine, 23 risperidone) and 1 year (20 risperidone, 17 quetiapine). Since youth are expected to gain weight as part of normal development, body mass index (BMI) z-score and BMI % weight classification (underweight, normal, overweight, obese) are used to describe if weight gain is unhealthy, i.e., exceeds expected trajectory for growth. Mean BMI z-score increased significantly from baseline for both groups at 6 months (risperidone 0.75; quetiapine 0.60) and 1 year (0.78 risperidone; 0.59 quetiapine), and approximately 40% of risperidone-treated and 50% of quetiapine-treated youth who remained on medication for 1 year became overweight/obese.

New-Onset Diabetes and Diabetic Ketoacidosis

Medication-induced T2DM is a rare pediatric treatment outcome. A Canadian national surveillance study identified 58 new pediatric cases of medication-induced T2DM over a 2-year period, which included two cases attributed to antipsychotic medication treatment [18]. A query of the FDA MedWatch Drug Surveillance system of pediatric risperidone adverse events from 1993 to 2002 identified ten adolescent cases of newly diagnosed diabetes [19]. In the Canadian sample, youth with medication-induced T2DM were less likely to be obese (at time of diagnosis) and less likely to have a family history of T2DM compared to youth with non-medication-related T2DM, but most of the medication-induced cases were attributed to glucocorticoid exposure [16].

A national observational study of Medicaid-insured youth with a mental health diagnosis compared new-onset T2DM among SGA initiators to non-SGA-treated youth over a mean 17-month follow-up period [20]. SGA treatment was associated with a 50% increase in T2DM risk. Co-treatment with stimulant medication, a drug that suppresses appetite, did not have protective effects on T2DM risk. An unexpected result of the study was that aripiprazole and ziprasidone treatment were associated with greater risk than risperidone treatment. Treatment occurred between 2003 and 2007, so prescribers may have been influenced by the 2004 ADA/APA consensus statement to preferentially treat high-risk youth with lower metabolic risk agents. Co-treatment with antidepressant medication was also associated with greater T2DM risk. This finding may be due to direct effects of the medication (e.g., increased appetite and weight gain) and/or association of depression with behavioral (e.g., sedentary lifestyle, substance use) and pathophysiologic changes (e.g., increased inflammation) that may increase obesity/diabetes risk.

A systematic review and meta-analysis by Galling and colleagues [21] investigated T2DM incidence among antipsychotic-treated youth compared with both a psychiatric comparison group and healthy controls after at least 3 months of medication exposure. Incidence of T2DM was three times higher compared to healthy controls and 1.8 times higher compared to psychiatric controls. Olanzapine treatment and duration of antipsychotic exposure were identified as modifiable risk factors for T2DM.

Pediatric diabetic ketoacidosis is a potentially life-threatening condition that can occur among youth with type 1 or T2DM; it is characterized by hyperglycemia, dehydration, hyperosmolarity, acidosis, and electrolyte disturbances [22]. Guenette and colleagues [23] reviewed reports of diabetic ketoacidosis associated with antipsychotic treatment. They identified 69 cases, three of which occurred in patients <18 years old. Two of the youth were treated with aripiprazole and one with olanzapine. Of note, a third of all cases were not associated with antipsychotic-induced weight gain, so weight monitoring alone is not an effective strategy to identify high-risk patients.

Dyslipidemia

A Bayesian meta-analysis of 41 short-term, controlled treatment trials (3–12 weeks) investigated metabolic adverse events for youth treated with aripiprazole, olanzapine, quetiapine, ziprasidone, and clozapine [24]. Over half of all medication-treated youth (59%) received risperidone or aripiprazole. Olanzapine and quetiapine were associated with a 20 mg/dL increase in triglycerides, and olanzapine and risperidone with a 2–4 mg/dL increase in glucose, during short-term treatment (sample sizes for clozapine trials with metabolic laboratory data were small so data are less conclusive).

Antipsychotic-naïve youth may be especially vulnerable to metabolic side effects. The SATIETY study [25] assessed metabolic outcomes in youth who received non-randomized SGA treatment (community provider recommended SGA treatment; youth whose parents opted against medication treatment served as the comparison group). After a median of 10 weeks of treatment, mean weight gain was with 8.5 kg with olanzapine, 6.1 kg with quetiapine, 5.3 kg with risperidone, and 4.4 kg with aripiprazole compared to 0.2 kg for untreated youth. Triglyceride levels significantly increased in all groups except aripiprazole and untreated youth, and the olanzapine and quetiapine groups also had significant increases in total cholesterol.

Summary Points

- SGA are associated with significant metabolic side effects, including increased blood sugar, dyslipidemia, and weight gain.
- SGA-induced new-onset diabetes during pediatric treatment is very rare, but metabolic changes detected after acute treatment (e.g., weight gain, dyslipidemia) increase risk of future diabetes and heart disease in adulthood.

Potential Mechanisms of SGA-Induced Side Effects

Energy Balance

Obesity is generally due to an imbalance in energy intake and expenditure. Energy expenditure includes physical activity and resting metabolic rate. SGA-induced weight gain is primarily attributed to increased food intake. Cuerda and colleagues [26] reviewed the effects of SGA on food intake, resting energy expenditure, and physical activity. SGA treatment was associated with increased food intake in most studies, with increased hunger, food cravings, and binge eating in specific studies that assessed these parameters. Physical activity was generally low in the studies reviewed, but most of the studies lasted 4 weeks or less so they may reflect acute sedation during drug initiation rather than sustained effects of drug on physical activity. Studies of resting energy expenditure have yielded conflicting results, possibly due to differences in the patient populations studied (age, clinical diagnosis, antipsychotic-naïve vs. chronic treatment). Only one study [27] included a sample of >10 youth. In this prospective investigation, overall resting energy expenditure of SGA-treated, antipsychotic-naïve youth followed up for 1 year was unchanged, but resting energy expenditure adjusted for body weight decreased significantly. This finding suggests that increases in fat storage exceeded increases in lean body mass.

Glucose Homeostasis

A highly controlled study of healthy adults exposed to brief SGA treatment indicates that SGA-induced changes in insulin sensitivity can be detected prior to significant increases in appetite and weight [28]. Non-mentally ill adults were randomized to brief treatment with olanzapine, aripiprazole, or placebo. Participants resided in an inpatient setting with supervised physical activity and standardized meals prior to an overnight fast. Participants were assessed using an euglycemic-hyperinsulinemic clamp study or mixed nutrient meal challenge in randomized order at baseline and after 9 days of blinded drug administration. Both the olanzapine- and aripiprazole-treated participants had significantly greater decreases in insulin sensitivity compared to placebo-treated participants measured by clamp study after short-term medication treatment. Only olanzapine-treated participants had significant increases in postprandial insulin, glucagon-like peptide-1, and glucagon after the mixed meal challenge. Thus, some SGA-induced metabolic changes may occur early in treatment and prior to weight gain. Early metabolic changes with olanzapine may be mediated through direct effects on insulin sensitive tissues.

Neurotransmitters

SGA that are associated with higher risk of obesity have high affinities for serotonin (5-HT2C, 5-HT1A), dopamine (D2), and histamine (H1) receptors [29]. Histamine affects food intake, energy expenditure, and lipolysis [30]. Histamine H1 receptor activation in the paraventricular and ventromedial nucleus of the hypothalamus induces satiety, so H1 antagonism increases food intake [31]. Of note, H1 receptor affinity corresponds with SGA obesity risk; H1 affinity is highest for the most obesogenic SGA (clozapine, olanzapine), intermediate for lower risk agents (risperidone, quetiapine), and lowest for SGA least likely to cause obesity (ziprasidone, aripiprazole). Betahistadine, a combined H1 agonist/H3 antagonist, is being studied as an emerging experimental strategy to reduce SGA-induced weight gain [31].

Serotonin 5-HT2C receptor activity antagonism is implicated in both obesity and diabetes risk of SGA treatment. The FDA-approved anti-obesity medication lorcaserin is a 5-HT2C agonist [32]. Dopamine D2 receptor activity may influence reward/motivation related to eating behaviors and may play a role in development of compulsive eating [33]. Aripiprazole, a SGA with lower risk of obesity, has partial D2 agonist properties [34].

Hormones

There are several gut hormones that provide feedback to the brain on energy state, including ghrelin, peptide YY, glucagon-like peptide 1, oxyntomodulin, glucagon, amylin, cholecystokinin, and pancreatic polypeptide [35], providing several avenues of investigation for possible SGA mechanisms of obesity. Ghrelin is the only known orexigenic gut hormone, i.e., this hormone signals "hunger" [35]. Ghrelin also has been implicated in stress-induced food reward behaviors [36]. In one study, ghrelin levels differed among healthy controls and youth treated with olanzapine and clozapine (healthy controls > clozapine treated > olanzapine treated), and differences remained significant after adjusting for age and BMI, suggesting that SGA may induce direct changes in ghrelin pathways independent of weight gain [37]. Zhang and coworkers [38] report that ghrelin responses may change over the course of SGA treatment, with an initial increase in ghrelin, followed by secondary decrease after weight gain, and then a final increase to reach a new equilibrium.

Leptin, a peptide hormone secreted by adipocytes, has opposite effects of ghrelin on appetite, i.e., signals satiety [39]. It has been hypothesized that SGA may cause leptin resistance, which would lead to weight gain [40]. The NIMH Research Units on Pediatric Psychopharmacology (RUPP) autism network trials (N = 225) determined that leptin promotor gene variability was independently associated with weight gain risk after 8 weeks of risperidone treatment [41].

Antipsychotic medications increase levels of the pituitary hormone prolactin through dopamine D2 receptor blockade. Hyperprolactinemia varies among agents (risperidone > ziprasidone, olanzapine > aripiprazole, quetiapine, clozapine) and is highest among medications with greater dopamine D2 affinity, low lipophilicity, and high peripheral-to-central dopamine D2 receptor occupancy ratio [42]. In one study of antipsychotic-naïve youth treated with risperidone, risk for hyperprolactinemia was also influenced by patient factors, including gender, pubertal stage, psychiatric disease, and personal/family history of autoimmune disorders [43]. Antipsychotic-induced hyperprolactinemia is known to cause sexual side effects, including gynecomastia, amenorrhea, and galactorrhea, and increased bone demineralization. However, altered prolactin levels may also effect metabolic functioning. Hyperprolactinemia can increase fat mass by stimulating lipogenesis in adipose tissue, reducing CNS dopaminergic tone, altering other pituitary axes to cause hypothyroidism, and disrupting circadian neuroendocrine activities in the hypothalamus [44]. Preliminary studies suggest that metformin may lower prolactin levels among antipsychotic-treated patients [45], and the prolactin-releasing peptide receptor has been proposed as a novel target for obesity treatment [46].

Inflammatory Factors

Long-term antipsychotic treatment is associated with immune system changes, including *decreased* expression of inflammatory cytokines (e.g., IL-6), nitric oxide release, reactive oxygen species (oxidative stress markers), and microglia activation, as well as *increased* anti-inflammatory cytokines (e.g., IL-10) and S100 B (marker for astrocyte activity) [47]. Inflammatory cytokines, along with satiety hormones leptin and insulin, provide central signaling of adiposity to the hypothalamus, so reduced inflammatory cytokines alters anorexigenic responses [47]. Since inflammatory changes may be associated with different psychiatric conditions, independent of drug exposure, research is needed in specific pediatric populations to better understand the impact of drug-induced inflammatory outcomes on different metabolic outcomes.

Gut Microbiota

The gastrointestinal system is inhabited by trillions of microbes that interact with their host through a complex ecological system that influences health [48]. Gut microbiota have been suggested to play a role in etiology of obesity through hormonal, metabolic, and inflammatory processes that notably target adipose tissue, the hypothalamus, and the liver [49]. Normal variation in gut microbiota is influenced by age, environment, diet, and genetics; in disease states variation in the microbiome is affected by medication exposure and physiological state of the host [48].

In animal studies, SGA treatment with olanzapine has been associated with a shift toward an "obesogenic" microbial profile beyond the effect of high-fat diet consumption [50]; the altered microbiota profile appears to occur in both genders [51]. In one pediatric study, chronic risperidone treatment was associated with a gradual decrease in the *Bacteroidetes*/*Firmicutes* ratio compared to psychiatric controls, and magnitude of differences was greatest when comparing youth with SGA-induced weight gain to controls [52]. While pediatric studies are very limited in this emerging field and there is considerable inter-individual variation in gut flora, this area of research suggests that gut environment may be a potential target for future interventions (e.g., dietary, antibiotic strategies) to reduced SGA-induced weight gain.

Pharmacogenetics

Pharmacogenetic research is critical to develop an understanding of inter-individual variation of adverse drug events and to identify predictors of drug outcomes. Zhang and coworkers [53] completed a systematic review and meta-analysis

of pharmacogenetic associations of antipsychotic-induced weight gain. They reported that 13 single nucleotide polymorphisms (SNPs) from nine genes were significantly associated with antipsychotic-induced weight gain; these included the serotonin 2C receptor (*HTR2C*), the dopamine 2 receptor (*DR2*), the alpha adrenergic receptor (*ADRA2A*), the melanocortin 4 receptor (*MC4R*), and the g protein beta 3 subunit (*GNB3*). The most consistent evidence was associated with the serotonin HTR2C receptor gene. The *HTR2C*, *DRD2*, and *MC4R* genes have all been implicated in the brain's reward circuitry and feeding behaviors [29]. The *ADRA2A* gene has been implicated in the inhibition of lipolysis in adipose tissue. There have also been some positive association findings regarding polymorphisms in the leptin (*LEP*), leptin receptor (*LEPR*), and cannabinoid 1 receptor (*CNR1*) genes [54], but these did not replicate in the above meta-analysis, which included more studies.

There are limited pharmacogenetic studies in youth investigating antipsychotic-induced weight gain. Cote and coworkers [55] studied a variant in the catechol-O-methyltransferase (*COMT*) gene, which is known to be associated with adult hypertension. The investigators completed genotyping of a sample of youth treated with a variety of SGA and youth with no SGA exposure. SGA-treated youth with a Met allele had high blood pressure and fasting glucose compared to SGA-treated youth with the Val/Val genotype. This association between genotype and metabolic parameters was not observed in the sample of SGA-naïve youth, suggesting a drug-gene interaction.

Most other pharmacogenetics studies of SGA-induced weight gain have been conducted among risperidone-treated youth with autism. In a study by del Castillo and coworkers [56] of 124 autistic youth treated with risperidone for a mean of 2.8 years, there were no differences in weight gain susceptibility based on variation in 759C/T variants in the promoter region of the 5HT2C receptor gene. The results may have been influenced by polypharmacy treatment, since 73% of youth were co-treated with stimulants, 51% with SSRI antidepressants, and 31% with alpha agonists. Stimulants and alpha agonist medications are known to affect cardiometabolic parameters, including blood pressure and pulse. In a small sample of 45 risperidone-treated youth with autism, *CYP2D6* polymorphisms were found to be associated with SGA-induced increases in BMI or waist circumference [57]. The *CYP2D6* liver enzyme metabolizes risperidone to its active metabolite 9-OH-risperidone, and there is considerable variability in the population in terms of protein activity, ranging from ultra-rapid metabolizers to poor metabolizers. Thus, larger studies are needed to investigate pharmacogenetics of SGA-induced obesity in cohorts of youth with different clinical disorders and different SGA drug treatments in order to support identification of clinically meaningful genetic predictors of SGA-induced obesity.

Summary Points

- SGA treatment is associated with complex changes in hormonal, immunologic, and biochemical processes that affect metabolic health outcomes.
- Pharmacogenetics research may help to identify predictors of SGA metabolic side effects and support personalized care treatment strategies to reduce risk.

Clinical Management of SGA Metabolic Side Effects

Metformin

Metformin is the most widely studied pharmacologic intervention for prevention and treatment of SGA-induced obesity. Metformin is a first-line treatment for management of type 2 diabetes and is a commonly prescribed "off-label" treatment for obesity in the general population. Metformin's effect of increasing insulin sensitivity is thought to be critical to stabilizing or reducing obesity [58]. In an animal study of metformin co-treatment with olanzapine, metformin treatment was effective in reducing hepatic insulin resistance but not peripheral insulin resistance. This observation suggests that combination therapies

to improve insulin sensitivity may be necessary for some patient subgroups [59].

Two recent reviews investigated metformin as a strategy to manage antipsychotic metabolic side effects. De Silva and coworkers [60] studied metformin for both prevention and treatment of antipsychotic-induced weight gain. The authors included 12 studies with double-blind weight gain outcome assessment in the meta-analysis and reported significant reduction in BMI and insulin resistance, but not fasting glucose, among metformin-treated patients compared to placebo-treated patients. Mean weight difference between the metformin and placebo groups was −3.27 kg. Interestingly, in adult studies, weight loss with metformin accounted primarily for this weight difference, whereas, in the pediatric studies, the between-group weight differences were primarily due to increases in weight in the placebo group (i.e., weight gain stabilized in the metformin-treated group). Significant between-group changes in BMI favoring reduced BMI in the metformin group were seen in both the adult and pediatric studies. Zheng and coworkers [61] completed a meta-analysis of 21 studies of metformin for antipsychotic metabolic side effects. Metformin was superior to placebo in improving body weight, BMI, fasting glucose, fasting insulin, triglycerides, and total cholesterol. Gastrointestinal side effects were more common in the metformin-treated group, including nausea/vomiting (14%) and diarrhea (7%), though these seldom led to treatment discontinuation.

Pediatric metformin studies have yielded promising results for modest reduction in BMI z-score compared to placebo-controlled groups. A 12-week, open-label trial of metformin to manage SGA-induced obesity was conducted by Shin and coworkers [62] in a small sample of 11 youth. Mean triglyceride values decreased significantly, but there were no significant changes in weight, BMI, or glucose. Klein and colleagues [63] completed a 16-week parallel, double-blind, placebo-controlled trial of metformin for 39 youth who had >10% baseline weight gain with olanzapine, quetiapine, or risperidone treatment. Weight remained stable in metformin-treated subjects, in contrast to placebo-treated youth who continued to gain weight, resulting in a significant difference in weight between the metformin-treated and placebo-treated subjects. A similar multicenter, 16-week, double-blind, placebo-controlled trial targeting antipsychotic-associated weight gain was recently conducted in 61 youth with autism spectrum disorder [64]. This trial reported significant between-group differences in weight and BMI z-score with the metformin group showing a minimal increase in weight (0.07 kg) and the placebo group showing a significant increase (2.80 kg) producing a between-group difference of −2.73 kg (−4.04 to −1.43 kg). The BMI z-score significantly decreased in the metformin group (−0.08) and nonsignificantly increased in the placebo group (0.02) for a between-group difference of −0.10 (−0.16 to −0.04). No treatment discontinuations were caused by adverse gastrointestinal effects, but participants in the metformin group experienced gastrointestinal effects on about 25.1% of treatment days compared to 6.8% of treatment days in the placebo group ($P = 0.005$).

Metformin safety has been reviewed in treatment of non-diabetic pediatric obesity. A meta-analysis by Bouza and coworkers [65] of nine adolescent trials (six studies were for 6 months) reported no significant difference in adverse events in metformin (33%) versus placebo (32%) treatment conditions or withdrawal due to adverse events (2.7% versus 2.5%, respectively). Differences in gastrointestinal adverse effects between the two groups did not reach statistical significance. Prevalence of gastrointestinal side effects among youth in psychiatry clinical trials may differ related to the psychiatric illness, drug interactions from polypharmacy treatment, and/or duration of the study. A review of pediatric obesity treatments by Boland and coworkers [66] reported that there were no cases of lactic acidosis in metformin pediatric clinical trials; however, one study identified a significant reduction in B12. Co-treatment of metformin with a B12-containing multivitamin is recommended, especially for youth receiving chronic treatment.

The effect of metformin on lipid parameters for SGA-treated patients is less clear compared to effects on weight and glucose homeostasis. Baptista and colleagues performed several small placebo-controlled studies lasting 12–14 weeks in adults treated chronically with clozapine ($n = 54$)

[67] or olanzapine (n = 72) [68] or to prevent weight and metabolic adverse effects in patients transitioning from a first-generation antipsychotic to olanzapine (n = 37) [69]. Only the trial in individuals treated chronically with clozapine reported significant between-group differences in any lipid measures. In that study, the metformin group showed improved (increased) HDL cholesterol compared to the placebo group at both weeks 7 and 14. At week 14, the triglyceride-to-HDL cholesterol ratio was improved (lower) in the metformin group compared to the control group. A more recent study by Wu and coworkers [70] included pooled data from two randomized controlled trials conducted at the same site in China evaluating the impact of 24-week metformin or placebo treatment in 201 adults who had developed dyslipidemia during the first year of antipsychotic medication and continued treatment with the same antipsychotic throughout the studies. The primary outcome measure was the proportion of the sample who had dyslipidemia defined by LDL cholesterol ≥3.37 mmol/L (130 mg/dL) at 24 weeks; the proportion was significantly lower in the metformin group (25.3%) than in the placebo group (68.4%, $P < 0.001$). In a mixed model analysis, significant between-group differences in lipid concentrations emerged for HDL cholesterol at week 12, whereas at week 24, all lipid comparison significantly favored metformin. Further investigation, which included changes in insulin resistance as a covariate, demonstrated that the between-group HDL cholesterol differences disappeared but that the between-group differences for all other lipid measures remained significant. This suggests that only HDL cholesterol changes are directly mediated by improvements in insulin sensitivity. The difference between this study and those done by Baptista's group may reflect this study's larger sample size, racial or ethnic differences, or difference in the duration of the studies.

Behavioral Strategies

Unfortunately, there are very limited pediatric evidence-based behavioral weight loss strategies to guide treatment of SGA-induced obesity among youth with mental illness. A 2010 updated review by the US Preventative Services Task Force [71] on pediatric weight loss interventions identified only 11 fair- to good-quality behavioral studies, with only three studies that had >40 youth per treatment condition at follow-up. Pediatric weight loss or obesity prevention strategies need to address the specific needs of the individual (e.g., concentration/impulse control difficulties, discomfort with social/group format, poor frustration tolerance, social/developmental delay) and his/her family (high appointment burden, parent-child conflict with behavior changes, competing priorities for mental health and physical health concerns). Additionally, healthy dietary changes may be difficult for low-income parents who are trying to provide enough food for their child (who has increased appetite) and their family on a limited budget. A small survey of parents of obese youth with mental illness reported significant barriers to weight loss, including the child's strong preference for energy dense food and dislike of physical activity [72]. Emerging behavioral weight loss strategies have been developed for SGA-treated youth using brief motivational interviewing to prevent weight gain [73] and a family-based treatment to promote weight loss [74].

Non-pharmacologic strategies tested primarily in adults to reduce SGA-induced appetite changes include diet regimens that are less restrictive on calorie intake and encourage satiety (e.g., low carbohydrate, high fat), targeting thirst to reduce sugar-sweetened beverage intake that may be triggered by anti-cholinergic side effects and reducing/eliminating cannabis use [75]. Adult behavioral interventions studied in randomized trials have included nutritional, exercise, and cognitive behavioral therapy interventions [76].

Future Directions

Given the challenges of reducing SGA-induced obesity, strategies that integrate behavioral

and pharmacologic approaches that are feasible for families of youth with mental illness are greatly needed. The NIMH-funded IMPACT study (Improving Metabolic Parameters of Antipsychotic Child Treatment [77]) completed enrollment in an open-label, randomized trial of healthy lifestyle education plus: (1) metformin treatment, (2) switch antipsychotic medication to a lower risk agent, or (3) no pharmacologic changes. This study included youth with non-psychotic conditions (e.g., severe mood dysregulation), so results will help to inform treatment of youth who most often receive SGA treatment in community care.

New pharmacologic strategies to manage SGA-induced weight gain are rapidly emerging, including studies of glucagon-like peptide-1 agonists, betahistine, and omega 3 fatty acids. Additionally, recently FDA-approved SGA medications (e.g., lurasidone, asenapine) are being studied to determine if any of these agents have lower metabolic side effect risks.

Finally, public policy changes have been enacted to reduce inappropriate SGA treatment of youth. Over 30 state Medicaid programs have implemented pediatric antipsychotic prior authorization programs [78]. These programs can help providers optimize the use of alternative treatment resources for youth who do not meet an appropriate clinical threshold for antipsychotic treatment and to provide resources on safety monitoring for youth who require ongoing medication treatment.

Summary Points

- Metformin treatment of SGA-induced obesity is generally well tolerated and limits weight gain or promotes modest weight loss.
- Combined behavioral-pharmacological strategies are needed to optimize obesity prevention and management for youth who require chronic SGA treatment.
- Obesity prevention strategies for youth are critical since SGA metabolic changes occur early in treatment and youth appear to be more vulnerable to metabolic side effects than adults.

Conclusions

SGA treatment of youth is common in community care. Metabolic side effects are concerning because of the potential impacts on diabetes and heart disease risk. Metabolic side effect outcomes are influenced by a variety of patient (diagnosis, baseline obesity risk), treatment (drug choice, dose and duration of treatment), and environmental (access to healthy food options and opportunities for physical activity) factors. The complex biologic determinants of body weight provide several options for investigation of new treatments that address malleable environmental and biologic targets for obesity prevention and treatment.

Editor's Comments and Question

Obesity is typically characterized by a pro-inflammatory profile; see Chap. 22 by Drs. Alwarawrah and MacIver. Pro-inflammatory cytokines reduce food intake; thus increases in inflammatory cytokines in childhood and adult obesity may represent an adaptive response to prior weight gain.

It is remarkable that treatment with second-generation antipsychotic agents is accompanied by *reductions* in proinflammatory cytokines (IL1, IL2, IL6, IL6R, and TNFα) and increases in anti-inflammatory cytokines like IL10. Reductions in inflammatory cytokines are postulated to provide neuroprotection in children with mental illness, at the expense of increases in food intake and weight gain[a]. Interestingly, there is emerging evidence that metformin also has anti-inflammatory and anti-apoptotic properties in the nervous system[b,c] and thus might combine neuroprotection with weight control.

What is the role of neuroinflammation in the pathogenesis of childhood schizophrenia and other childhood mental illnesses?

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Authors' Response

Evolving research suggests that several neuropsychiatric disorders, including schizophrenia, may be associated with immune system dysregulation[a–d]. Some have postulated that immune system dysregulation may play a pathogenic role by impacting synapse development and refinement[e]. Others have argued that the co-occurrence of neuropsychiatric illness and immune system dysregulation may reflect some shared underlying genetic vulnerability, such as serotonergic gene dysregulation. The relationship between inflammation and childhood-/early-onset psychopathology could also be mediated by shared environmental exposures. For example, higher levels of prenatal and childhood social adversity are associated with higher levels of C-reactive protein in adulthood[f] and are also well-known risk factors for the development of schizophrenia. Similarly maternal immune activation has also been shown to heighten immune responses in offspring and is a risk factor for both autism spectrum disorders and schizophrenia.

Altered inflammatory processes may be associated with core symptoms shared by multiple psychiatric disorders. For instance, both autism and schizophrenia involve disordered social cognitive processing. A study of healthy individuals showed that administration of endotoxin caused worsening on a social cognition task[g]. There is some evidence that cytokine receptors and key neurotransmitter receptors including the NMDA glutamatergic receptor and the DRD2 dopamine D2 receptor may form heterodimers; cytokines binding to cytokine receptors may physically interact with the neurotransmitter receptor portion of the heterodimer, thus subtly altering the level of neurotransmitter activation[h].

Although there is evidence of immune dysfunction in many childhood-onset psychiatric disorders, the particular immune components as well as the alterations at various stages of illness often differ among disorders and sometimes across research labs. In some cases, specific markers correlate with the severity of specific symptoms. For example, a recent review by Bjorklund and colleagues[b] outlines the complex association of autism with alterations in a range of immune cell types, including T cells, B cells, granulocytes, natural killer cells, monocytes, and innate cells. Plasma levels of IL-6, IL-8, and IL-1ß are increased among youth with autism, and levels of these inflammatory cytokines correlate with severity of some behavioral and communication symptoms[i].

Novel immunomodulatory factors, including intravenous immunoglobulin (IVIG), macrophage activating factor,

antioxidant compounds, and anti-inflammatory agents, are being investigated for many psychiatric disorders, with autism being the most frequently studied in childhood[d]. The effect of psychiatric medications on inflammatory processes in childhood is challenging to study because it may be influenced by many factors, including underlying somatic conditions (e.g., history of atopy, asthma), co-prescribed medication, psychiatric comorbidity, concurrent substance use, and developmental/pubertal phase. Drugs used to treat a particular disorder may also have differing effects on inflammation. For example, treatment with the antidepressant medication fluoxetine is associated with decreased pro-inflammatory cytokines IL-6 and TNF-a, whereas treatment with the antidepressant medication mirtazapine increases these levels[j]. In a study comparing antipsychotic-naïve, first-episode psychotic patients with carefully matched healthy controls, patients with psychosis had inflammatory and growth factor markers consistent with low-grade inflammation at baseline; symptom improvement after treatment was accompanied by reductions in IL-2, IL-4, and endothelial growth factor[k]. The development of antipsychotic-induced weight gain, despite a reduction in inflammatory factors, may reflect complex processes whereby an antipsychotic medication may promote obesity through multiple pathways (e.g., direct effects on glucose homeostasis and on central regulation of appetite). Future studies on drug-induced inflammatory changes are needed to better characterize the effects of specific medications on specific patient subgroups and to identify how drug development can be enhanced to reduce metabolic adverse events associated with treatments.

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Bariatric Surgery in Adolescents

38

Daniel Relles and Jeffrey L. Zitsman

Introduction

Extreme obesity is defined as a body mass index (BMI) that is 120% greater than the 95th percentile for age and gender. According to the most recent Centers for Disease Control and Prevention (CDC) data from 2011 to 2014, the prevalence of obesity and extreme obesity among children and adolescents in the United States was 17 and 5.8%, respectively [1]. The rate of obesity in teenagers is as high as 20% and has increased over the past 40 years [2]. The consequences of this public health crisis include both immediate and long-term effects: obese children are more likely to develop type 2 diabetes mellitus (T2DM), fatty liver disease, and focal glomerulosclerosis and are at higher risk of cardiovascular complications if they remain obese as adults.

Lifestyle-, behavior-, and family-based weight loss programs have moderate success at best in producing long-term results in children [3, 4]. Success rates range from 2 to 20% for weight loss maintenance based on lifestyle changes without surgery [5, 6]. One recent review found an attrition rate of 27–73% for pediatric weight management programs [7].

Comorbidities frequently associated with overweight and obesity in adolescence include insulin resistance, T2DM, metabolic syndrome, hypertension (HTN), dyslipidemia, steatohepatitis, pseudotumor cerebri, obstructive sleep apnea (OSA), polycystic ovary syndrome, depression, and low self-esteem. The benefits of weight loss to teenagers with obesity include resolution of comorbidities and normalization of the cardiovascular risk profile. Although some have voiced concern that early weight loss surgery (WLS) in prepubertal children would negatively impact growth trajectory and bone maturity, several studies have demonstrated that these children attain normal height [8–11].

Adolescents with obesity who successfully lose weight are likely to have continued health benefits into adulthood [12]. Similarly, those who have obesity as children but are nonobese as adults have no greater risks of T2DM, HTN, and dyslipidemia than those who never had obesity [13]. Given the modest results of nonsurgical strategies of weight loss in children and adults alike, the abundance of positive results in adults who undergo weight loss surgery argues in favor of its utility in a younger population.

In the adult population, bariatric surgery has been demonstrated to be an effective weight loss strategy in the appropriate patient [14–25]. For

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example, T2DM remits in as many as 70% of patients, and HTN improves in 40% [26, 27]. In teenagers, improvements in obesity-related comorbidities may exceed those in adults [28–30]; see the section on Patient Outcomes. Multiple studies demonstrate greater efficacy of bariatric surgery than diet and exercise in obese adolescents [28, 31–34], underscoring its value as an effective therapy for weight loss.

Preoperative Considerations

Patient Selection

Criteria for adult weight loss surgery in the United States were developed in 1991 by the National Institutes of Health. Guidelines for adolescents were initially proposed in 2003 with stricter criteria, in part because Roux-en-Y gastric bypass (RYGB) was the main operation that was being performed at that time. As experience with RYGB and the eventual introduction of laparoscopic adjustable gastric banding (AGB) in adolescents provided additional outcome data, the criteria were revised. Recent best-practice guidelines for weight loss surgery in adolescents (defined by the WHO as aged 10–19 years) consider potential candidates to be those with BMI of 35 kg/m^2 or higher with serious comorbidities (T2DM, moderate or severe OSA, pseudotumor cerebri, and/or severe steatohepatitis) *or* with BMI of 40 kg/m^2 in the presence of other comorbidities (mild OSA, HTN, insulin resistance, glucose intolerance, dyslipidemia, and/or impaired quality of life or activities of daily living) (Table 38.1) [35–37]. Other eligibility criteria include physical maturity (Tanner stage IV or above and skeletal maturity) and appropriate psychosocial attributes (Table 38.2) [35, 38, 39].

Table 38.1 Candidates for adolescent obesity surgery

BMI > 35 kg/m^2 with severe comorbidity
Type 2 diabetes mellitus
Moderate or severe obstructive sleep apnea
Pseudotumor cerebri
Severe steatohepatitis
BMI > 40 kg/m^2 with other comorbidities
Mild obstructive sleep apnea
Hypertension
Insulin resistance/glucose intolerance
Dyslipidemia
Steatohepatitis
Venous stasis
Panniculitis
Urinary incontinence
Gastroesophageal reflux
Weight-related arthropathies
Severe psychosocial distress
Impaired quality of life/activities of daily living
Candidates should also (must satisfy all):
Have attained >95% of adult stature
Failed previous organized weight loss attempts
Commit to psychological pre- and postoperative evaluation
If psychiatric condition is present, it is under treatment
Agree to avoid pregnancy for at least 1 year postoperatively
Commit to nutritional guidelines postoperatively
Demonstrate decisional capacity to give informed assent
Have a stable and supportive home environment

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Preoperative Assessment (Table 38.3)

A multidisciplinary team is necessary for evaluation of an obese child who is interested in surgical options. This team should include an experienced bariatric surgeon, a pediatric specialist (endocrine, gastroenterology, nutrition, or adolescent medicine), a registered dietician, a mental health specialist (psychiatrist, psychologist, or social worker), a program coordinator, and an exercise physiologist or therapist [36]. The American Society of Metabolic and Bariatric Surgery (ASMBS) suggests that procedures be performed at surgical review committee centers of excellence. Because adolescent bariatric surgery requires expertise in both pediatric medicine and bariatric surgery, numerous programs in the United States have been established in medical centers with both adult and pediatric patients. This allows

Table 38.2 Suggested attributes of a "good" adolescent bariatric candidate

- Patient is motivated and has good insight
- Patient has realistic expectations
- Family support and commitment are present
- Patient is compliant with healthcare commitments
- Family and patient understand that long-term lifestyle changes are needed
- Patient agrees to long-term follow-up
- Decisional capacity is present
- Weight loss attempts are well documented and at least temporarily successful
- No major psychiatric disorders are evident that may complicate postoperative regimen adherence
- No major conduct/behavioral problems are noted
- No substance abuse has occurred in the preceding year
- No plans for pregnancy are present in the upcoming 2 years

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the pediatric surgeons to partner with adult WLS programs to integrate resources and expertise, thereby reducing costs and improving outcomes [35]. This also enables a smooth transition of the adolescent patients to the adult WLS program, as these patients require lifelong postoperative monitoring. It is also recognized that freestanding children's hospitals with appropriate resources whose surgeons have expertise with weight loss surgery can provide safe and effective care.

The preoperative evaluation begins with a thorough history and physical examination, including an assessment of eating habits and behavior, activity and exercise levels, and a detailed family history. Additionally, the team must identify and manage secondary causes of obesity including genetic, neurologic, psychological, drug-induced, and endocrine disorders. Comorbidities of obesity should be identified, including T2DM, HTN, cardiomyopathy, proteinuria, dyslipidemia, OSA, musculoskeletal

Table 38.3 Preoperative recommendations for sleeve gastrectomy

	Routine	Selective	Not recommended
Labs	CBC, BMP, LFTs, albumin, HbA1c, INR/PT/PTT, TSH, vitamin B1, vitamin B12, vitamin D, micronutrients, urinalysis, urine βHCG (females)	*H. pylori*, urine nicotine, urine toxicology screen	
Screening	OSA, malignancy (age/gender dependent), functional status, smoking, substance abuse		
Diet	Liquid diet 1–2 weeks preop		Mandatory preoperative weight loss, routine bowel prep
Consults	Nutrition, psychology	Anesthesia, cardiology, endocrine, gastroenterology, hematology, infectious disease, nephrology, neurology, OB-GYN, orthopedics, pain medicine, pulmonary, pharmacy, rheumatology, sleep medicine, urology	
Testing	EKG, CXR	Endoscopy, UGI series, pH/manometry, DEXA scan, sleep study, colonoscopy, mammography, ultrasound, gastric emptying study	Routine IVC filter placement

From Telem D. The American Society for Metabolic and Bariatric Surgery: Care Pathway Development for Laparoscopic Sleeve Gastrectomy [Internet]. 2016 Sept. https://asmbs.org/wp/uploads/2016/09/Telem-et-al_LSG-Pathway_2016_Final.pdf

complaints, menstrual irregularities, polycystic ovary syndrome, and psychiatric sequelae. Any significant findings warrant subspecialty referral for evaluation and treatment.

Laboratory values commonly sought as part of the preoperative evaluation include a complete blood count, comprehensive metabolic panel, fasting and postprandial glucose levels, glycosylated hemoglobin (hemoglobin A1c), lipid panel, and urinalysis. We also recommend checking serum levels of vitamin D, thiamine, folic acid, and iron. Female patients should have pregnancy testing. We recommend sleep studies to evaluate for OSA and cardiology consultation with echocardiogram for any patient diagnosed with moderate to severe OSA or hypertension. Patients with glucose intolerance should be evaluated by endocrinologists. Proteinuria is an indication for nephrology consultation. Transaminitis (transaminases double the upper limit of normal) should prompt a gastroenterology evaluation. Preoperative imaging includes abdominal ultrasound and a bone age study. Patients with dysphagia or symptoms of gastroesophageal reflux disease (GERD) undergo endoscopy as well. Routine contrast esophagram requires greater radiation exposure in obese patients and need not be performed in the absence of symptoms or indications from the medical history.

When the patient and family decide to proceed with WLS, the preoperative assessment has been completed, and the patient is deemed an appropriate candidate; an operative date is set. Patients are put on a preoperative 2-week liquid, high-protein diet. They must fast on the day of surgery and should be instructed to bring their own continuous positive airway pressure machine to the hospital with them if they use one at home. Patients with diabetes mellitus (either type 1 or type 2) requiring >100 units of insulin per day require careful management during the fasting period on the day of surgery; early admission may be considered. Similarly, patients with severe cardiac disease may require preoperative admission to change medications from oral to parenteral delivery. Patients are advised that they should expect to be able to return school or work within 2 weeks of surgery and will be advised to avoid strenuous activity for the first 4–6 weeks in the postoperative period.

Consent

Informed consent for any surgical procedure includes a discussion of surgical options, risks, benefits, and alternative approaches. The surgical options are reviewed in detail, including a description of each procedure and the expected possible perioperative risks, in the context of the expected benefits of weight loss and resolution of comorbidities. Discussion of the alternatives should include members from the multidisciplinary team and must address the expected consequences of untreated obesity, including increased risk of adult obesity and associated comorbidities, parental obesity, and prolonged exposure to obesity in childhood [35].

Although the parent or guardian of any patient under 18 years old will sign the consent paperwork, the discussion must include the patient and confirm his or her assent [37]. The family and the adolescent must have similar interest in WLS and understanding of the expected outcome. The adolescent is assessed regarding the capacity to participate in an informed decision process. Evidence of coercion from the guardians is a “red flag” and must be discussed and addressed by the team.

Surgical Approaches

Bariatric procedures were historically considered to reduce weight by two general mechanisms: restriction and malabsorption. The restrictive component reflects the reduced volume the stomach can tolerate postoperatively, hastening satiety and limiting caloric intake. The malabsorptive component reflects the reduced amount of the small bowel that is exposed to gastric contents in combination with pancreaticobiliary digestive secretions. Historically, the adjustable gastric band (AGB) and sleeve gastrectomy (SG) were viewed as purely restrictive procedures, while Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD)

comprised both restriction and malabsorption. Recent investigations, however, suggest that weight loss with SG (and BPD which includes SG) and RYGB is achieved not only through restrictive effects but at least in part through gastric resection, which affects the secretion of gastrointestinal hormones such as ghrelin, peptide YY (PYY), glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide 1 (GLP-1) (Table 38.4).

For example, plasma levels of ghrelin, an orexigenic hormone produced largely in the fundus of the stomach, may be decreased [40], although studies have not demonstrated consistent results. The rise in ghrelin that normally accompanies weight loss or calorie restriction may be blunted with gastric resection or diversion of nutrients.

PYY and GLP-1 are anorexigenic peptides that are co-secreted by L cells in the terminal ileum. They promote satiety and inhibit food and water intake. Plasma levels of PYY and GLP-1 have been shown to increase as soon as 2 days after RYGB and may be sustained at 1 year post-op. Similarly, following SG, PYY and GLP-1 levels are increased, although to a lesser extent compared to RYGB. The mechanism for this increase is not completely understood. In contrast, weight loss through nonsurgical methods has been shown to have no effect on or to decrease PYY and GLP-1 levels. Postsurgical changes in ghrelin, GLP-1, and PYY likely support long-term weight loss [40].

The impact of gastrointestinal hormones on satiety, food intake, hunger, and subsequent weight loss following WLS is a topic of ongoing research and may help clinicians understand the mechanism of weight loss related to each different procedure; see also Chap. 3 on GI Hormones.

Table 38.4 Summary of weight loss method effects on gastrointestinal hormones

Procedure	Ghrelin	PYY	GLP-1
Nonsurgical weight loss	↑	– or ↓	– or ↓
SG	↓	↑	↑
RYGB	Variable	↑	↑
AGB	Variable	–	–

↑ Increased, ↓ Decreased, – No change

Surgical Procedures

The ASMBS provides estimates of the numbers of each type of bariatric procedure performed predominantly in adults annually (Table 38.5). In 2011, 158,000 bariatric procedures were performed; RYGB, AGB, and SG represented 36.7, 35.4, and 17.8% of the procedures, respectively. By 2015, 196,000 bariatric procedures were performed annually, and a dramatic shift in the proportions of procedures has occurred, with RYGB, AGB, and SG now accounting for 23.1, 5.7, and 53.8%, respectively (ASMBS website). While no single surgical approach has demonstrated clear superiority in patients under 18 years of age,

Table 38.5 Estimate of bariatric surgery numbers, 2011–2015

	2011	2012	2013	2014	2015
Total	158,000	173,000	179,000	193,000	196,000
RNY	36.7%	37.5%	34.2%	26.8%	23.1%
Band	35.4%	20.2%	14%	9.5%	5.7%
Sleeve	17.8%	33%	42.1%	51.7%	53.8%
BPD/DS	0.9%	1%	1%	0.4%	0.6%
Revisions	6%	6%	6%	11.5%	13.6%
Other	3.2%	2.3%	2.7%	0.1%	3.2%
Balloons					~700 cases
vBloc					18 cases

ASMBS total bariatric procedures numbers from 2011, 2012, 2013, 2014, and 2015 are based on the best estimation from available data (BOLD, ASC/MBSAQIP, National Inpatient Sample data and outpatient estimations)
From the ASMBS Website, July 2016: https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers. Reprinted with permission of American Society for Metabolic and Bariatric Surgery, copyright 2015, all rights reserved

many studies support the safety and effectiveness of these procedures [35].

Various procedures were attempted in adolescents until the adult literature confirmed the safety and successful weight loss and resolution of comorbidities after RYGB. Thereafter, centers that formalized adolescent surgical weight loss programs predominantly performed RYGB. AGB drew particular interest as an option for adolescents because of its very low surgical risk and reversibility. In the decade 2000–2010, a trend developed to favor AGB [41, 42], but gastric sleeve resection has now emerged as the preferred operation for adolescent patients with obesity. AGB remains available for adolescents on FDA-approved studies or who have reached 18 years; it may also be used off-label. RYGB continues to be an option for adolescents with severe obesity and may be preferable for individuals with GERD.

A laparoscopic approach is used for adolescent weight loss surgery. Four working ports and a separate site for a self-retaining liver retractor are standard, and an additional working port may be placed to facilitate the operation. In adults, single-incision procedures are sometimes used, but this technique is not commonly employed in adolescents. Patients are in supine position during surgery, carefully secured to the operating table, and appropriately padded to allow them to be moved to a more upright position, necessary for exposure of the proximal stomach and esophageal hiatus.

Laparoscopic Sleeve Gastrectomy (SG)

Sleeve gastrectomy was initially performed as the first stage of a two-stage procedure, the second component being biliopancreatic diversion. It subsequently gained popularity as a stand-alone procedure after clearly demonstrated safety and effectiveness [43–45].

The first series of SG in children from 2008 supported SG as a stand-alone technique in children and adolescents [46]. Four patients (average age of 14.5 years) with mean BMI of 48.8 kg/m^2 preoperatively were found at 1-year follow-up to have striking weight loss, with mean BMI of 37.2 kg/m^2. There were no intra- or postoperative complications, supporting investigation of SG as a surgical option for children with obesity. In 2012, the ASMBS issued a position statement recognizing SG as an acceptable primary bariatric procedure or as a first-stage procedure as part of a planned staged approach.

SG involves removal of the fundus of the stomach with preservation of the antrum and pylorus. This converts the remaining stomach into a narrow tube or "sleeve" (Fig. 38.1). This limits food intake through reduced stomach volume and creates its effect without inducing malabsorption. Compared to RYGB, there are fewer complications. Still, patients who undergo SG must be followed for technical and surgery-related complications, including staple-line leak, bleeding, infection, stricture formation, bowel obstruction, and venous thromboembolism; see the section on Complications and Postoperative Considerations. Additionally, although pediatric patients have less likelihood of developing nutritional and micronutrient deficiencies following SG compared to RYGB [47, 48], the patients receive supplementation and are followed for evidence of deficiencies.

As with adult patients, pediatric patients see a reduction in excess body weight (EBW) of 50–80% 1 year after surgery [49]. Long-term results for SG are similar to those of other bariatric procedures; see the section on Outcomes.

Most bariatric surgeons reinforce the long staple line when completing the gastric resection. A survey of expert bariatric surgeons revealed that 100% believed that staple-line reinforcement reduced leak rates [50]. Despite some controversy related to the benefits of such reinforcement, several studies report the elimination of staple-line leaks, a serious complication of SG [51, 52].

Several intraoperative maneuvers can assess the integrity of the staple line in SG or anastomosis in RYGB. These include endoscopy, insufflation with air while immersing the staple line/anastomosis in saline/fluid, or instilling

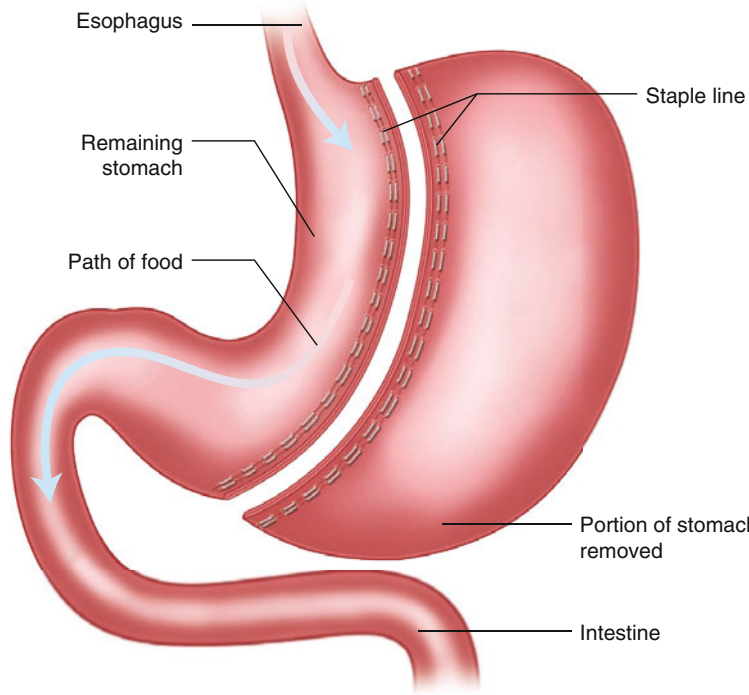

Fig. 38.1 Sleeve gastrectomy

endoluminal methylene blue while observing the site laparoscopically.

Roux-en-Y Gastric Bypass (RYGB)

Although RYGB has evolved since it was originally performed in the 1960s, the fundamental principles of the operation have remained consistent and involve both restrictive and malabsorptive mechanisms to achieve weight loss. As mentioned above, SG has supplanted RYGB as the most common bariatric procedure performed in the United States; nevertheless, RYGB is still considered the standard to which other procedures are compared. RYGB is more technically demanding than SG or LGB. A 20- to 30-mL gastric pouch is created by dividing the stomach near the gastroesophageal junction (Fig. 38.2). The small bowel is divided; the distal portion of the separated bowel (Roux limb) is brought up to the gastric pouch, where a gastrojejunostomy is performed. This Roux limb can be fashioned in a retrocolic (tunneled behind the colon, through the mesocolon) or antecolic (anterior to the colon and stomach) manner. The proximal portion of the previously divided bowel composes the "biliopancreatic limb" and encompasses the excluded stomach, duodenum, and 30–60 cm of jejunum. This carries bile and pancreatic enzymes to the jejuno-jejunal anastomosis, which is 75–150 cm from the gastrojejunostomy. That anastomosis (of the biliopancreatic limb to the Roux limb) creates the common channel, which then traverses the remaining small bowel. In super-obese patients (BMI >50), a "long-limb gastric bypass" or "distal gastric bypass" involves fashioning a longer (150 cm) Roux limb, which increases the malabsorptive effect of the operation. Reported EBW loss for adults and adolescents who undergo RYGB is 60 and 82%, respectively [35, 43, 53, 54]; see the section on Outcomes. Postoperative complications unique to RYGB include anastomotic or staple-line leak, micronutrient deficiencies, marginal ulcer formation, and internal hernia; see the section on

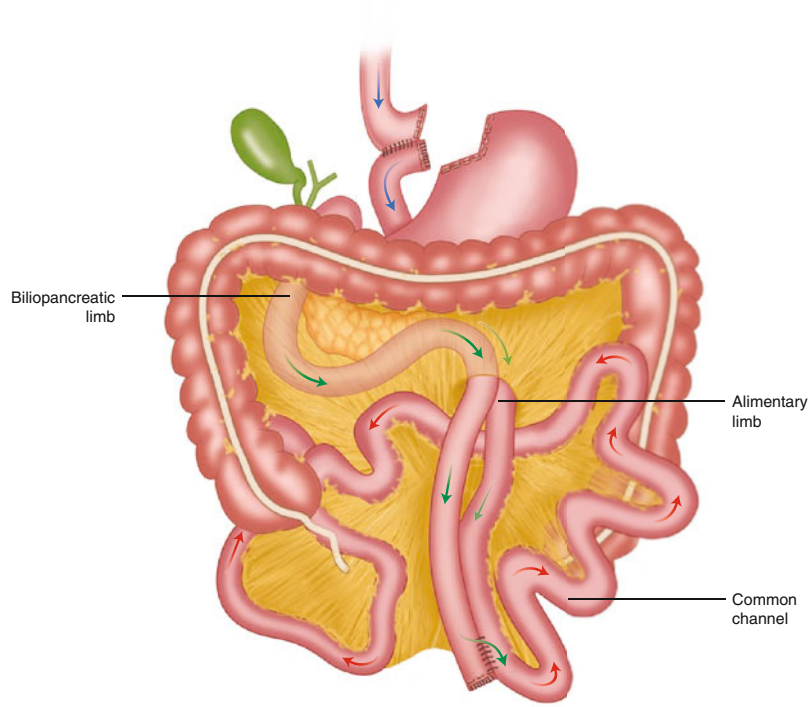

Fig. 38.2 Roux-en-Y gastric bypass (RYGB)

Complications and Postoperative Considerations. Some patients also develop postprandial hyperinsulinemia with hypoglycemia.

Laparoscopic Adjustable Gastric Banding (AGB)

AGB produces weight loss only through its restrictive effects on the stomach, which limits the amount of food a patient can consume. In the United States, the gastric band was originally used as an investigational procedure in adults. It was approved for use in adults in 2001 by the Food and Drug Administration but remained available to adolescents as an investigational device. During the procedure, the band is placed around the upper portion of the stomach, 1–2 cm below the gastroesophageal junction. This creates a small (approximately 30 milliliter) pouch. Various techniques are utilized to help prevent band migration or herniation of the fundus [55–57]. The size of the stomach can be adjusted postoperatively by adjusting the amount of saline injected into the band via a tunneled, subcutaneous port (Fig. 38.3).

Although results vary widely, reported weight loss from AGB ranges from 40 to 60% of excess body weight (EBW, [58–61]). In the pediatric population, similar results have been demonstrated, with reductions of 37–63% EBW [31, 62–64]; see the section on Outcomes. Complications of AGB are related to band misplacement or slippage, problems with the band system (port malfunction, tubing disruption), band erosion, and esophageal reflux or dilation.

The reversible nature of AGB originally made it appealing to the pediatric patient. This, in combination with its low operative complication rate, initially suggested that it could become the procedure of choice in adolescents. In the adult population, sleeve gastrectomy has largely supplanted the use of AGB, and the same trend has occurred in the pediatric population. AGB has been associated with a reoperative rate of 8–10% [31, 62–64]; see the section on Complications.

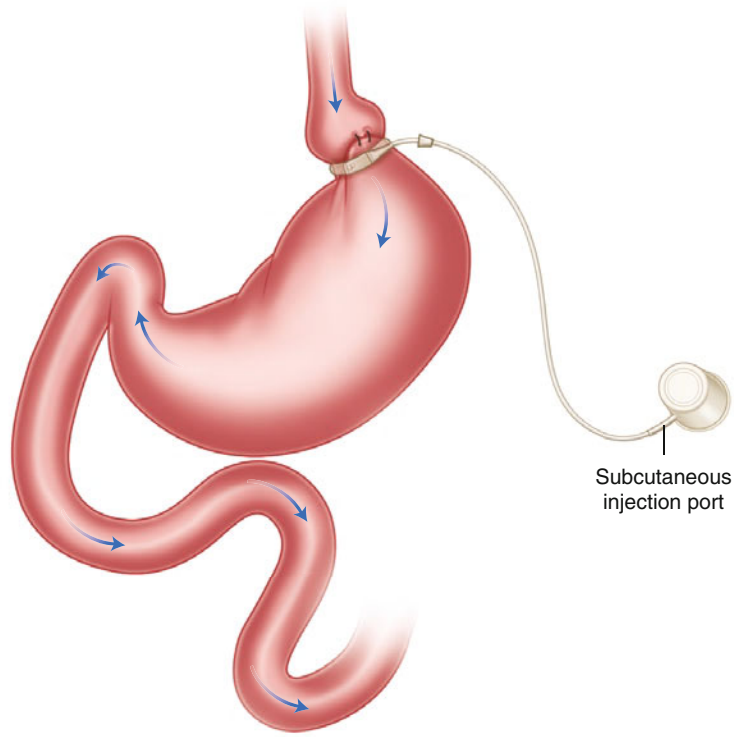

Fig. 38.3 Adjustable gastric banding (AGB)

In all of the operations described thus far, it is essential to examine the esophageal hiatus for the presence of a hernia. Reducing the size of a dilated hiatal opening with one or two sutures can minimize the potential backup of food and gastric content into the esophagus, particularly in SG and AGB procedures.

Additional Procedures

Several endoscopic weight loss procedures have been described, although these have not been approved in children. The *intragastric balloon* is endoscopically inserted and filled to occupy space in the stomach, with the currently approved model remaining in site for 6 months. In 2015, approximately 700 such devices were placed (ASMBS website). Meta-analysis of 17 studies including 1638 adult patients demonstrated a 25% excess weight loss at an average of 1-year follow-up [65]. Newer models may be implanted for longer duration or may be deployed or removed without endoscopy; the device is swallowed and self-excreted.

Gastric partitioning via *plication* is also being explored. This is achieved by laparoscopically (LGP) or endoscopically reducing the luminal size of the stomach. Several techniques have been described; the main benefits are that procedures are quicker, less invasive, and theoretically reversible. Reported results vary greatly, with excess weight loss as high as 57–67% at 3 years [66]. In adolescents, 12 patients who underwent LGP were reported to have had mean excess weight loss and mean excess BMI loss of 68 and 79%, respectively, and improvement of comorbid conditions 2 years after the procedure [67]. *Endoluminal bypassing devices* can also be placed. These must be anchored endoscopically at the pylorus

or esophagus but are designed to emulate the malabsorptive effects of RYGB.

Gastric electrical pacing and vagal nerve stimulation involve placement of leads into the gastric wall and around the gastric vagal nerve branches, respectively. Although the exact mechanism is not understood, the result is early satiety through delayed gastric emptying, perhaps related to direct mechanical, neurohormonal, or central nervous system effects. Neither procedure is approved for use in patients <19 years of age.

Perioperative Care

Care Pathways

The ASMBS recently released an evidence-based care map to help guide the pre-, intra-, and postoperative management of patients who undergo sleeve gastrectomy (Tables 38.3, 38.6, and 38.7) [68]. Care pathways/maps have been defined for many general surgical procedures and help optimize quality while minimizing cost. They do so by providing a structure for patient care and reducing

Table 38.6 Intraoperative recommendations for sleeve gastrectomy

Routine	Selective	Not recommended
VTE prophylaxis: chemoprophylaxis, sequential compression device	Buttressing/oversewing staple line	Routine drains: nasogastric tube, closed-suction abdominal drain, urinary catheter
Antibiotics: non-penicillin allergic, penicillin allergic	Leak test: endoscopic, air insufflation, methylene blue	Routine invasive monitoring: central venous line, arterial line
Patient positioning guidelines	Protective specimen retrieval	
Bougie >34 French	Endoscopy	
Hiatal inspection: hiatal repair if identified	Hiatal dissection	
Preop diet: clears until 2 h preop		
Goal-directed fluid therapy		

From Telem D. The American Society for Metabolic and Bariatric Surgery: Care Pathway Development for Laparoscopic Sleeve Gastrectomy [Internet]. 2016 Sept. https://asmbs.org/wp/uploads/2016/09/Telem-et-al_LSG-Pathway_2016_Final.pdf

Table 38.7 Postoperative recommendations for sleeve gastrectomy

Routine	Selective	Not recommended
Prophylaxis: postop nausea and vomiting, VTE	Monitoring: finger sticks, continuous pulse oximetry	Routine GERD therapy
Multimodal pain management: PCA, IV acetaminophen	Medications: extended VTE prophylaxis	
Supplements: chewable multivitamin, vitamin D, vitamin B12, elemental iron		
Monitoring: routine vitals ± tele, strict ins/outs	Consultations: nutrition, physical therapy, acute pain management, cardiology, endocrine	
Length of stay: 1–2 nights	Radiographic studies: UGI/CT	
Diet: NPO or clears POD #0, bariatric full diet POD #1, puree 2–4 weeks postop		
Postoperative visits: 2–3 weeks, 6–9 weeks, 6 months, annually		
Early ambulation		

From Telem D. The American Society for Metabolic and Bariatric Surgery: Care Pathway Development for Laparoscopic Sleeve Gastrectomy [Internet]. 2016 Sept. https://asmbs.org/wp/uploads/2016/09/Telem-et-al_LSG-Pathway_2016_Final.pdf

variation in patient management. The ASMBS care pathway defines several preoperative, intraoperative, and postoperative metrics and categorizes each recommendation as routine, selective, or not recommended. Additional clinical pathways have been described for WLS in children [69], as well as "fast-track surgery" or "enhanced recovery after surgery" programs in adults [70–72].

High-Volume Centers/Centers of Excellence

For many complex abdominal operations, the relationship between patient outcomes and hospital and surgeon volume has been well established. These "high-volume centers" (HVCs) have been shown to improve patient care and quality while reducing costs, supporting an argument for regionalization of certain procedures. The first study of HVCs for bariatric procedures in adults demonstrated shorter length of stay, fewer complications, lower costs, and (in a subset of patients) lower mortality [73, 74].

In 2012, the American College of Surgeons (ACS) and ASMBS combined their bariatric surgery center accreditation programs to form the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP). The purpose of the program is to develop standards for accreditation, verify that each center meets those standards, collect data on patient outcomes, and coordinate efforts of quality improvement, collaboration, and best practices.

One retrospective cohort study comparing adult patients who underwent procedures at centers of excellence compared to those without the designation demonstrated decreases in mortality (0.1 vs. 0.3%), 90-day reoperations (0.5 vs. 0.8%), complications (27.6 vs. 36.4%), and readmissions (8.8 vs. 10.8%) [75].

Mentoring

Pediatric surgeons who are performing weight loss surgery have far less volume than their adult counterparts. Surgeons who have limited experience with these procedures should be mentored and monitored by more experienced bariatric surgeons until they have a mutual agreement on developing independence.

At our center, experienced adult bariatric surgeons mentored each of the initial 25 procedures, acting as first assistant on the first 10–12 and observer in the operating room for the remainder. They also have been consulted for special situations (e.g., high-risk patients, extremely high BMI).

Postoperative Considerations

Despite the presence of comorbid conditions, most adolescents who undergo weight loss surgery are in better general health than comparable adult patients. Monitoring of most adolescents postoperatively can be safely done on the general patient floor. Monitoring should include routine assessment of vitals, intake and output, and pulse oximetry. Special monitoring (including ICU or intermediate unit admission) should be considered for any patients with a history of sleep apnea. Patients using home CPAP should make plans preoperatively and can use the machine in the recovery unit or ICU. Adolescents with type 1 diabetes mellitus, insulin-resistant type 2 diabetes mellitus, or cardiomyopathy should also be monitored in an ICU setting following weight loss surgery.

Pharmacy/Medications

Medications used routinely in the immediate postoperative period address expected symptoms (e.g., nausea, vomiting, pain) as well as prophylaxis against venous thromboembolism. Additionally, appropriate fluid maintenance and antibiotic prophylaxis are important considerations. In some cases, a low-dose diuretic (e.g., furosemide) can be used for patients who cannot tolerate liquids in the early postoperative period.

Upon discharge, patients should expect to take multiple medications to avoid short- and long-term complications. These include pain, nausea, gastroesophageal reflux, and venous thrombosis in the perioperative period and GERD and cholelithiasis later in the postoperative period. Expected

postoperative pain can be managed with a combination of nonnarcotic and narcotic medications, but oral nonsteroidal anti-inflammatory drugs should be avoided. All patients are discharged with anti-nausea medications, as this is an expected problem and if unmanaged will result in inadequate nutrition and hydration. While antacids need not be given routinely, any patient with prior reflux or symptoms in the postoperative period is placed on acid suppression. Patients resume medications that were taken preoperatively for comorbid conditions; however, they should be followed closely to avoid complications (e.g., hypotension, hypoglycemia) if those comorbid conditions resolve quickly. Although nutritional and metabolic concerns vary slightly depending on the procedure, all patients will need to take vitamin and nutrient supplements including iron, folate, calcium, and vitamin B12. Patients should be counseled on the importance of ambulation and can be discharged with an incentive spirometer to encourage adequate pulmonary toilet. Finally, we recommend that patients be continued on outpatient thromboembolism prophylaxis, including either low molecular weight heparin or heparin injections, for a period of 2 weeks following their procedure.

Feeding Regimen

Feeding is typically initiated on the first postoperative day and begins with small aliquots of clear liquids. Patients are counseled preoperatively regarding what changes to expect in postoperative feeding regimens. Any suspicion of leak must be investigated prior to initiating feeds, and some centers perform routine upper gastrointestinal (UGI) series following RYGB to assess the patency of the gastrojejunal anastomosis. Progression to full liquids and eventually pureed food for several weeks continues after discharge from the hospital. Thorough patient education is vital to prevent problems with hydration, nutrition, and other complications. Because of the restrictive nature of the procedures and loss of some muscle mass during weight loss, patients are counseled to maintain relatively high intake of protein (60–70 g/day).

Radiography

Imaging studies (UGI or CT scans) can be utilized in the postoperative period to assess for leak. The ASMBS recommends selected use of these modalities, at the discretion of the surgeon. Radiation exposure is a particular concern in the pediatric population, and therefore postoperative imaging should be reserved for patients in whom there is clinical suggestion of a leak. It is important to note that the amount of radiation exposure in an obese patient undergoing UGI is comparable to or greater than that of a CT scan.

Follow-Up

Patients who undergo WLS require long-term follow-up to monitor health, screen for nutritional problems, and provide support for healthy eating behavior and exercise. In the immediate postoperative period, they are seen within 1 month of discharge. They return to clinic monthly for several additional visits to assess weight loss and dietary compliance, to provide additional education, and to identify potential or real complications (particularly vitamin deficiencies). After 3–6 months, the frequency of visits can be decreased until they are followed semiannually and then annually. Adolescents with long-term health problems are known to miss follow-up visits, so centers must maintain contact postoperatively to monitor nutritional intake and overall health. Patients whose care is provided by pediatric specialists should eventually be transitioned to an adult weight loss program, although no specific age cutoff has been identified and many patients will continue to see their pediatric surgeon well into their twenties.

Complications and Postoperative Considerations

Complications following WLS can be thought of in relation to timing (immediate vs. late), predictability (expected vs. unexpected), severity, technical factors, and patient disease. Atelectasis

is a common complication of any surgical procedure in any obese patient. Immediate complications related to WLS in particular include leak, bleeding, wound infection, nausea/vomiting (expected), pain, and venous thromboembolism (VTE). Late complications include oral feeding intolerance (perhaps related to technical issues), internal hernia, and nutritional deficiencies. Complications related to patient disease can occur in the immediate (cardiac events, sleep apnea, hypo/hyperglycemia) or late postoperative periods.

Anastomotic or Staple-Line Leak

Anastomotic or staple-line leak is among the most concerning complications in the immediate postoperative period. In RYGB, this can occur at either the gastrojejunal or jejuno-jejunal anastomosis and in SG anywhere along the gastric staple line. Care providers must be vigilant to detect tachycardia, fever, increasing oxygen requirement, or oliguria following the operation. These findings should prompt immediate investigation, most often with CT scan, but could include re-exploration with or without imaging investigations.

All surgical procedures carry risks of bleeding and infection. Possible sites of bleeding can include anastomosis or staple lines (which can bleed into the bowel lumen or peritoneum, depending on the site) as well as the mesentery, omentum, or abdominal wall. Any evidence of intraperitoneal bleeding must be investigated prior to completion of the procedure.

Staple-line reinforcement includes oversewing the staple line or the use of an absorbable or nonabsorbable material as a buttress to the sealed gastric surface. Although staple-line reinforcement has debatable utility from the standpoint of leak prevention, an expert panel survey of bariatric surgeons in 2012 thought that staple-line reinforcement reduced bleeding along the staple line in SG [50]. The evidence relating staple-line reinforcement with leaks and bleeding is inconsistent. One recent study suggests that staple-line reinforcement increases leak rates, without reducing the incidence of bleeding [75]. The ASMBS recommendation leaves the use of reinforcement to the surgeon's discretion.

Infection

Wound infection is of particular concern in RYGB and SG. Both of these procedures are considered "clean-contaminated" since the gastrointestinal mucosa is violated in a controlled manner. In SG, the resected stomach must be removed from the abdominal cavity, and this is typically done through the largest incision. Although wound protectors have demonstrated efficacy in other gastrointestinal procedures, the ASMBS recommends selective use of wound protectors for specimen removal in sleeve gastrectomy. Care is always taken when removing the resected stomach to avoid rupture.

Technical Error/Complications

Technical issues that can result in postoperative complications relate to the particular surgery performed. All procedures, even when performed laparoscopically, can cause adhesion formation and subsequent small bowel obstruction. In SG, there can be problems related to construction of the sleeve, with excess stomach left behind or a sleeve construction that is too narrow or compromises the gastroesophageal junction. For RYGB, efferent limb syndrome results when the gastrojejunal anastomosis is too narrow, which leads to gastric outlet obstruction. Additionally, RYGB leaves a mesenteric defect, which can be an opening for an internal hernia. To prevent the potentially catastrophic complication of bowel herniation and intestinal loss, the mesenteric defect should be closed surgically. In AGB, the band itself can be malpositioned, changed in position (slip), or eroded, resulting in obstruction, pouch dilation, and inadequate weight loss. These may necessitate urgent band adjustment, repositioning of the band, or removal. Displacement of the port may prevent access and require resuturing. Conversely, fixation of

the port tightly through the abdominal wall may result in persistent pain at the site and lead to revision.

Venous Thromboembolism

Obese patients are at an elevated risk of venous thromboembolism, including deep vein thrombosis, pulmonary embolism, mesenteric vein thrombosis, and portal vein thrombosis. All patients must receive VTE prophylaxis perioperatively with either heparin or enoxaparin, as well as mechanical sequential compression stockings. Additionally, many centers (adult and pediatric) are continuing self-administered chemoprophylaxis upon discharge for 2–4 weeks.

Gastrointestinal Complications

Nausea, vomiting, and symptomatic reflux are common in the immediate postoperative period. This underscores the importance of appropriate counseling and provision of adequate anticipatory pharmacotherapy. In one large series of pediatric patients who underwent SG, only 2% experienced these symptoms. However, antiemetics are often given routinely, and reflux medication should be provided if patients had GERD preoperatively or are symptomatic. A single dose of furosemide may benefit patients who cannot tolerate liquids when started on POD 1.

Mortality

Mortality in the postoperative period has become an increasingly rare event as the shift in procedures moves away from RYGB in favor of SG. The most common causes of mortality are leaks (at either of the anastomoses in RYGB or the staple line in SG) resulting in sepsis or fatal venous thromboembolism, including pulmonary embolism and portal/mesenteric venous thrombosis. In most adult series, mortality is well below 1%, with the largest meta-analysis including almost 8558 patients who underwent SG demonstrating a 0.3% mortality rate [76]. In the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study, which prospectively enrolled 242 adolescents undergoing WLS, only 1 mortality was noted in the follow-up period (3.3 years postoperatively) [28]. This was due to a hypoglycemic event in a patient with known type 1 diabetes. Almost all series of WLS in the pediatric population have no mortalities [77–82], although fatal cases have been reported [83, 84].

Vitamin/Nutrient Deficiencies

Postoperative complications related to vitamin and nutrient deficiencies can occur even in patients who are taking supplements. These are most common in patients who undergo RYGB but can develop following any WLS. One consequence of resecting stomach includes malabsorption of vitamins B12, C, and D and iron. Additional deficiencies seen postoperatively include vitamins A, B1, B2, and B6 and zinc resulting in beriberi, peripheral neuropathy, Wernicke's encephalopathy, osteoporosis, or anemia. Medication adherence challenges are significant in adolescents, and so the importance of continuing supplementation must be reinforced strongly and assessed at all follow-up visits. A list of common vitamin and nutrient deficiencies, associated complications, and recommended supplementation is listed in Table 38.8.

Pregnancy

Pregnancy following WLS is generally considered safe 12–24 months following surgery, when the body's nutritional state and body weight have stabilized [85, 86]. The risks of adverse maternal or fetal outcomes are reduced in women who undergo WLS, including preeclampsia, gestational diabetes, intrauterine growth retardation, and macrosomia. Because of the risk of vitamin deficiencies following WLS, female patients must adequately supplement their vitamin intake and have levels checked prior to and during pregnancy.

Table 38.8 Nutrient deficiencies after weight loss surgery

Nutrient	Complication	Association with surgical procedure [95]			RDA	Supplementation [96]
		SG	RYGB	AGB		
Protein	Anemia, edema, alopecia, hypoalbuminemia,		[a]		46–56 g	
Calcium	Osteoporosis				1000–1200 mg	1.2 g elemental calcium, daily
Iron	Anemia	[a]	[b]	[a]	8–18 mg	Iron/vitamin C complex with meals (TID)
Thiamine (B1)	Beriberi				1.1–1.2 mg	100 mg BID or 100–250 mg IM monthly
Niacin (B3)	Pellagra					500 mg TID
Cobalamin (B12)	Neuropathy, anemia	[a]	[b]		2.4 μg	1000 μg IM monthly or 500 μg sublingual daily
Folate	Macrocytic anemia	[a]	[b]		400 μg	1–5 mg daily
Vitamin D	Osteoporosis				600–800 IU	Vitamin D 50,000 IU once weekly × 12 weeks and then vitamin D3 1000 IU BID with meal
Vitamin A	Vision changes		[a]		700–900 μg	10,000 IU daily
Vitamin E	Muscle weakness, ataxia				15 mg	800–1200 IU daily
Vitamin K	Bleeding				90–120 μg	5–20 mg daily
Zinc	Dermatitis, glossitis, alopecia,				8–11 mg	50 mg Zinc gluconate or 220 mg Zinc sulfate daily
Copper	Neutropenia, anemia, myelopathy		[a]		900 μg	2-mg capsule daily

[a]Infrequent but associated
[b]Common

Menstrual cycle disorders in nonpregnant women often resolve [87] after WLS. Female patients should be counseled about the importance of contraception, and this should be offered to patients in follow-up. Given the increased risk of thromboembolic events in obese patients, the use of an intrauterine device may be preferred to estrogen-containing contraceptives [87].

Outcomes

In the adult population, bariatric surgery has been demonstrated to be an effective weight loss strategy in the appropriate patient. T2DM resolves in as many as 70% of adults, and HTN improves in 40% [26, 27].

Multiple institutions have published positive results demonstrating benefits to obese children who undergo SG [28, 78, 79, 88–90], RYGB [28–30, 79, 91, 92] and AGB [30, 82, 90, 92–94]. Although long-term data are limited in these series, they demonstrate sustained weight loss up to 3 years postop, as well as immediate and long-term comorbidity resolution.

In the short term, bariatric surgery in adolescents can reduce excess body weight by 50–80% [35, 43]. Improvements in obesity-related comorbidities may be even better in teenagers than adults, with 95% resolution of DM and 80% of HTN [28–30]. Multiple studies demonstrate positive results of bariatric surgery in children vs. diet and exercise [28, 31–34, 88], underscoring its value as an effective therapy for weight loss.

SG

One of the early series of SG in adolescents demonstrated mean excess weight loss (EWL) of 40% at 1-year follow-up in 23 patients [88]. Subsequent series with longer follow-up have reported EWL at 3 years of 70–80% [78, 90]. In terms of comorbidities, in a series of 135 patients, all patients with T2DM had complete resolution of their comorbidity, as did 75% of patients with HTN. The largest series of SG in patients is from King Saud University [89]. At 3-year follow-up, remission or improvement was seen in 86% of patients with HTN, 100% with T2DM, 99% with OSA, 100% with prediabetes, and 83% with hyperlipidemia. More recently, the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) consortium has reported interim results of a multicenter, prospective study of bariatric surgery in adolescents [28]. Three-year results were published regarding weight loss and health status. For the 67 patients who underwent SG, mean weight decrease was 26%; remission was seen in 100% of patients with diabetes, 100% with prediabetes, 56% with HTN, and 55% with dyslipidemia.

RYGB

The reported series of RYGB in adolescents have had similarly positive results. In addition to the 67 patients who underwent SG, 161 patients were included in the Teen-LABS study. In that cohort, mean weight decrease was 28%; remission was seen in 94% of patients with diabetes, 74% with prediabetes, 78% with HTN, and 69% with dyslipidemia [28]. A single-center, longitudinal outcome study of 61 patients who underwent RYGB reported in 2010 that mean BMI decreased to 37.4% 1 year after surgery [92]. There was an 8.8% reduction in systolic BP, 13.5% reduction in diastolic BP, 75.8% reduction in fasting insulin, 16.8% reduction in total cholesterol, 17.7% reduction in LDL, and 37.3% reduction in triglyceride. In a 2-year follow-up of a series of 81 Swedish adolescents who underwent RYGB, there was a decrease in average BMI from 45.5 to 30 and associated improvements in HbA1c, LDL, HDL, triglycerides, and blood pressure [29].

AGB

Our series of 137 patients who underwent AGB demonstrated a decrease in BMI from baseline (48.3 kg/m^2) at 6, 12, 24, and 36 months (43.8, 41.6, 41.5, 40.5). However, 22% of patients underwent one or more additional procedures for complications, and 20% had their bands removed or converted to a different weight procedure [82]. Resolution of comorbid conditions ranged from approximately 30 to 50%. In comparison with that series, a smaller group of patients who underwent SG demonstrated greater percent excess weight loss at 24 months, with fewer surgical complications [90]. Additional single-center series of adolescents who underwent AGB demonstrated mean EWL of 40–61% at 2-year follow-up [93, 94]. In one of those series (n = 73), 86% of patients had resolution or improvement of comorbid conditions.

Summary

Obesity is a chronic illness that presently can be most successfully managed with bariatric surgery. SG, RYGB, and AGB are effective and safe approaches to weight loss in pediatric patients with severe obesity. Patient selection and evaluation involves a multidisciplinary team, and the appropriate children and families will do well with any of the three commonly performed surgeries. Additional procedures will likely become available in the future. A better understanding of perioperative care and complications will improve the outlook of patients who undergo WLS. The results of surgical treatment have thus far been encouraging; long-term data will permit us to assess the utility of WLS in the multimodal care of children with obesity.

Editor's Comments and Question

In a recent paper[a], you cited high rates of current or past depression (32%), suicidal ideation (13–50%), suicidal behaviors (13%), and self-harm (~25%) among adolescents followed in a center for bariatric surgery. It is encouraging to note that depressive symptoms declined after surgery, though boys appear more recalcitrant than girls. But at least some adolescents with no clear psychiatric history commit suicide after treatment. Likewise, substance abuse may emerge following bariatric surgery in adults, though premorbid use of drugs, alcohol, and tobacco predicts postoperative behavior[b]. How might these psychiatric problems be explained and prevented?

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Authors' Response

Remission of psychological conditions following weight loss surgery (WLS) has been reported, but suicidal behavior and self-harm following WLS are well documented. Many adolescents seeking WLS have sought psychological counseling prior to entering a bariatric program. The majority report having been bullied. Weight loss surgery frequently changes the patient's relationship with food; no longer being able to engage in unlimited eating may be destabilizing for those who use food to cope with anxiety or depression. Other activities including tobacco, alcohol, and drug use may become substitutes. Ongoing psychological support and, where indicated, therapy must be available as a part of comprehensive postoperative care.

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Part X

Challenges to Long-Term Success

39 The Role of the Primary Care Provider in Long-Term Counseling: Establishing a Therapeutic Alliance with the Child and Family

Sarah Armstrong, Joseph A. Jackson Jr., and Jessica Lyden Hoffman

Shifting Roles: From Acute to Chronic Disease Management

Traditionally, primary care pediatricians assess growth and development and treat acute illnesses. However, there is an increasing need for chronic disease management, including long-term counseling for both the patient and their family [1]. With respect to obesity counseling, providers cite lack of knowledge and skills, lack of training, insufficient reimbursement, and lack of confidence as reasons for the lack of priority given to long-term obesity counseling [2, 3]. While many primary care providers strive to balance their varied roles, it remains true that discussions about weight can be uncomfortable, and managing obesity over a long period of time requires time, knowledge, communication skills, and patience.

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The Primary Care Provider as Counselor

Primary care providers include physicians, physician's assistants, nurse practitioners, registered nurses working in a primary care setting (e.g., community health center), and other clinicians working in school-based health centers. The primary care pediatric provider assumes first-line responsibility for the diagnosis and management of children and adolescents with obesity [4]. The trusted and longitudinal relationships with patients, families, and communities place primary care providers in good position to impact the obesity epidemic [2, 4]. For these reasons, it is important that they are well equipped to leverage these relationships by using best-practices strategies. This chapter describes the current evidence on primary care strategies, which if used effectively have the potential to positively affect child health outcomes.

The Therapeutic Alliance

The therapeutic alliance is a term taken from the psychoanalytic theory literature highlighting the relational aspect of counseling and emphasizes the trust that must occur between the patient and provider for the counseling to be effective. The strength of the therapeutic alliance is a strong predictor of positive treatment outcomes and is

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directly related to the likelihood of a positive behavior change [5]. *Communication* is one important component of the therapeutic alliance. "Therapeutic communication" expresses support, provides information and feedback, corrects distortions, and provides hope to the patient [6]. The primary care provider who uses therapeutic communication is likely to establish the therapeutic alliance. To strengthen the therapeutic alliance once trust has been established, the provider must allow a patient the autonomy to express concerns and make decisions on behalf of their own health—even when the provider disagrees. Using nonjudgmental listening skills will further strengthen the patient's trust in the provider, and empowering the patient to set goals that are important to him/her will strengthen the therapeutic alliance and also will increase the likelihood of behavior change [5, 6].

The intentional pursuit and demonstration of *empathy* in each clinical encounter is a key means of strengthening the therapeutic alliance. Using prompts that validate a patient's feelings further reassures patients that they are safe and supported in their relationship with the provider. Greater emotional support from providers strengthens the therapeutic alliance, improves adherence to recommendations, and improves the effectiveness of behavior change counseling [7]. Empathy includes understanding that behavior change is not always successful and helping to normalize that experience for patients. The provider who accepts failures can help patients to develop resilience. Weight bias is common among healthcare professionals. An empathetic approach is not consistent with bias; thus, providers should allow self-reflection in order to identify and address personal biases. In particular, using "person-first" language ("person with obesity" rather than "obese person") will help the patient understand that you see the patient, not the condition, first [8].

Another critical step to strengthen the therapeutic alliance includes prioritization of the *shared decision-making* role between the provider and patient. Shared decision-making is the pinnacle of patient-centered care [9]. Recently, a shift from paternalistic, doctor-driven decision-making to a more patient-focused and patient-led informed decision-making process has emerged. Shared decision-making leads to better patient engagement, improved provider-patient relationships, and more positive health outcomes [9].

Barriers to a Healthy Therapeutic Alliance and Solutions

Many challenges threaten a strong therapeutic alliance. A patient's lack of engagement, or *poor compliance*, with stated goals can be frustrating and discouraging to the healthcare provider. Expressed frustration at the patient's inability to meet goals, however, only weakens the patient's self-confidence and may even cause shame or embarrassment. Providers can strengthen the therapeutic alliance even in these situations by seeking to understand, in a nonjudgmental way, the wide and varied reasons why the patient is struggling to meet their goals. Factors may include inadequate resources, challenging social contexts, negative emotions, and denial, all of which can easily derail people from their goals [9].

Cultural differences between patient and provider may also threaten the therapeutic alliance. Recognizing and respecting cultural differences by giving attention to the cultural context in which their patient lives greatly improve the therapeutic alliance. For example, if a patient comes from a culture where obesity is seen as a sign of prosperity and health, the provider must strive to fully understand the motivation of the patient and the potential ways to acknowledge the patient's cultural heritage while still informing the patient of the associated complications that may result from excessive weight gain. Various misunderstandings about health and nutrition remain in cultures where overweight and obese children have the appearance of health, resulting in overfeeding by caregivers [10]. The following four skills can improve a provider's cultural competence specific to child obesity treatment: (1) demonstrate awareness and knowledge of weight perceptions in the culture; (2) understand preferences for food and physical activities that are culturally acceptable; (3) utilize interpreters and translators to ensure accurate and intentional written and verbal communication; and (4) identify the degree of acculturation to local customs [11].

Social determinants of health include the conditions in which families live, work, and play. These conditions are largely determined by economic and social norms that are shaped at the global, national, and local level. Recognizing the social determinants of health during patient encounters can further minimize barriers in the therapeutic alliance. A recognition that socioeconomic inequalities may limit access to and availability of healthy food and the opportunities for physical activity, and knowledge of how to overcome these obstacles, will ensure a lack of blame and judgment in patient encounters [12].

Providers can lessen the barriers of the therapeutic relationship by avoiding negative effects of weight talk among patients and their parents. Adolescents, in particular, are susceptible to adopting *disordered eating behaviors* while attempting to lose weight [13]. Although well intentioned, adolescents may hear weight-related conversations as shaming, with resultant social isolation, body image distortion, unhealthy eating practices, and self-loathing. Providers can also encourage families to not talk about weight and to instead focus on healthy eating and remaining active.

Once the primary care provider has established the therapeutic alliance, there are a host of management principles that can be employed to effectively counsel the patient and families toward improving health outcomes. *Motivational interviewing is among the most accessible strategies within the therapeutic alliance that is both well studied and correlated with improved health outcomes.*

What is Motivational Interviewing?

Motivational interviewing (MI) is a skill that can be used by healthcare providers to cultivate and convey empathy with patients. It is evidence based and has demonstrated effectiveness in eliciting behavior changes that promote healthy weight in children. Initially used in substance abuse treatment programs, MI is now applied throughout many avenues of healthcare, particularly in the treatment of chronic disease [14]. MI is the skill that allows providers to develop a healthy therapeutic alliance.

There are three primary communication styles that the skilled provider naturally uses interchangeably throughout conversations with patients depending on the situation: *directing* (telling the patient information or providing advice on what to do), *following* (primarily listening to the patient), and *guiding* (encouraging and motivating patients to find their own solutions). While the *directing* style is certainly essential in some healthcare situations, it is much less effective for lifestyle and behavior changes, where the patient has to have intrinsic motivation to carry out a desired behavior. Telling the patient what to do gives the patient a passive role in the process and can prevent the formation of the therapeutic alliance discussed earlier. The *following* style can be appropriate and desirable in many situations in practice, and it helps to build rapport with the patient. However, it does not provide an agenda or focus for addressing lifestyle and behavior changes within the limited time frame of an office visit [14].

MI hinges upon the *guiding* communication style, which involves collaboration and joint decision-making with the patient, evoking the patient's own motivations and resources for change and honoring the patient's own choices. Those three qualities together—collaboration, evocation, and honoring of patient autonomy—are termed *MI spirit*. It is up to the patients to make their own decisions when it comes to changing behaviors in their everyday lives, but providing support and encouragement through collaboration, and helping patients to better understand their own motivations for change rather than just hearing what the provider thinks is best will help guide them along on the path to a better health [14].

How to Apply Motivational Interviewing in Practice

Four guiding principles to keep in mind when using MI can be remembered by the acronym "RULE" [14]:

- *Resist the righting reflex*: When it comes to obesity, the patient and family likely already know that they should eat better and exercise more. Telling the patient and family what they

are doing wrong and what they should do instead encourages defensiveness, which can decrease their likelihood of making any changes.

- *Understand your patient's motivations*: Find out more about their personal concerns, values, and motivations. Instead of telling the patient and the family what they should do, ask them *why they want to make a change* and *how they might do it*. The more these arguments for change come from the patient, the more likely the patient is to make the change.
- *Listen to your patient*: Good empathic listening skills are vital to building rapport, showing patients that you care about them, and understanding your patients' perspectives. The patient should always be doing the most talking when using MI.
- *Empower your patient*: Help the patient and family explore their own ideas and resources, and then provide them with the support and optimism they need to feel confident in their own abilities to accomplish the goals they set out.

The core skills of MI include *asking the right questions* to evoke the person's motivations for change, *informing the patient about various therapeutic options* to help the person and family to decide what change would best work for them, and *listening to the person's desires, motivations, and resources* to help guide them appropriately in this process [14].

Asking the Right Questions

Ambivalence is often perceived as a negative trait. Rather, ambivalence is an indicator that a patient can see both sides of an issue. Ambivalence is a normal and healthy step on the road to behavior change. Using guiding questions, the provider can help the patient "see" the positive sides of change and the negative sides of the status quo. The more time the patient spends discussing these, the more the scale tips toward change. This is called "change talk" and helps guide patients past ambivalence. For example, ask patients *why* they want to change, *how* they would do it, *what reasons* they have for making a change, *how important* it is for them to make a change, and *how confident* they are that they will be able to make a change. Utilize open-ended questions (cannot be answered by yes or no):

"What concerns you most about your child's/family's health?"

"What changes, if any, would you like to make?"

"How might you and your family make this change together?"

The use of "rulers" to assess for importance, confidence, and readiness is a key MI skill. For example, "On a scale of 1 to 10, how important is it to you/confident are you/ready are you to make this change?" The provider can then probe further. Asking "Why didn't you give yourself a (lower number)?" can help the patient express strengths in themselves. Conversely, the provider can also uncover any barriers to change by asking "Why didn't you give yourself a (higher number)?" These questions can lead to rich conversations that help both the provider and patient better understand the patient's own motivations and barriers to success.

Some patients are not ready to make changes right away. In these cases, the provider can utilize hypothetical questions or ask about the future to guide them toward a vision of when they might feel ready to make that change. For example, you could ask "What would you like to see happening for your family's health in 1 year, 5 years, or even 10 years?"

Asking Permission

Before offering advice, *ask for permission*. This keeps in line with the MI spirit of both honoring the patient's autonomy (giving them the choice of hearing the information) and collaborating with the patient and family. If you have suggestions, *offer the patient several choices* at the same time and *let them decide*, which allow them to think about what might work best for them. For example, if the family would like to work on increasing physical activity, you can offer several possible ways that the family could accomplish this goal together slowly. You can also mention

that "other families have found ____ or _____ helpful" when providing options. This puts you the provider in a neutral yet collaborative position, ready to help guide the patient along whichever direction he or she would like to go but not force them down to any particular path they might not be ready or willing to take.

Listening to Understand

Good listening skills are necessary for any strong patient-provider relationship, and they are especially important for executing MI well. Listening intently helps the provider to better understand the patient's perspective and experience, thus helping to guide the conversation by asking the right questions. Nonverbal skills—eye contact and nodding—show the patient that you are listening intently and care about what they have to say.

Reflections and Summaries

Reflections can range from short summaries of what the patient has just said to more complex interpretations of what the patient might be thinking or feeling based on what they are telling you. For example, Mom might say: "I have tried everything, but she just keeps gaining weight!" You can reflect this statement back to her by responding: "You are feeling helpless that your child keeps gaining weight despite your efforts to make healthier changes at home." Utilizing these skills helps to further strengthen the therapeutic bond with the family by indicating that you care about them, support them in their choices, and are doing your best to understand them.

Practical Considerations and Solutions

Time Constraints

Having a discussion on such a sensitive topic as pediatric obesity and discussing lifestyle behavior changes can take a significant amount of time and be particularly challenging to cover when there are other pressing items, such as the comprehensive well-child checkup. The general principles and techniques of MI are very flexible, which allows them to be applied in multiple settings, even the time-limited space of a well-child visit [15]. MI spirit can be used in any interaction with families, though there will often be no enough time to fully address every problematic behavior or situation impacting the child's health with other MI techniques. One solution is to schedule multiple visits in regular intervals. This will also allow for more contact time with families, which then helps both the provider and family get to know each other better and build upon their therapeutic relationship together. In addition, regular follow-ups will allow for more opportunities to use MI, regular evaluation of progress in making behavior changes, discussion of barriers to making change as they come up, and consistent support from the provider to help the patient maintain adherence to changes.

Another approach is to address one behavior change at a time. The patient very well may need to improve their diet, physical activity, sleeping habits, coping with stress, etc. However, changes are difficult to make and even more difficult to sustain. Focusing on just one change in a visit improves the likelihood that making that change will be successful, prevents the patient and family from feeling too overwhelmed, and saves the provider time in the office visit. The patient and family can then use what they learned from making the first change in their efforts to make changes in other aspects of their health, and other changes can be addressed in future visits [16].

Ambivalence

Ambivalence, often viewed as negative, is in fact a normal, healthy part of a behavior change process. Ambivalence is also an opportunity for the provider to explore both the pros and cons of the desired behavior change. Open-ended questions can help the patient explore their own ambivalence and allow the provider to drive "change talk" by reflecting back the patients' own reasons to change and encouraging more discussion in the positive direction. It is important to avoid persuasion and overuse of the directing style with patients who seem reluctant to change. Instead, seek clarity and meet patients where they are. Listen for subtle

change talk, which might include words such as "want" or "like" (he/she has a desire to change), "could" or "might be able to" (he/she is thinking about their ability to change), or "should" (he/she feels the need to change). When the patient seems reluctant, reflecting this change talk or asking questions to elicit this sort of change talk can help evoke the patient's own motivations for change. It is ultimately up to patients to decide whether they want to change or not, and keeping this in mind can help to prevent provider burnout [17].

Attrition

Despite the care provider's intent to engage families and form a strong alliance, families may not return to the clinic for obesity treatment for various reasons. Attrition rates are remarkably high in childhood obesity treatment programs, ranging from 27 to 73% [18]. In a systematic review of satisfaction with pediatric obesity treatment programs, Skelton and colleagues recommend that programs should ask detailed questions about aspects of care and pay attention to patient satisfaction in order to help address any manageable issues and decrease attrition [19]. Working to build strong therapeutic alliances with families through the use of empathic listening, sensitivity around discussions of the child's weight, and motivational interviewing can ideally provide enough engagement to decrease attrition. However, there are some factors outside the provider's control—such as life stress and cost of appointments—that will prevent some families from coming back for treatment. It is important to be aware of these issues and to provide families with resources to assist them when available. The providers must also think about the "MI spirit" of honoring the patient's autonomy—this will help to prevent frustration and burnout when patients miss appointments or lack the ability to meet behavioral goals.

Tailoring the Approach According to Age, Gender, and Maturational Status

For younger children, it is best that providers direct MI to the parents, who have the greatest control over their child's health behaviors [2]. By teaching parents about healthier lifestyle practices and motivating parents through MI techniques, the parents become the agents of change in the home and best role models for the child. This also keeps the entire family engaged, creating a very supportive environment for the child. Several family-based pediatric obesity interventions with MI directed toward the parent have shown significant improvement in health-related outcomes for both the parent and child [16, 20, 21].

Once children become adolescents and teens, however, efforts should be made to address behavior change directly with the patient [2]. Parents should still be involved to help create a supportive environment in the home in order to best reinforce changes, and some adolescents and teens may be strongly influenced by their parents depending on their developmental stage and maturity. Similarly, some older children might be mature enough to benefit from direct MI counseling. In general, the power of teen autonomy needs to be recognized and appreciated, and therefore individual conversations with the mature child, adolescent, or teen are often necessary. The "MI value trial" for children ages 11–18 involved MI sessions directly with the adolescent/teen along with a multidisciplinary family-based treatment program called TEENS (Teaching, Encouragement, Exercise, Nutrition, and Support) Program [22]. TEENS involved physical activity, dietary intervention, and behavioral support and consisted of sessions that run independently with the parents/caregivers and adolescents. Those TEEENS participants randomized to receive the MI intervention had significantly greater 3-month and 6-month adherence to the TEENS program, thus demonstrating that MI can help to increase engagement and reduce attrition.

Success with MI in the Literature

MI has been shown to be successful in studies of adults, particularly in substance abuse and weight management [23]. Among pediatric populations, MI has been found in several

studies to produce statistically significant changes in child BMI along with improvements in behavioral outcomes, and it is the recommended form of counseling with patients and families in the prevention and management of childhood obesity [23, 24]. The success of MI in the literature has led to the implementation of MI training at all levels of medical education, including primary care practices, with evidence of significant benefits in patient outcomes in some studies [17, 25–30]. MI is associated with high satisfaction rates among patients. An evaluation of parent perceptions of an MI-based prevention intervention in the primary care setting geared toward parents, called "High Five for Kids," demonstrated that the majority of parents reported being very satisfied with the intervention and 91% stated they would recommend it to other families and friends [20]. The use of MI is also associated with decreased provider burnout, an important and welcome side effect for burdened healthcare workers [17].

Limitations of MI

Although MI is the recommended counseling method of choice, there are some conceptual issues with using MI effectively in practice [15]. The literature on MI for pediatric obesity is still somewhat limited, and despite the evidence discussed showing positive effects, some other studies have demonstrated more mixed results [24]. It is also difficult to tease apart in research which effects of MI interventions are due to MI itself versus the more general empathetic concern and attention given by providers using this method [15].

Moreover, despite the recommendations discussed, it is unknown at which age to begin using MI directly with youth versus with their parents [15]. Additionally, some individuals might prefer a more directive method whereby the provider tells patients what they should be doing, which is in contrast to the guiding style utilized in MI. These last two points emphasize the importance of tailoring the intervention to the needs of the patient and family, which requires skilled clinical judgment. MI might not be the best method of choice for everyone, and so the provider must be flexible and adapt to what will best serve the patient and family.

Conclusion

Motivational interviewing is the skillset that allows the primary care provider to develop a therapeutic alliance with the patient and family. For weight-related discussions and behavior change counseling sessions, these skills strongly predict success with patient adherence and outcomes. Primary care providers can inadvertently harm the therapeutic alliance by displaying judgment or making assumptions about patients' inability to meet goals that seem clear and achievable. However, providers can strengthen the relationship and leverage it to create better outcomes for patients by listening to understand, reflecting change talk, and, above all, displaying true empathy for the patient's circumstances, cultural context, social determinants, and natural fluctuations in motivation. Primary care providers are the first line to combat the obesity epidemic, and their most powerful tool is a cultivated and open relationship with patients that allows for long-term management of what is now understood to be a chronic disease.

Editor's Comments and Question

Management of childhood (and adult) obesity can be a frustrating experience; the approach outlined in this chapter makes eminent sense and offers the best hope for an outcome satisfactory to the patient as well as the provider.

There are of course teenagers (and parents) who express at the outset a lack of interest in changing behavior, but most others have the desire to change for reasons related to appearance, social acceptability, and/or long-term health. Appearance and acceptability are conditioned by social and

ethnic context and vary among girls and boys, but concerns about health outcomes are often shaped by the family's experience with the metabolic and cardiovascular complications of obesity. In that regard, the primary care provider can assist the family by explaining, in a nonjudgmental manner, the relationship between childhood and adolescent obesity and long-term comorbidities.

Still, I have found it difficult to predict with certainty which children and families will be receptive to behavior change. Can you identify factors that clearly predict a response to counseling? Do these factors modify your therapeutic approach?

Authors' Response

Engagement with behavior change counseling is largely determined by factors discussed in this chapter, namely, the relational aspects of the physician-patient or physician-parent conversation. The way in which the physician engages the patient in this discussion far outweighs any stable traits or patient-level demographics at baseline. However, several factors specific to the parent and child may influence how receptive the family is to counseling and how able they are to adopt recommended lifestyle habits. One of the strongest factors predicting positive child health outcomes in weight management is a highly motivated parent. The parent's confidence in managing their own weight is strongly predictive of the child's ability to reduce BMI in treatment. In addition, parents with a greater degree of obesity are less likely to complete treatment with their child. Families who are living at or near the poverty line are less likely to be successful, largely because of lack of access to safe and attractive spaces to be active, living in "food deserts" where fresh and healthy foods are not available or are too expensive, and reliance on school lunch programs for the child's daily meals.

For more on the topic of parental confidence and motivation, see the references below:

Parental Confidence

- Phan TL, Curran JL, Abatemarco DJ. Disparities in parent confidence managing child weight-related behaviors. Patient Education Counseling 2015;98(1):85–9.
- Parent confidence is a strong predictor of treatment completion and child weight loss.
- Arsenault LN, Xu K, Taveras EM, Hacker KA. Parents Obesity related behavior and confidence to support behavioral change in their obese child: data from the STAR study. Academic Pediatrics. 2014;14(5):456–62.
- The parent's personal obesity-related behaviors are factors that may affect their confidence to support their child's behavior change. Article describes how PCPs should seek to prevent child hood obesity by addressing parent/family behaviors as part of their obesity prevention strategy.

Parental Motivation

- Wilfley DE, Kass AE, Kolko RP. Counseling and Behavior change in Pediatric Obesity. Pediatric Clinic North America. 2011;58(6):1403–x.
- Understanding parent motivation may be relevant given that providers rate lack of parental involvement as a common barrier to obesity treatment.

Parental Involvement

- Parental obesity is a risk factor for childhood obesity.
- Child's weight-related behaviors are developed and maintained within the context of the family.
- Wilfley DE, Kass AE, Kolko RP. Counseling and Behavior change in Pediatric Obesity. Pediatr Clin North Am. 2011;58(6): 1403–x.

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40 The Sociocultural Context for Obesity Prevention and Treatment in Children and Adolescents: Influences of Ethnicity and Gender

Shiriki Kumanyika

Introduction

Obesity prevention and treatment ultimately involve changing individual eating and physical activity behaviors. These behaviors are strongly influenced by sociocultural variables (i.e., norms, values, and beliefs) and by aspects of related environmental contexts (i.e., physical and economic characteristics, policies, and practices) in communities, homes, schools, and media environments. Racial/ethnic groups identified by the US Census Bureau as minority populations now comprise more than one-third of the US population, are projected to become more than half of the population within a few decades, and are already the majority of the populations in some states [1, 2]. Health profiles of children in many minority populations reflect higher than average risks of obesity and obesity-related risk factors and diseases. Thus, from a population perspective, obesity prevention and treatment efforts must prioritize reaching these high-risk groups. This chapter includes a conceptual framework of pathways whereby sociocultural and environmental factors influence obesity, draws primarily on evidence from studies of black or Hispanic children, and describes potential solutions. The main focus is on obesity interventions outside of clinical settings.

Background

US Minority Populations

US minority populations are classified into the following broad racial/ethnic categories: "black or African American," "Hispanic or Latino American," "American Indian or Alaska Native," "Native Hawaiian or other Pacific Islander," and "Asian American" [1]. Because Hispanics can be of any race, a designation of "non-Hispanic" is often applied when Hispanic ethnicity has not been indicated. In this chapter, for brevity, this designation is not always used. The Census Bureau categories are useful for identifying general patterns of ethnic variation, although the substantial heterogeneity within each of these categories must be recognized, including socioeconomic variation. However, on average, children in minority populations are socially disadvantaged in comparison to non-Hispanic whites [3]. Census data indicate that 66 and 42% of black and Hispanic children, respectively, live in single-parent families, compared to only 25% of non-Hispanic white children [4]. As shown in Table 40.1, the highest poverty rates are among children living with single mothers and, within this group, black and Hispanic children. Maternal

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Table 40.1 Selected sociodemographic characteristics of US white, black, and Hispanic households with children, 2015

Variable	Racial/ethnic category		
	Non-Hispanic white	Non-Hispanic black	Hispanic
% of the child population	57.4	14.5	20.1
% of children ages 6 to 18 whose mothers have less than a high school education	5.0	9.0	34.3
% of children ages 6 to 18 whose mothers have at least a bachelor's degree	43.0	22.4	14.1
% of children living in households below the federal poverty line	12.1	32.9	28.9
% of children living in households with incomes below 50% of the poverty line	5.8	15.8	11.5
% of families headed by single mothers with incomes below the poverty line	35.7	46.2	48.8
% of children in food-insecure households	13.7	26.9	23.8

Source: Child Trends. Data Bank Indicators, 2015. http://www.childtrends.org/databank-indicators/

education at the bachelor's degree level as an indicator of more favorable social position is much more common among whites than either blacks or Hispanics (Table 40.1).

Obesity Prevalence and Trends

The National Health and Nutrition Examination Survey (NHANES) data for 2–19-year-olds in 2011–2014 show obesity prevalence at 14% for white males, 12% for Asian American males, 18% for black males, and 22% for Hispanic males. For females, obesity prevalence was 15% in whites, 5% in Asians, and 21% in black and Hispanic females [5]. These data use the 95th percentile cutoff on the Centers for Disease Control and Prevention age-specific BMI reference curves. One caveat regarding the prevalence in Asians is that the interpretation of BMI percentiles might underestimate obesity-related risks due to ethnic differences in body fatness or body fat distribution at the same BMI level [6, 7]. Figure 40.1 shows obesity prevalence by ethnicity-gender-age groups [5]. The relatively higher prevalence in black and Hispanic vs. white children is most evident in the 2–5- and 6–11-year-olds. Among adolescents, the percent with severe obesity (BMI ≥ 120 of the 95th percentile for age and gender) is 6 and 7% in white males and females, respectively; 11 and 13% in black males and females, respectively; and 9 and 8% in Hispanic males and females (not shown), respectively [5]. These patterns of obesity prevalence are similar to the ethnic differences observed in adults [8].

The Centers for Disease Control and Prevention (CDC) reported trend data for low-income children aged 2–4 years in five ethnic groups, based primarily on data for children enrolled in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). The overall data showed an increase between 1998 and 2003 and then a small decline (less than 1 percentage point) by 2011 [9]. Ethnicity-specific data for white, black, and Hispanic children followed this pattern, although the prevalence in Hispanic children in 2011 was substantially higher (19%) than in white and black children (13 and 12%, respectively). Obesity prevalence in Asian and Pacific Islander children showed a consistent decline (from about 14 to 12%). In contrast, prevalence increased steadily for the American Indian/Alaska Native children, whose 2011 prevalence was the highest of all ethnic groups (21%). High and increasing levels of obesity were noted in American Indians/Alaska Natives, including children and adolescents [9], a finding that can easily be overlooked because data for these populations are not routinely reported in national data sets and are of great concern [10].

Figure 40.2 shows obesity trends in NHANES data over two decades for school-aged children and adolescents [11]. Within each age category, initial upward trends are observed after some level off or decline. Gender differences are observed for all three ethnic groups and between ethnic groups. In 6–11-year-old black children, obesity prevalence increased steeply in boys, closing a notable gender gap observed in the 1990s. An opposite gender difference in trends was observed in Mexican American children in this age group, also closing a previously observed gender gap. Obesity in girls increased steeply to a level equivalent to that in boys, among whom prevalence began to decline. A transient gender difference in white 6–11-year-olds was also observed in the period between 2010 and 2014. Trajectories were more mixed in the data for the

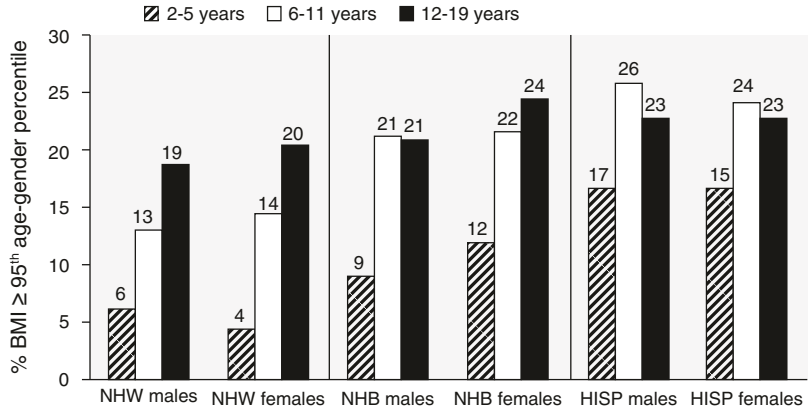

Fig. 40.1 Obesity prevalence in non-Hispanic white, non-Hispanic black, and Hispanic children by age, USA, 2011–2014. Percentages are rounded. Estimate for 2–5-year-old white males has a relative standard error greater than 30% (Data from: Ogden CL, Carroll MD, Lawman HG, Fryar CD, Kruszon-Moran D, Kit BK, et al. Trends in Obesity Prevalence Among Children and Adolescents in the United States, 1988–1994 Through 2013–2014. JAMA. 2016;315(21):2292–9)

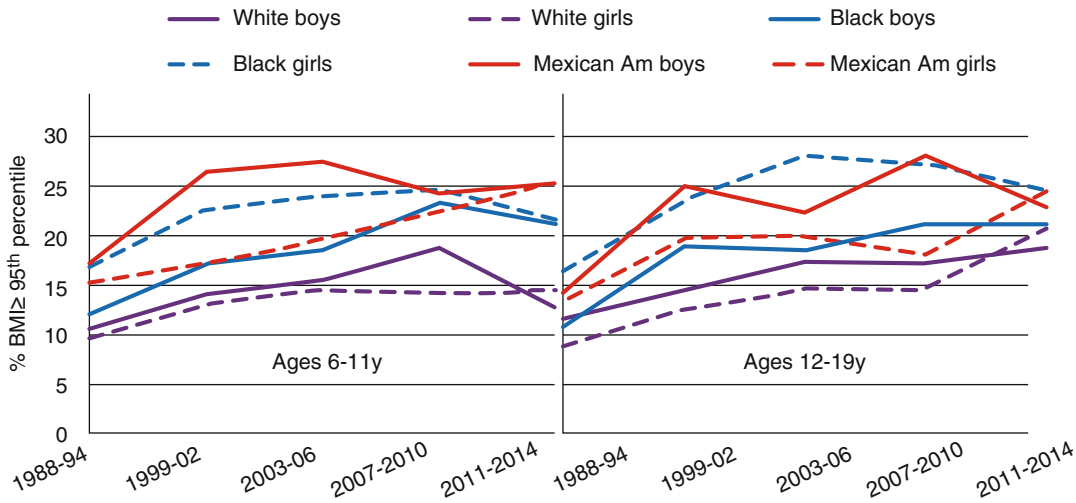

Fig. 40.2 Obesity prevalence trends by ethnicity-gender categories in US children ages 6–11 years (*left panel*) and 12–19 years (*right panel*). 1988–1994 estimates for 6–11-year-old white girls and 12–19-year-old Mexican American girls have relative standard errors of 20–30% (Data from: National Center for Health Statistics. Health, United States, 2014: With Special Feature on Adults Aged 55–64. Washington, DC: U.S. Government Printing Office; 2015)

12–19-year-olds with a suggestion that obesity prevalence was converging across ethnicity-gender groups toward the end of the period.

Obesity prevalence varies with socioeconomic status (SES) but not consistently across ethnicity-gender categories or over time, with some observations of less favorable trends in lower-SES population subgroups [12–14]. For example, as shown in Fig. 40.3, white children in households where the head of household was a college graduate had the lowest obesity prevalence and, among girls, declining obesity prevalence; in contrast, there was no clear association of head of household education and obesity rates in black boys and girls [15].

Pathways of Sociocultural Influences on Obesity-Related Behaviors

Pathways linking ethnicity to weight status, shown in Fig. 40.4, are applicable to children generally and relevant to the above-average

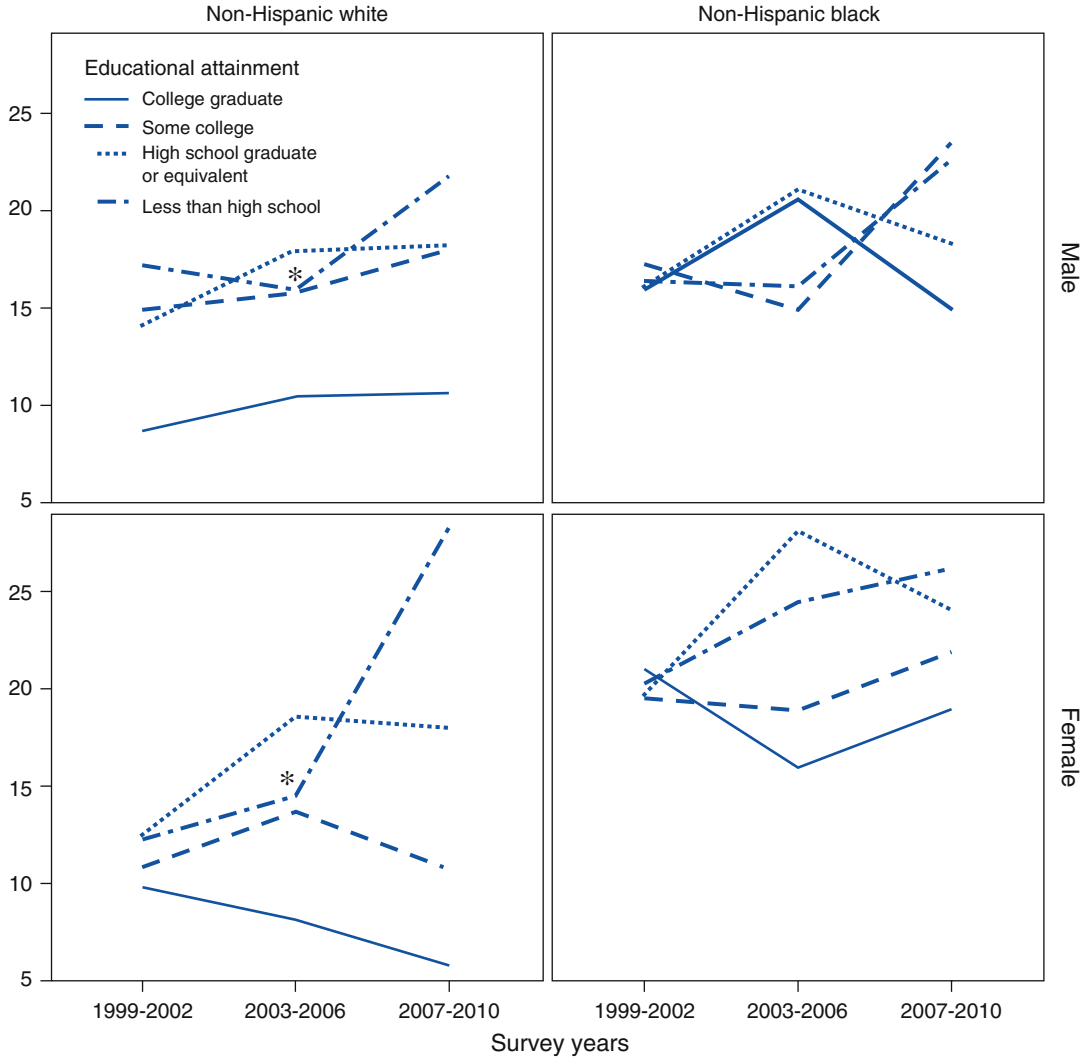

Fig. 40.3 Prevalence of obesity among children and adolescents aged 2–17 years, by sex, race/ethnicity, and educational attainment of adult head of household—National Health and Nutrition Examination Survey, USA 1999–2010. *indicates a relative SE between 30 and 40% of the prevalence (Public Domain: Used from May AL, Freedman D, Sherry B, Blanck HM. Obesity - United States, 1999–2010. MMWR supplement. 2013;62(3):120–8)

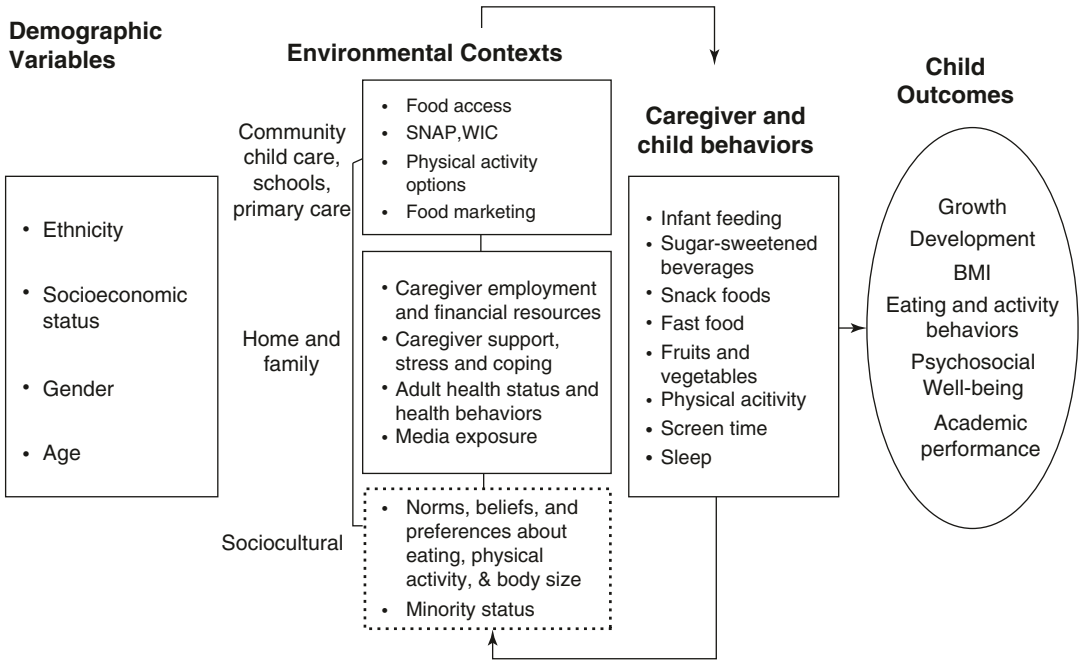

Fig. 40.4 Pathways for ethnic and gender influences on prevention and treatment of child and adolescent obesity. See text for explanation

obesity risk among children in high-risk ethnic groups. Demographic variations by ethnicity and gender must be considered in light of the age at which various influences may become relevant and also in light of the socioeconomic differences as potential components of obesogenic impact. Situational factors with a direct influence on eating and activity are grouped according to three types of interrelated environmental contexts. These situational variables and their effects provide intervention targets for environmental and policy changes to improve physical or economic support for obesity prevention and family-based treatments. Exposures in the neighborhood, school, home, and media environments may contribute to ethnic disparities or gender differences in obesity risk or prevention and treatment contexts. In addition, male and female children will experience the same environments differently with respect to physical, social, or cultural influences on eating and physical activity behaviors. Some examples of these differences follow.

Culturally influenced attitudes and beliefs are shown with a dotted line in Fig. 40.4 to indicate that they are probably not directly amenable to obesity prevention and treatment interventions. However, awareness of these variables is critical for tailoring interventions and understanding responses to interventions, and they are discussed later in this chapter within this context. "Minority status" refers to psychosocial variables that are not intrinsically related to ethnicity but may emerge from disadvantaged social position of ethnic minorities within the larger society. For example, certain types of coping responses emanating from experiences of oppression, deprivation, bias, and discrimination may have adverse health consequences.

The child and caregiver behaviors in Fig. 40.4 are the proximal mediators of child weight outcomes and where ethnicity and gender influences will operate. The reverse arrow from these behaviors to the sociocultural norms suggests that aggregate behavior changes would feed back on sociocultural influences and change what is viewed as normal and health protective. This would, in turn, be expected to foster receptivity to prevention and treatment interventions.

Environmental Influences on Child Obesity

Neighborhood and Community

Neighborhood food and fitness resources vary greatly among communities of different ethnic and socioeconomic composition and across spatial uses. There are high levels of residential segregation by ethnicity, race, religion, income, and variables such as proximity to high-quality schools, services, retail, and other resources. Black and Hispanic Americans live in neighborhoods that are predominantly minority. On average across the USA, the neighborhoods of black Americans are 45% black, 15% Hispanic, 4% Asian, and 35% white, and neighborhoods of Hispanic Americans are 46% Hispanic, 11% black, 7% Asian, and 35% white [16]. In contrast, the average white American lives in a predominantly white neighborhood (75% white).

Studies of neighborhood influences on obesity indicate less contextual support for healthy eating and physical activity in communities that are systematically disadvantaged because of ethnicity or SES. A systematic review [17] concluded that availability of food stores, products within stores, and food promotions within stores in communities with high proportions of African American residents were consistently less conducive to healthful eating compared to those in predominantly white neighborhoods. A comprehensive review of studies published over the 15-year period between 1995 and 2009 concluded that there were relatively fewer supermarkets or good sources of produce and relatively more small grocery and convenience stores in black, Hispanic, or poor neighborhoods; however, data indicating whether there were more fast-food restaurants were inconclusive [18]. Nevertheless, targeted marketing of fast foods to black and low-income communities may increase the patronage of fast-food restaurants in these communities [19, 20]. Yancey and colleagues [21] reported that African American neighborhoods had the highest densities of obesity-promoting outdoor advertisements (i.e., fast food and sedentary entertainment), closely followed by Latino neighborhoods. Similarly, Hiller [22] found disproportionate clustering of outdoor advertisements for less healthful products around schools in black neighborhoods in Philadelphia.

Reviews of food prices have generally not reported differential exposure according to ethnicity or income [17, 18]. This apparently also applies to price promotions (i.e., advertised sales or discounts); no differences were observed by community demographic characteristics in a nationwide sample of food stores [23]. However, the reported high frequency of price promotions for sugar-sweetened beverages (18% on average) may be relevant in that these products are much more heavily promoted to black and Hispanic children and adults [19, 24] and are more likely to be purchased when on sale [25].

Gender and ethnic differences are reported in relation to neighborhood environments for outdoor physical activity, including walkability and recreational facilities, and crime. Studies have found sex-specific effects for neighborhood design, with preschool girls less likely to be overweight or obese in "walkable" neighborhoods with a greater number of intersections [26]. In a different study, adolescent girls made more active trips per week in communities with more traffic lights; boys were more active if living on a cul-de-sac rather than off a main road and in neighborhoods with more speed bumps [27]. Data from the National Longitudinal Study of Adolescent Health reveal less access to recreational facilities in neighborhoods with high proportions of minority or low-SES residents [28]. Crime is another key environmental factor: youth in high-crime areas are less likely to walk to the store or play outside. Areas around schools with greater poverty and Hispanic student populations have been shown to have higher crime rates [29]. A meta-analysis of environmental factors that affect obesity found that crime was inversely associated with adolescent physical activity in two out of three studies [30]. The importance of safety for facilitating and sustaining physical activity in children in minority and low-income communities is also supported by studies described in other reviews [18, 31].

School and Child Care

Policies and practices in schools and child care homes and centers impact children's weight status as well. Children in ethnic minority or low-income populations should have the same options as their white or higher-income peers. Ideally, federal policies such as the Healthy, Hunger-Free Kids Act of 2010 and subsequent related initiatives will contribute to childhood obesity prevention in all children at schools and centers that participate in school or child care food programs [32]. Because these programs require adherence to specific health-oriented policies and are targeted to children in low-income areas, full implementation would be expected to address any disparities that were present in prior times.

However, full implementation does not take place automatically or at the same level in different demographic areas. For example, Hood and colleagues reported that school wellness policies and access to healthy foods were less likely in schools that were nonwhite (defined as having more than 66% children from minority populations) [33]. The authors also reported poorer access to physical activity options in schools in low-income communities [34]. Provision of physical activity opportunities at school may be especially important for children who do not have adequate opportunities in their neighborhoods. For example, parents may keep children indoors because of parent work schedules that preclude adult supervision of outdoor activity, lack of access to organized and supervised recreation, or concerns about neighborhood safety.

With respect to feeding of infants and preschool children, federal guidelines address practices related to cooperation with mothers who provide breast milk for their children, availability of water, and timing of introduction of solid foods. However, the reach of policies oriented toward healthier eating and healthy growth will vary according to ethnicity and income; these factors are associated with the percent of children in organized child care and the type and quality of that care.

Home

Homes are the most critical environments for children's development, health, and mental well-being. Overall, the same types of home and family environment factors relate to obesity risk in all ethnic groups. However, the specific associations vary with ethnicity [35, 36]. Obesity prevalence is 57 and 46%, respectively, in black and Hispanic women and 38 and 39%, respectively, in black and Hispanic men [37]. This high prevalence of obesity among adult caregivers implies potential obesity-promoting influences through weight-related attitudes and norms, home food availability, and modeling of eating and physical activity behaviors. As previously noted, having college-educated parents may not be protective against obesity development in black children as observed for white children. However, caregiver employment and income may determine the types of child care arrangements caregivers need or can afford as well as their ability to afford certain types of recreational activities for their children, especially if these require transportation outside of the neighborhood.

Targeted income and nutrition assistance programs such as the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) or the Supplemental Nutrition Assistance Program (SNAP) are intended to increase the likelihood that children living in families with incomes below or near the poverty line will have adequate and appropriate food and nutrition. Compared to earlier versions of the program, WIC now provides pregnant women and caregivers of children up to 5 years of age with a healthier package of supplemental foods (e.g., whole grain products, fruits and vegetables, and less fruit juice) and continues to provide nutrition education. SNAP augments family resources for food purchases and has tested various programs to incentivize the use of SNAP dollars for purchases of fruits and vegetables. When considering the aforementioned access of children in low-income families to meals in school and in child care settings and the improvement of nutritional standards for these meals, the nutritional quality of foods available to children

in low-income families in all ethnic groups may prove to have a major protective effect on child obesity nationwide.

Lack of resources, health issues, and other factors may cause stresses for caregivers that directly or indirectly influence children's weight [38–41]. Interviews with low-income parents revealed a stressful work-family balance that constrains healthy family food choices [42]. In a study of black parents, perceived stress was associated with haphazard meal planning and emotional eating as well as snacking on sweets among those who were overweight [43]. A study with black parent and grandparent caregivers suggested that how they cope with stress or the degree of structure in their household routines may modify effects on children. Some black parent and grandparent caregivers reported strategies for coping with stress that would predispose to children's consumption of high-calorie, nutrient-poor foods or higher screen time, while others described strategies to avoid adverse effects on their children's or grandchildren's eating and activity [44].

Media

Parental restrictions or lack of restrictions on children's media use influences their children's risk of obesity in several ways. Long hours of TV watching or other screen use predispose to inactivity, exposure to advertisements for unhealthy foods, and reduced sleep duration [45]. Data on media use patterns suggest that restrictions on screen time may be less common in black and Hispanic compared to white families and in low-income families [46–48]. Black, Hispanic, and Asian American children (ages 8–18 years) use media four and a half more hours each day than their white peers, of which TV watching is the biggest component. Most black and Hispanic (84 and 77%) children have a TV in their bedroom. TV watching begins at an early age. Project Viva found that 32% of black children between 6 months and 2 years of age watched two or more hours of TV per day, on average [47]. TV watching was lower for white and Hispanic children (15 and 11%, respectively). A later study in this cohort confirmed that longer hours of TV watching were associated with less sleep and that having a TV in the bedroom had an adverse effect on sleep duration in ethnic minority children over and above the hours of TV watched [49].

With respect to advertising, black and Hispanic children and children in low-income communities have disproportionately high exposure to child-targeted and ethnically targeted marketing of fast food, sugary beverages, and high-calorie snack foods through TV and digital channels [17, 50, 51]. Grier and Kumanyika [17] found consistent evidence of greater than average frequency and intensity of advertisements for less healthful foods and beverages in television and digital media markets that reach African Americans. Television advertising exposures of Latino children appear to be similarly adverse [52, 53]. Some of this excess exposure is mediated by longer hours of TV viewing [54], but the above-average frequency of advertising specifically for unhealthy food products on shows watched by black and Hispanic audiences is also a major factor. Exposure to a high frequency of marketing designed to have ethnic salience and appeal combined with marketing in and around food outlets may be synergistic in promoting purchases of unhealthy foods among children and families in black and Hispanic and low-income neighborhoods [20, 24].

Obesity-Related Behaviors

The principles, considerations, and approaches for obesity prevention and treatment discussed elsewhere in this book apply to all children. A key question with respect to addressing risks associated with ethnicity and gender is which of the established obesity-related behaviors and influences should be targeted for greatest impact. Of the child and caregiver behaviors listed in Fig. 40.4, infant feeding, sweetened beverage consumption, physical activity, and screen time have especially strong support as focal points for impacting disparities in childhood obesity.

Infant and Young Child Feeding

Obesity development may be influenced by duration of breastfeeding and by the timing of formula feeding and introduction of solid foods. These variables are also critical for development during the first 2 years of life. Exclusive breastfeeding for 6 months and gradual introduction of complementary foods after that time are recommended by the American Academy of Pediatrics [55]. Even though breastfeeding rates have increased over time, national survey data for children born in 2013 show continuing evidence of lower rates of breastfeeding initiation among black mothers: 66% compared to over 80% in all other ethnic groups except American Indians, among whom only 68% of mothers initiate breastfeeding [56]. Only 39% of black mothers breastfed at 6 months. Breastfeeding initiation and breastfeeding at 6 months are higher among Hispanic mothers (83 and 46%, respectively). However, more non-Hispanic white (58%) and Asian (64%) than Hispanic mothers breastfed at 6 months. Teen mothers, i.e., women who are under age 20 years at the time of the baby's birth, are the least likely to breastfeed for 3 months or more. Breastfeeding rates increase with increasing income.

The role of the WIC program in patterns of infant feeding has been of concern as a possible deterrent to breastfeeding based on findings that low-income women who participate in WIC are less likely than income-eligible nonparticipants to breastfeed [57]. Supplementing breastfeeding with formula early on has been linked to less successful breastfeeding and early discontinuation of breastfeeding. Employment considerations, e.g., the need to return to work and a lack of breastfeeding support in the workplace, may discourage low-income mothers from breastfeeding. Full-time employment and earlier return to work have also been noted as factors associated with shorter breastfeeding duration in African American women [58].

Sugar-Sweetened Beverages (SSBs)

SSBs are prime targets for obesity-related interventions because they contribute more than 40% of the added sugar in the diets of young children [59], have been related to excess weight gain, and are expendable from a nutritional perspective because they do not contain essential vitamins or minerals. As shown in Table 40.2, the percent of students reporting consuming at least one soft drink or pop per day was similar in boys among the three ethnic groups but higher among black girls than other girls [60]. Daily sports drink consumption was higher in boys in all ethnic groups but also higher in black and Hispanic girls compared to white girls. Black students consume less water and milk, suggesting relatively greater reliance on SSBs as beverage choices compared to other groups. Patterns of SSB consumption types differ by ethnicity, with relatively higher consumption of fruit drinks in black children of all ages and Hispanic adolescents and a shift away from regular soda toward sports drink consumption during adolescence [61].

Physical Activity and Screen Time

Gender and ethnic differences in patterns of physical activity become prominent during the transition into adolescence. Decreases in physical activity during this period have been linked with increases in BMI, especially for girls [62] and more so for African American than white girls. In addition, findings that decreases in sedentary behaviors such as screen time correlated with lower prevalence of obesity [63] for girls suggest a possibly important focal point for gender-specific interventions. Table 40.2 shows the consistent gender difference (lower in females) in physical activity across all four variables shown, with the exception of sports participation in white children, which is similar for girls and boys. The lower sports participation in black and Hispanic girls compared to their male counterparts is striking. With respect to inactivity, the higher media use of black and Hispanic children was noted in the prior section. This is also indicated in the data for TV watching in Table 40.2. A combined focus on increases in physical activity for girls and decreased screen time for both boys and girls in these minority populations is indicated.

Table 40.2 Ethnic and gender variation on obesity risk behaviors in the US High School Youth Risk Behavior Survey, 2015

	Non-Hispanic white		Non-Hispanic black		Hispanic	
Variable	Females[a]	Males	Females[a]	Males	Females[a]	Males
Food and beverage intake						
No fruit or 100% fruit juice in the last 7 days	4.3	5.4	5.2	***8.6***	4.0	5.7
No vegetables[b] in the last 7 days	3.7	***6.0***	8.8	***13.0***	7.7	9.2
No milk in the last 7 days	***24.0***	12.1	***44.6***	25.8	***26.3***	13.0
Had ≥1 can, bottle, or glass of soda or pop/day in the last 7 days[c]	15.0	***24.5***	21.6	23.7	18.1	***25.1***
Had ≥1 sports drink/day in the last 7 days[c]	6.7	***18.1***	14.3	***25.2***	12.2	***19.0***
No water in the last 7 days	2.5	2.9	9.0	7.8	2.8	3.8
No breakfast on all 7 days during the last 7 days	***65.2***	56.7	***75.3***	69.2	***69.9***	60.5
Physical activity						
Not physically active for ≥60 minutes on 5 of the last 7 days	***56.5***	38.0	***66.6***	47.8	***66.9***	46.5
Did not attend physical education class on all 5 days in an average school week	***79.8***	70.4	***67.8***	61.1	***67.0***	57.6
Did not play on at least one sports team in past year	39.3	35.6	***52.3***	33.5	***59.3***	43.7
No muscle or strengthening activities on ≥3 or more of the last 7 days	***53.9***	37.0	***65.5***	30.2	***60.1***	35.6
Screen time and sleep						
Played video or computer games or used a computer other than for schoolwork ≥3 h/day, on average school day	38.3	38.9	48.4	41.2	47.4	45.1
Watched TV ≥ 3 h/day, on average school day	18.8	21.4	41.5	37.0	29.2	27.4
Did not sleep for at least 8 h	***75.1***	68.9	***79.4***	74.4	***73.2***	67.1

[a]Bold, italicized estimates are significantly higher within ethnic group
[b]Excluding French fries, fried potatoes, or potato chips
[c]Excluding diet or low-calorie versions
Source: Data were generated from Ref. [60]: Centers for Disease Control and Prevention, Youth Online, High School Youth Risk Behavior Survey, United States 2015 results

Interventions

The ultimate goal in considering the pathways shown in Fig. 40.4 is to provide preventive or treatment interventions that will reach and engage the populations of interest with relevant environmental and behavior change strategies. Cultural adaptations are important aspects of such interventions. Environmental and policy change strategies are also needed to address contextual factors that can affect individual behaviors indirectly. The overall approaches are the same for all children. What differs for interventions with an intentional focus on a single- or multiethnic minority population or on children in low-income families is the explicit attention, in program or policy design and implementation, to sociocultural and contextual factors.

Cultural Adaptations

Cultural adaptation may be necessary to maximize the potential of evidence-based interventions, in which case the objective is to alter the intervention in ways that increase the participation and salience for the population of interest while preserving the elements that are important for effectiveness. This is not necessarily easy to achieve, especially when the evidence-based approach was identified in efficacy studies that constitute treatment in "best case" scenarios—scenarios that are not applicable in community settings. Program assumptions, provider characteristics, and settings may need to be tailored for translation to diverse client populations or communities. A study of cultural adaptation of evidence-based sex education interventions for implementation in black churches provides a good example of what might be involved in maintaining fidelity to the core elements needed for effectiveness while also achieving fit with the intervention setting [64].

Focal points for cultural adaptations include attitudes and beliefs about food, activity, and body size that may influence participation in and response to interventions. For example, body image norms that are accepting of weight levels in the range that is considered unhealthy from a clinical perspective are more common among many cultural groups; this has been noted particularly for black females [65–67]. The high prevalence of obesity among adult caregivers may both reflect and reinforce these norms. Low-income mothers may consider children who are overweight to be well fed and healthy and worry more about children being hungry. Thinness may be associated with having HIV or using drugs [68]. Such attitudes may hinder parental awareness of clinical obesity in their children to some extent. Favorable attitudes and beliefs about eating high-fat and high-sugar foods are consistent with the sensory properties of these foods and may be very difficult to change, even among the motivated, in population groups that are disproportionately exposed to ethnically targeted promotion of such foods and where the availability of these foods is high.

With respect to physical activity, social norms and expectations for girls compared to boys may be a major factor underlying the low physical activity participation of adolescent girls, working in concert with neighborhood factors that discourage outdoor activity. Norms promoting activity may apply more to boys, and norms limiting activity may apply more to females. Factors such as cultural perceptions about femininity, hairstyles, personal hygiene (i.e., not wanting to become sweaty), and the importance of caregiving roles for girls may discourage physical activity of girls directly or by inference from the behavior of adult female role models [69, 70].

Approaches to cultural adaptations have been described by Resnicow and colleagues [71] and Kreuter and colleagues [72]. Distinctions are made between (a) accounting for surface or peripheral influences to increase familiarity, salience, or accessibility of an intervention and (b) accounting for more fundamental or deeper cultural constructs that may reflect differences in world views, explanatory models, or ways of

knowing. In Kreuter' s typology, approaches that only or primarily modify characteristics of materials or other elements to be recognized as culturally relevant are termed "peripheral"; those that use ethnically based health information to contextualize the salience of the intervention for the population are termed "evidential"; altering language to increase accessibility of the information including translated or bilingual formats is "linguistic"; the use of experiences or input from the target group to inform the study design or procedures is a "constituent-involving" approach; and incorporating content that aligns with the underlying beliefs, values, and group norms is called "sociocultural" [72]. Interventions that attempt to work with cultural "deep structure," to use Resnicow's terminology, frame or reframe intervention concepts, processes, and desired outcomes to fit with those of the population of interest and attempt to leverage cultural assets and strengths to facilitate positive outcomes. However, these approaches may be underspecified if culture is defined too narrowly to refer only to attitudes, beliefs, and values without acknowledging the extent to which culture interacts with the relevant social and environmental contexts.

The terms "targeting" and "tailoring" are often used interchangeably to describe cultural adaptations. However, Kreuter and colleagues make important distinctions between these terms [72]. They recommend the use of "targeting" to refer to group-level strategies such as focusing an intervention on only black or only Hispanic participants. This strategy facilitates program delivery in settings and ways that are familiar to and preferred by group members and often involves having providers from the same ethnic group. Kreuter and colleagues reserve "tailoring" for adaptations that consider diversity among individuals within a specific group rather than treating all group members the same. From this perspective, the strongest approach would be to combine targeting and tailoring by making provisions for individualized counseling and support to members of targeted groups. However, given that selecting children in one ethnic subgroup for an intervention may not be possible or appropriate in multiethnic settings, effective interventions based on a broad embrace of diverse cultural perspectives are needed as well.

Gender-specific studies are often an aspect of cultural targeting. For example, the Girls Health Enrichment Multisite Studies focused on African American girls during the prepubertal period (8–10 years of age). The two full-scale studies in this research program, conducted in Memphis, Tennessee, and Palo Alto, California, were carefully designed to achieve cultural relevance and salience and were informed by insights from randomized controlled pilot studies in a first phase [73–75]. However, these ethnically and gender-targeted studies, which were conducted in community settings, did not yield a significant preventive effect on excess weight gain. The lack of a supporting environmental change component may be at least part of the explanation for the null results.

Changing Environments and Policies

As the society-wide nature of forces driving the US and global epidemics of obesity has become undeniable, interventions targeting policy and environmental changes to enable obesity prevention have become a main focus of obesity research and community programs [76–78]. Many such efforts have focused on children, although those that focus on communities at large are also relevant to children through influences on eating and physical activity options for adults and families and on social norms. Mutually reinforcing, multilevel, and multi-sectoral approaches that target obesity-promoting influences in localities and nationally are recommended and are being pursued.

For example, some obesity policy interventions focus on changes in transportation infrastructure, community design, housing and other buildings, and the accessibility of parks and recreational facilities to increase support for active living. Others focus on the accessibility of supermarkets and availability of fresh fruits and vegetables, policies to improve school nutrition programs and other aspects of food and physical

activity options in schools and child care, fiscal strategies (subsidies or taxation) that change the relative cost of healthy or unhealthy products, and social marketing of healthy eating and active living. Social marketing to promote healthy eating and physical activity in the larger message environment is also important to counter children's heavy exposure to commercial marketing for unhealthy foods and sedentary entertainment. These approaches are complementary to education and counseling to influence parent, child, or healthcare provider behaviors, for example, in home visiting programs, primary care settings, or WIC programs [79].

Identifying What Works

There are, as yet, no definitive answers as to what obesity prevention strategies work best in ethnic minority populations. The following summary draws on relevant systematic reviews of interventions with African American and Hispanic children, focusing on preschool, school, and outside-of-school time and family-based approaches [80–85], as well as a comprehensive review of early-life interventions with children in low-income families, which included several studies in US ethnic minority populations [86]. The evidence base is far from adequate. The number of studies is small and many are pilot studies or of low quality. Eligibility criteria are often broad (e.g., at least 50% of the population is from the group of interest), meaning that applicability to that population is not always clear. Data synthesis also suffers from problems common to obesity prevention and treatment studies generally, e.g., reliance on variably assessed self-report data for diet and physical activity outcomes, which are inherently less reliable than objective measures but which are more likely than BMI to respond to short-term interventions. Notwithstanding their limitations, studies conducted to date are valuable in providing examples of what has been attempted in terms of culturally adapted interventions and comprehensive approaches involving environmental and policy changes.

Laws and colleagues identified 32 studies published between 1993 and 2013 that focused on the prevention of unhealthy weight gain in children ages 0–5 in socially disadvantaged communities [86]. Most (n = 22) of the studies were US based, and 14 were conducted in ethnic minority populations (8 in Latinos, 4 in black Americans, and 2 with Native Americans). Interventions were of varying duration and focused on parental or child behaviors, BMI, or all of these. In spite of the mixed nature and low quality of the available studies, the authors identified elements of interventions found to be effective, with the caveat that the studies in Native Americans did not lead to clear conclusions. For children ages 0–2, interventions in home settings or primary care settings (primary WIC programs) to provide anticipatory guidance (support and advice to parents) and initiated prenatally or at birth were found effective with respect to breastfeeding and timing of introduction of solid foods. In children ages 3–5, these authors found evidence to support interventions with a dual focus on obesity prevention and school readiness, inclusion of weight screening and referral, tailoring for cultural appropriateness, and engaging children in educational activities and positive nutrition and physical activity experiences. They emphasized the critical importance of successful engagement of parents in skill building and behavior change counseling and activities.

Interventions continuing throughout the 0–5 age range were not identified in the Laws and colleagues review.

However, a report from the Australian Healthy Beginnings Study with socially disadvantaged families strongly suggests the need for such linked or sequential interventions covering this developmental period. This trial involved an intensive intervention with home visits by community nurses, beginning in the prenatal period and continuing through 2 years. Findings at 2 years included a significant reduction in child BMI and BMI z-score along with increased vegetable consumption in association with the intervention as well as less time spent watching television at age 2, relative to controls [87]. However, these effects were no longer present

after an additional 3 years of follow-up during which there was no further intervention [88]. Continuity of interventions, appropriate to age, during these critical developmental periods may be necessary to overcome the ever-present contextual forces that promote obesity.

Knowlden and Sharma [83] reviewed school-based interventions targeting African American and Hispanic children. Their recommendations, based on characteristics of interventions found to be effective, were for more explicit operationalization of social and behavioral theories, incorporation of process evaluation at multiple levels, measurement of long-term intervention effects, inclusion of cultural tailoring, and reaching beyond the school setting to the family and home environment. One aspect of the emphasis on the family and home environment was to preserve or include school-based intervention effects during summer and winter breaks. These authors also noted the desirability of policy-based interventions when possible but acknowledged that these were not always feasible. Barr-Anderson's review of the effectiveness of outside-of-school time programs (including both after-school and summer programs and policies) raised the need for continuity throughout the year. The effectiveness of obesity- or physical activity-related interventions with African American children in school and child care settings was also supported in a review of several types of environmental and policy change approaches [84].

Although not yet a main focus of research and practice in the obesity field, awareness of the need to link obesity interventions to broader societal efforts to improve overall health equity is increasing. The question of whether underlying causes of disparities in obesity can be addressed separately from efforts to address social determinants such as poverty, limited educational attainment, segregation, discrimination in housing, and access to resources must be considered. Improving food and physical activity options and removing deterrents to healthy behaviors, even when combined with educational and counseling efforts, may be insufficient if community and individual resources and capacity for taking advantage of healthier options are not also addressed by direct interventions [89].

Conclusion

This chapter has highlighted sociocultural and contextual influences on obesity with specific reference to pathways for prevention and treatment in ethnic minority and low SES populations with above-average obesity risks. Recognizing contextual challenges is important for setting realistic expectations of what can be accomplished by counseling individual children or their family members and for identifying needs and opportunities for interventions in community settings. Infant feeding practices, SSB consumption, physical activity, and media use are strongly supported as behavioral foci for interventions to address ethnic disparities in obesity. Gender variation within and across ethnic groups argues for paying close attention to differences in responses to home, school, and neighborhood environments. Differences in sociocultural expectations, roles, and concerns for boys and girls appear to have important implications for weight status, particularly during the pubertal transition and in adolescence.

Group-targeted programs, particularly those that are community based and involve community members in ways that enhance the cultural and contextual relevance of policies and programs, offer opportunities to influence environmental context variables, e.g., to change food availability or physical activity options and to shift social norms away from those that promote overeating and inactivity. Facilitating maximum utilization of nutrition assistance programs such as SNAP and WIC that are already targeted to low-income families is another important strategy. Several examples of potential intervention settings and approaches have been cited, although research related to how best to use knowledge of environmental and sociocultural variations in obesity influences is still very limited. There is now greater emphasis in this area of clinical and public health practice and research. The next generation of research in this area may offer more definitive insights for improving the long-term effectiveness of obesity prevention and treatment programs during

childhood and adolescence. Research and practice going forward will benefit from more deliberate efforts to ensure that health professionals engaged in obesity prevention and treatment find ways to link to colleagues in fields such as education, social care, and community development.

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Editor's Comments and Question

Parental education appears to have a striking effect on the rates of childhood and adolescent obesity in non-Hispanic American white girls and boys (Fig. 40.3); see also the discussion about obesity, income, and education in Chap. 1. The recent fall (in girls) or stabilization (in boys) in obesity rates in white children with highly educated parent(s) could reflect heightened awareness about the risks of obesity, increasing access to resources that promote weight control, and/or increasing sensitivity to dominant (white) cultural norms, which value thinness. The sharp rise in obesity rates among white children with less educated parents might reflect increasing rates of poverty and social disruption and/or targeting of weight-promoting fast foods to low-income people.

Interestingly, parental education appears to have a less pronounced effect on obesity rates in African American children. This suggests that factors in addition to education and economic status must be addressed in order to prevent and treat obesity in minority populations; in your view, these include racial integration of neighborhoods, provision of equitable school resources for black children, and limits on their exposure to obesogenic advertisements and social media.

You also intimate that there are differences in the perception and acceptability of weight variation between whites and African Americans; how might these differences be addressed in order to reduce obesity rates in children?

Author's Response

Your understanding of my perspective on the socioeconomic status issues is correct. One issue is that typical socioeconomic status variables are not equivalent across racial/ethnic categories. It has been well documented that the same level of education and income does not translate into the same opportunities or resources, such as employment opportunities, financial assets, or upward social mobility, for US minority populations. Moreover, it is also clear that socioeconomic variables would not "explain" all race-related effects that contribute to social or health disadvantage. In an ideal world, the contextual factors that differ by ethnic minority and socioeconomic status would be addressed by changes in the social structures that lead to the observed inequities. However, from a practical perspective, the focus is indeed on the types of specific contextual influences you identify, as I discuss in the chapter.

An interesting aspect of social norms about body weight is that they appear to become more relaxed as population weight levels increase, at least among adults, when judged by the percent of people who perceive themselves as overweight or the percent trying to lose weight. This has been demonstrated in two separate analyses of the NHANES data.[a] How this phenomenon translates into adult caregiver attitudes toward child weight levels is unclear.

As I note in the chapter and in Fig. 40.4, sociocultural norms and attitudes within ethnic groups are probably not accessible to change through direct intervention. My

reading of the evidence is that black caregivers' tolerant attitudes toward child overweight are not so much due to preferences for high levels of child weight but to a combination of (a) perceptions that children who are too thin are not healthy, (b) relatively less concern culturally about overweight from a cosmetic perspective, and (c) relatively lesser concern about health effects of overweight at a level that does not impair physical functioning or cause other obvious problems. Guidance to focus on eating and physical activity or inactivity and healthy growth, rather than weight as such, seems relevant generally. When counseling parents and children, too much direct emphasis on child weight leads to excessive weight concern, inappropriate dieting, and poor self-image. Also relevant in black populations is the higher prevalence of severe obesity. There will be more occasions when addressing the metabolic and psychosocial consequences and increased lifetime health risks of severe obesity becomes critical.

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Part XI

The Future of Childhood Obesity in the Global Marketplace

41 Fast-Food Value Chains and Childhood Obesity: A Global Perspective

Michelle Christian and Gary Gereffi

Introduction

A decade after Glass and McAtee's [1] groundbreaking article that called for an integration of the natural, behavioral, and social sciences to study childhood obesity, there is still a need for a broader analysis regarding the economic, political, and social contexts that shape children's food choices. This is particularly evident when we analyze the growth and diffusion of fast food globally. By 2020, expected yearly sales of fast food in the United States will total $257 billion [2]. As concern over fast-food consumption peaked during the last decade, fast-food companies changed their menus, adopted new marketing strategies, and, notably, looked abroad to open more fast-food outlets. This global push was accompanied by a steady rise in the rates of overweight and obese children in low- and middle-income countries, which now carry "the majority of the obesity and chronic disease burden" [3].

According to the World Health Organization (WHO), in 2013 there were roughly 42 million overweight children under the age of 5; 31 million were in developing countries [4]. Figure 41.1 shows the steady increase of combined prevalence of overweight and obesity in children aged 0–5 in developed and developing countries since 1990 [5]. Developing countries refer to the United Nations Classification Scheme which encompasses Africa, the Americas (excluding Northern America), the Caribbean, Central America, South America, Asia (excluding Japan), and Oceania (excluding Australia and New Zealand). The 2016 *WHO Report on Ending Childhood Obesity* documents that low- and middle-income countries have more absolute numbers of overweight and obese children under the age of 5 than high-income countries, although Europe still has the highest proportion of overweight children (Fig. 41.2). Asia had 48% of the world's children under 5 who were overweight and Africa 25% [6]. Although there is wide variation among countries, certain developing nations have seen drastic shifts. In China and Brazil, for example, obesity rates rose more rapidly in children than adults. By 2020 the number of children overweight or with obesity is estimated to reach 60 million [3, 7, 8].

The presence of the fast-food industry and its web of economic relations that connect the global food system together encompass the "complex system in which behavior is affected by multiple individual-level and socioeconomic factors" [9]. Food choices, as Glass and McAtee argue, are embedded within social contexts that place "constraints," "inducements," and "pressures" upon individuals and consumption habits. These multilayered, nested

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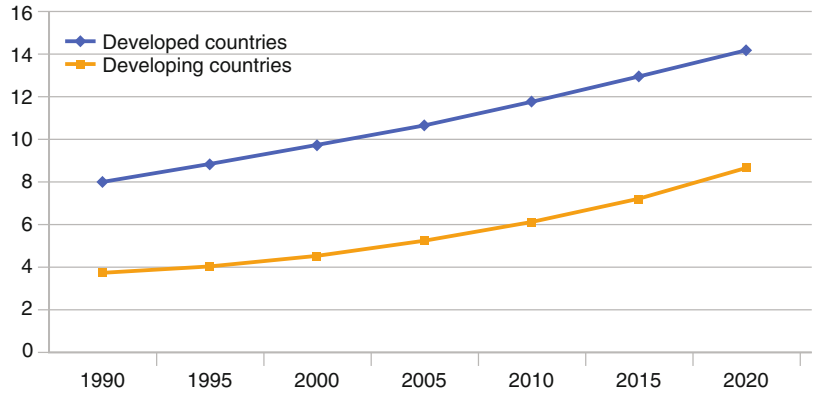

Fig. 41.1 Combined prevalence of overweight and obesity for preschool children in developed and developing countries (Data taken from Wang Y, Lim H. The global childhood obesity epidemic and the association between socio-economic status and childhood obesity. International Review of Psychiatry 24(3) (2012):176–188)

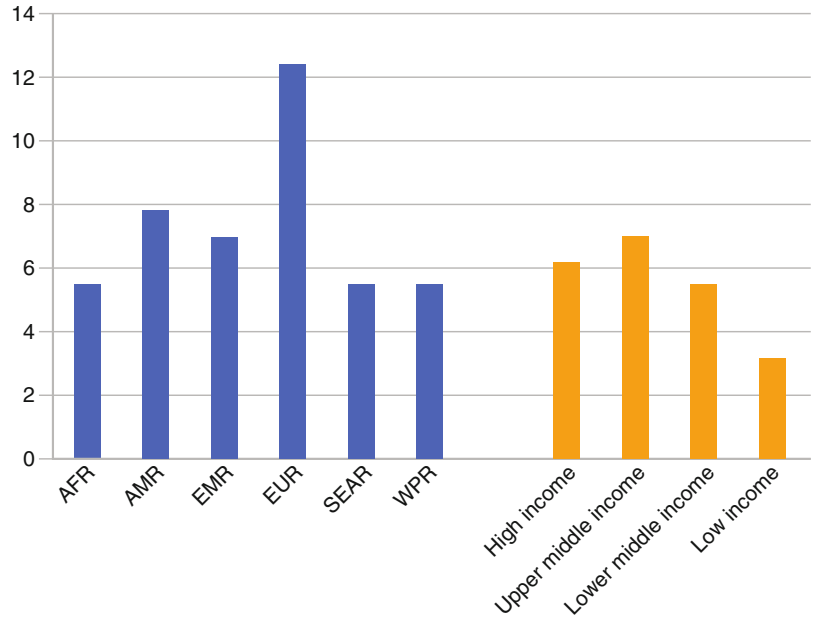

Fig. 41.2 Percent of overweight children under 5 years of age, by WHO region and World Bank Income Group, comparable estimates, 2014. Notes: AFR, African Region; AMR, Region of Americas; SEA, Southeast Asia Region; EUR, European Region; EMR, Eastern Mediterranean Region; WP, Western Pacific Region (Used with permission of WHO from World Health Organization, Report of the Commission on Ending Childhood Obesity, Geneva: WHO, 2016; p. 3)

social determinants exert influence at the micro level of households all the way to macro global systems. Although multiple factors influence childhood overweight and obesity rates, an analysis of the global food environment and the lead firms that shape it, such as fast-food TNCs, is necessary to fully understand the constraints and pressures on food choice in rapidly globalized geographies.

This chapter seeks to advance the multilevel approach to studying childhood obesity by focusing on the "macro" level of corporations in the global economy and connecting it to the theory of "dietary dependence" [10]. The theory of "dietary dependence" posits that a country's mode of integration into the global economy accelerates its population's dependence on imported products and processed

food from transnational corporations (TNCs). Here we use a global value chain (GVC) framework to explain how the structure of the fast-food industry shapes a country's role in the global economy and controls its food availability and food choices. We also seek to determine if or how the global fast-food industry, in general, and food value chains, in particular, have changed since the first publication of this volume in 2010. Essentially, our GVC approach highlights how these macrostructures in the global food system shape national food systems, while local actors impact food options (Fig. 41.3).

The GVC model is based on a series of steps that can be applied to any global industry in terms of how it is organized and evolves (for more information on global value chain analysis, see the Concepts and Tools section of the Global Value Chains website (http://www.globalvaluechains.org) maintained by the Center on Globalization, Governance & Competitiveness at Duke University). First, one identifies the lead firms in the industry and defines how their strategies and roles are changing. Second, the linkages between economic activities that constitute the input-output structure of the chain are highlighted, from raw materials to the production, distribution, and sale of the final product, which helps us understand how value is distributed across the chain and who captures value at each stage. Third, there is an analysis of the governance structure that dictates how the chain operates and who can control the diffusion of technology, standards, and business practices within the chain. Lastly, a review is carried out of the institutions (i.e., governments, unions, nongovernmental organizations, and multilateral agencies) that establish the rules, incentives, and norms that guide the behavior of firms in the chain.

The global value chain for food operates at both the global and local levels. In Fig. 41.3, we highlight the interactions of global and local food value chains that help to cultivate dietary dependence in developing countries. There are different types of lead firms at the global level, including the fast-food franchises that are household brand names in the United States (e.g., McDonald's, KFC, Wendy's, and Domino's), the TNC food and

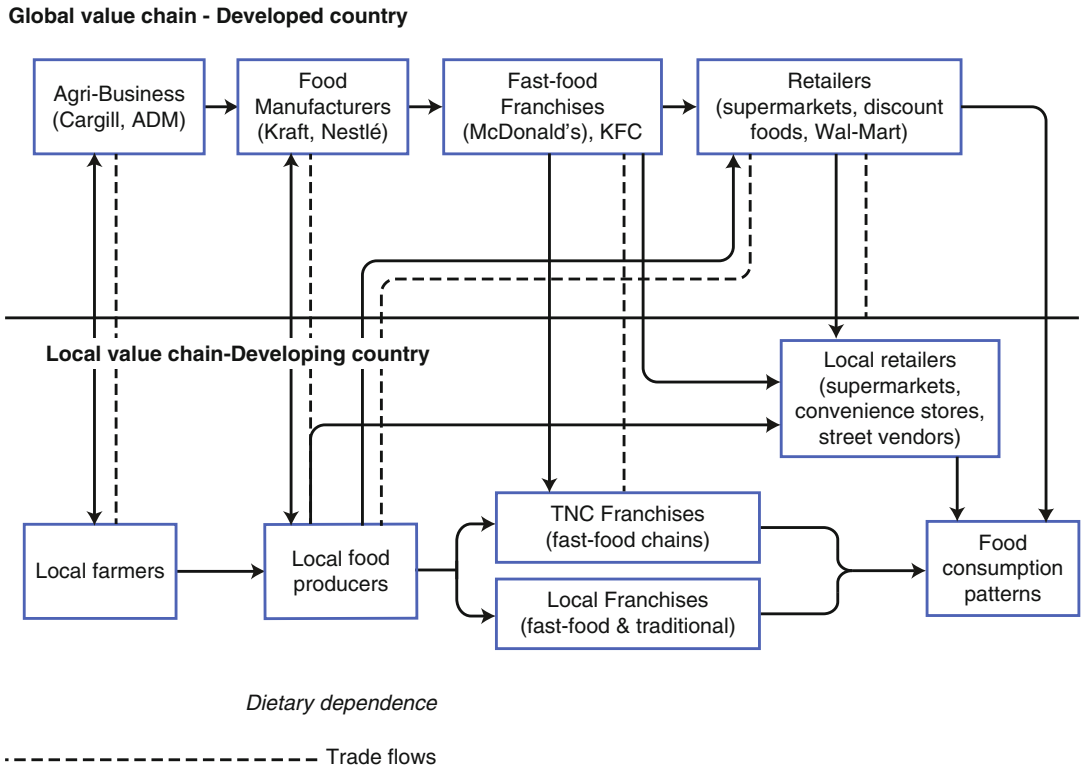

Fig. 41.3 Interaction of global and local food value chains and dietary dependence

beverage manufacturers (e.g., Kraft, PepsiCo, Coca-Cola, Nestlé), and large supermarkets and food retailers (e.g., Kroger and Walmart). These corporations develop elaborate global sourcing and production networks to procure agricultural and food inputs from around the world that are used to generate their final products.

We focus on the organization of the fast-food segment because of its connections to food consumption habits and obesity. A 2014 study in the *Bulletin of the World Health Organization* found that fast-food consumption is associated with an increase in mean BMI (body mass index) in high-income countries and in countries that liberalized their economies for globalization [11]. Several obesity studies over the last few years spotlight the global influence on changing national food systems that directly connect to GVC dynamics [3, 10]. At every stage where the global and local interact—liberalized trade dynamics, foreign direct investment, franchising, and firm imitation effects—the wider food systems are changed, which dramatically transforms people's food availability.

Global food value chains shape consumption and dietary dependence in various ways. Obviously they have a direct impact on the availability of food. Local agriculture producers and suppliers shift their production to cater to multinational firms or go out of business. New local businesses emerge that follow the industrial fast-food model. The international dissemination of Western consumption patterns through the interplay between global and local food chains accelerates. In this way TNCs play key roles in using marketing to define the consumer's perception of food.[1]

An industrial system of ultra-processed and fast foods greatly alters and constrains food choices. A powerful example is provided by an analysis of meat consumption connected to fast-food diets. Fast-food-led firms demand meat products of specific quantity, safety, and processing standards. To satisfy these requirements, meat manufacturing is commonly performed by TNCs that scale up and vertically integrate to guarantee meat supply. The new demand for meats shifts agricultural production from direct human consumption to animal feed. Therefore, meat production for fast food not only produces industrial meat but also facilitates ripple effects in agriculture and processed food varieties due to the new scale and technological diffusion of food manufacturing. In this way, fast-food GVCs establish a global political economic context that supports dietary dependence dynamics and its link to childhood overweight and obesity patterns.

In the remainder of this chapter, we first update fast-food trends in the United States and the emergence of new dominant fast-food companies such as Subway. Next we explore the continued growth of fast food in developing economies and the means by which they shape and impact food value chains by spotlighting China, India, and Russia. Lastly, we analyze recent limited legislative efforts to regulate fast food and the implications for healthier fast food with the recent protests over the wages of fast-food workers.

Fast-Food Trends in the United States

According to Austin and colleagues, US fast-food sales soared around 900% from $16 billion in 1975 to $153 billion by the mid-2000s [12]. By 2015, sales reached $228 billion [13]. Fast-food brands continue to lead chained restaurants in the United States, with McDonald's remaining the dominant firm with $35.8 billion in sales and 14,000 outlets, followed by Yum! Brands (KFC, Taco Bell, Pizza Hut), Subway, Burger King, and Wendy's. Yet, McDonald's is in a highly competitive industry as fast-food chains have looked to pricing deals and new menu items to retain and attract customers.

The recent growth of fast-casual operators, epitomized by the New York City-based Shake Shack (with the highest growing value shares at 59%) and

[1]For a more detailed analysis of GVC methodology and its linkage to consumption, see Gereffi G, Christian M. Trade, transnational corporations and food consumption: a global value chain approach. In Hawkes C, Blouin, Henson S, Drager N, Dubé L, eds. Trade, Food, Diet and Health: Perspectives and Policy Options. Oxford, UK: Wiley-Blackwell; 2010.

Panera Bread (in the top ten for chained fast-food company shares), along with newly dominant traditional brands like Subway, exposes a trend in fast-food consumption toward higher quality and healthier food options, while traditional fast food continues to dominate. Fast casual is a part of chained fast food but represents a slightly higher price point and the perception of higher quality. Chained fast-food categories include burger, convenient store, and retail shopping, in addition to various ethnic food chains. The value chain implications for how these firms may shape food choice differently and whether or not these growing fast-casual brands are indeed healthier overall remain to be seen, particularly with the strength and power of traditional fast-food marketing to kids and continued use of industrial food production.

The largest traditional fast-food chains (like McDonald's and Yum! Brands) brought the mass production concept to foodservice and, in the process, changed how food is produced, distributed, and marketed. These fast-food chains have the market power and visibility to shape consumer choices and business-to-business relationships throughout the entire industry. As lead firms they have dominant shares of the market, which gives them the power to set the performance standards for other firms along the chain. While purchasing power is key [14], the strength of lead firms also comes from their direct and/or indirect control of production, market concentration, brand recognition, and technological innovation.

Multidimensional control of market forces is integral to lead-firm status [15]. Hence fast-food lead-firm decisions have ripple impacts in agricultural inputs, food-processing techniques, and the types of food options that become more abundantly available. The fast-food brands determine the production of food through their requirements for how food products should be cultivated, manufactured, packaged, distributed, and displayed. They work directly with food processors, who in turn work with farmers (Fig. 41.3). The stringent standards placed on farmers and food suppliers spearheaded the rise of industrial agriculture and food processing.

The demands of fast-food brands on their suppliers facilitated the further concentration of giant firms throughout the chain (a process known as "coevolution"). French fries are a good example. The French fries served by fast-food chains (e.g., McDonald's, Burger King, and Wendy's) are supplied by a few very large manufacturers (e.g., McCain Foods and J.R. Simplot), which purchase russet potatoes from big growers/shippers (e.g., United Fresh Potato Growers of Idaho) that receive seeds, herbicides, and pesticides from a specialized corps of crop science firms (e.g., Bayer Crop Science and Monsanto). McDonald's is the largest purchaser of potatoes in the United States, with McCain Foods being the biggest supplier followed by J.R. Simplot. These two potato processors have expanded globally to meet McDonald's exacting standards as they enter new markets.

In addition to revolutionizing and expanding fast-food branded products, the rise of fast food created a platform for the proliferation of processed food varieties that typically are higher in saturated fats and sodium and lower in fiber, iron, and other nutrients [16]. Processed chicken (i.e., patties, breaded strips, and nuggets) is emblematic of the shift from whole foods toward processed varieties channeled through fast-food venues.

The trend of fast-casual and new lead-firm players like Subway raises interesting questions regarding how they shape the value chain and subsequently the quantity of healthy food options. Subway in particular has experienced enormous growth, surpassing McDonald's in 2010 to become the worldwide leader in unit restaurants with over 43,000 units in 2015 (Fig. 41.4). Subway had peak year-on-year growth percentages of 11% in 2010–2011 but has slowly declined since then, although it is still growing faster than McDonald's. Subway's marketing strategy of discounts and "Eat Fresh" slogan highlighted its weight loss potential if Subway was part of consumer diets. In 2015, Subway moved away from highlighting weight loss to a new tagline—"Founded on Fresh"—that sought to position how Subway was going to no longer source meat from animals treated with antibiotics by 2025 [17]. To further compete in the fast-casual market segment, Subway also said it was dropping artificial flavors, colors, and preservatives from its US menu.

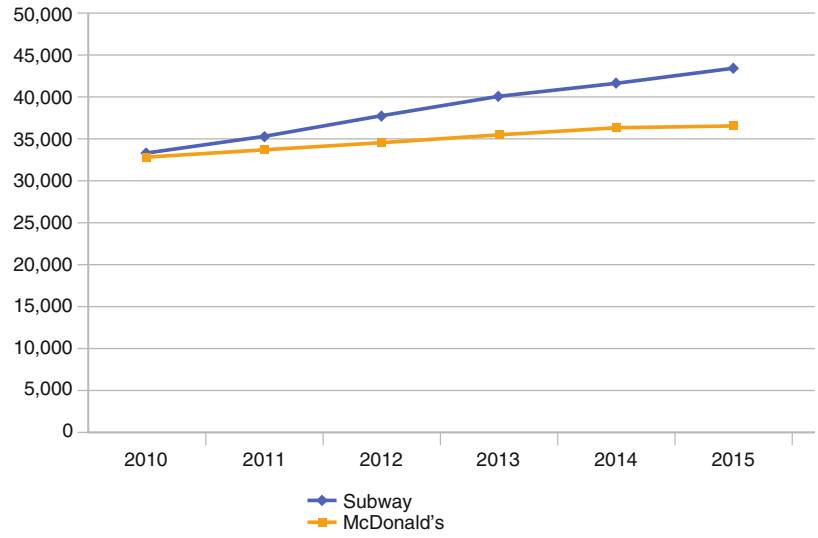

Fig. 41.4 McDonald's and subway: global unit restaurant growth (Data from: Euromonitor International. Fast Food in the United States, 2016)

It is unclear how these moves will shape health outcomes. Although Subway once lauded its weight loss potential, a 2011 study showed that the density of Subway outlets was positively associated with the prevalence of obesity [18]. Their menu options include a foot-long Big Philly Cheesecake containing 1000 calories and meatball subs. Subway's scale and demand for processed meats and ingredients with longer shelf lives follow traditional fast-food models even with the new push away from "flavor enhancers." Furthermore, Subway's value chain looks similar to traditional fast-food brands. Including cost standards, its value chain requires temperature-controlled transportation, speed in distribution, and meats and breads that withstand prolonged storage. Subway's franchisee-owned Independent Purchasing Cooperative works closely with suppliers to pursue efficiency in their supply chain. In essence, Subway relies on the same mass industrial meat production suppliers as other fast-food brands with similar coevolution, vertical integration, and scale dynamics, all of which are part of industrialized food production. Subway also spends heavily on marketing, about half a billion dollars each year during 2012–2014, like the other traditional fast-food brands [19]. Subway allocated $41 million to spend on advertising to children between 2014 and 2017 [20].

Marketing and branding helped to spur the meteoric rise of fast-food chains and to solidify their market power. Rather than being passive consumers subject to adult wishes, children are often the target in the messaging and creation of fast-food identities. In 2012, the fast-food industry spent $4.6 billion to advertise to young consumers while still advertising through popular film and television studios like Disney's Pixar. In addition to traditional television and print advertising, food marketing at schools occurs through product placements, soft-drink pouring rights, and sole vendor contracts [21], as well as fast-food global alliances with film studios. Social media and gaming is the latest expanding medium for marketing to children. Facebook placed 6 billion display ads from fast-food restaurants. Advergaming and informational exchange portals on sites like YouTube and other social media are new ways fast-food brands target children.

Global Fast-Food Expansion: China, India, and Russia

Global expansion of traditional fast-food brands was part of their rapid growth strategy and remains a path to continued growth in the increasingly competitive and health-conscious US market.

The pace has increased exponentially in developing countries since the 1990s, where the gradual removal of market barriers and trade restrictions made the process of internationalization smoother for leading companies. A United Nations Food and Agricultural Organization study on agriculture estimates that, between 2015 and 2030, developing countries will turn from net exporters to net importers of food commodities [22]. In 2015 McDonald's changed its organizational structure, placing high priority on international expansion under International Lead Markets, High-Growth Markets, and Foundation totaling 22,266 restaurants [23]. Yum! Brands opened 2365 global restaurants in 2015 for their brands (KFC, Taco Bell, Pizza Hut) [24]. When fast-food firms enter emerging markets, they have the strength, technological prowess, and modern Western image to impact local food projection in various ways. Matejowsky claims the "efficiency and regimentation" of fast-food production styles reinforce the idea that fast food is often superior to local food because it is "scientifically designed" [25].

Interaction effects between global and local fast-food value chains are seen in the global agribusinesses that buy products from local farms around the world or set up their own farms where they lease out plots to local growers to cultivate the crops that agribusinesses want. These local farms may supply internationally based fast-food units, local food manufactures, or TNCs that have set up operations in developing countries in order to serve the domestic market. In developing economies, TNCs are certainly not the only actors that practice industrialized farming, make processed foods, and set up fast-food restaurants. Domestic companies do this as well. However, the global and local food chains are connected because the standards, practices, and technological achievements of local farmers, manufacturers, and fast-food companies were generally adopted from Western firms [26]. Schlosser argues that McDonald's and other fast-food chains impart to developing countries new systems of agriculture and food production, which reorient local food systems from staple domestic crops to externally induced needs [27]. A closer look at China, India, and Russia highlights these trends.

China is one of the most important markets for fast-food expansion. Since China opened its global doors in the 1980s, the fast-food industry has attained high annual growth, amounting to 9% in 2015 [28]. China is part of McDonald's High Growth Market, with the company opening 400–500 stores there in 2016. Yum! Brands chose to spin off their China business as an independent company—Yum! China—becoming China's largest independent restaurant company with roughly 5000 KFC stores. Its growth is changing the local food system. When J.R. Simplot entered China in 1993 and created the first commercial French fry for the Chinese market, agricultural producers began cultivating potatoes to meet this new demand for processed food.

The food-processing industry in China has grown at double-digit rates. Large foreign food manufacturers continue to set up facilities and expand into China. Tyson Foods operates Jiangsu Tyson Foods Co. and Tyson Rizhao as fully integrated poultry complexes, Shandong Tyson Dalong Food Co. as two modern processing plants, and retail outlets with Tyson Shandong. Tyson's vertical integration strategy in China shapes agriculture as farmers switch to soybean cultivation to satisfy food manufacturing markets [29]. Imports of cereal crops for animal and human consumption are expected to increase with China accounting for 40% of the global demand for poultry by 2020 [30]. After Yum! China and McDonald's, the third largest fast-food company in China is the Taiwanese Ting Hsin International Group, which operates Dicos fast-food brand. Dicos draws from Fujian Sunner Food, China's largest breeder, and Tyson, further elaborating the imitation and interaction effect of fast food throughout the food system.

Marketing to China's youth is also part of fast-food companies' global strategy. McDonald's and KFC have appealed to kids through Internet texting, in-store prizes, and the marketing of "cool" [31]. KFC created a new mobile game app combining "K-pop and cute boy bands" and got 1.3 million downloads in a month. Campaigns centered on "love and friendship" to boost

"consumer affections" and loyalty were part of McDonald's and KFC's Chinese marketing strategy [32]. The nutrition transition in China, with the growth of cheap imported oils, a shift to animal-sourced foods over vegetables, and Western food supply cultivated through fast-food value chain dynamics, accentuates a dietary dependence on energy-dense highly processed foods [33].

The Indian global fast-food market is not as strong as that in China but is growing at a rate of 30–35% per annum, and many fast-food TNCs are expanding in India. Pizza fast food is particularly popular and commands the highest value [34]. Domino's Pizza is the largest chained fast-food brand at 32% of foodservice value. Domino's plans to open 60–65 outlets every year, with Yum! Brands (with KFC and Pizza Hut) following closely behind. After Domino's, McDonald's and KFC are the leaders. Burger King entered the market in 2013 with plans to invest over $100 million to open 500 outlets throughout the country over the next decade [35]. In addition to pizza fast food, dessert options such as ice cream brands like Baskin-Robbins (part of Dunkin' Brands) and Swirls (part of Unilever) are popular and growing.

As in China, India's food system is changing to meet the needs of these global firms. After importing processed French fries for several years, by 2010 each McDonald's French fry came from Indian soil but was processed by McCain Foods. McCain worked with Indian growers for 9 years to change their potato crop to the Shepody variety to meet McDonald's exacting standards [36].

Domino's supply chain tells a similar story of exacting standards. Only the largest food-processing companies can serve as suppliers. Chatha Foods is India's leading processed-meat company and not only supplies Domino's but also Subway and Papa John's. Domino's requires HACCP certification on food safety, to which vendors must comply. Hazard analysis and critical control points (HACCP) is a systematic preventive approach to food safety from biological, chemical, and physical hazards in production processes that has become a global industry standard. Domino's works closely with vendors in what they call "linking up the chain" to ensure consistency, efficiency, and storage [37]. India's rich culinary tradition is quickly being altered, contributing to a loss of traditional food practices according to what Kaushik and colleagues call the globalization of diet [38]. Moreover, the large fast-food outlets in India rely on similar marketing strategies to reach young consumers through social media, discounts, and television commercials.

Lastly, Russia's fast-food growth and impact on the value chain typify the global networks that spur local fast-food sales. McDonald's leads fast-food sales in Russia at 20%, operating 543 McDonald's and 64 McCafé stores in 2015. They are quickly expanding into regional and second-tier markets. McDonald's impact on the fast-food value chain is significant, as highlighted in Berman's [39] insightful study of the Russian fast-food value chain. Berman argues that the foods available in the domestic market are shaped by the "direction of global corporations" that supplies fast-food brands with ripple effects throughout the food system. Furthermore, global trade supports Russian fast-food expansion. Because local agriculture producers cannot meet the exacting standards of fast-food companies, almost all potatoes for fries, half of the ground beef McDonald's uses, and Brazilian poultry are imported. Supplier global firms like Heinz, Sadia, and McCain entered the Russian market to help fill demand.

The Chinese, Indian, and Russian cases expose how the expansion of fast food directly shapes food availability and food options in the global market, strengthening and expanding dietary dependence on imported, processed, and fast-food varieties. The long-term impacts of this process include negative health outcomes and the potential elimination of diverse food varieties and cultural social traditions.

Fast Food on the Defensive

During the mid- and late 2000s, health advocates and government bodies stepped up warnings about the health dangers of excessive fast-food consumption and the irresponsibility of fast-food marketing campaigns oriented toward children.

The US government responded by regulating trans fats, a common component of fast-food products, and requiring nutritional labeling, mostly on a state-by-state basis. Fast-food companies responded by attempting, with varying levels of success, to "re-brand" themselves in the United States by offering healthier options, advocating for healthy lifestyles, and agreeing to voluntarily monitor their marketing practices. Since 2010, the biggest trends shaping the US industry surround the passage of the Affordable Care Act, the power of the fast-food lobby in thwarting government legislation to curb fast-food consumption, and fast-food companies being less publicly targeted for dietary implications and more for the working conditions of fast-food employees, embodied by the Fight for $15 campaign.

The 2010 Affordable Care Act comprehensively changed how health-care insurance was structured, health-care provisions were provided, and individuals gained access to health-care options. It also focused on the prevention of maladies, including obesity prevention. Section 4205 of the Affordable Care Act mandates that chain restaurants display nutrition and caloric information on all menu items [40]. More stringent state regulation that monitored direct consumption was vigorously fought by the industry. In 2012, New York passed a ban on the sale of sugary drinks in quantities larger than 16 ounces, but after pushback from the industry, the New York Supreme Court rejected the ban in 2014 [41]. States such as Arizona, California, and Florida have attempted to pass "Happy Meal laws" that would require that children's meals containing toy merchandise meet certain nutritional standards. This was fought by the fast-food lobby, which succeeded in blocking the right of local governments to regulate consumer incentive items at restaurants in Arizona [42].

More indirect government actions to foster and promote healthy eating options are exemplified by local initiatives employing zoning and licensing laws to regulate the density of fast-food outlets and encourage grocery store development in underserved communities [43]. This is particularly meaningful since McDonald's has been criticized by Corporate Accountability International for "targeting children of color" in their marketing campaigns [44].

Fast-food companies have attempted to deflect criticism by voluntarily changing their menu items; this trend has continued most notably around additives. Subway is removing "flavor enhancers," and other companies such as Taco Bell, Domino's, Papa John's, Noodles and Co., and Chipotle have pledged to varying degrees to end or reduce the use of artificial flavors and colors [45]. This trend follows the re-branding begun by McDonald's after a widespread barrage of harsh criticism, notably in the 2004 documentary "Super Size Me" and bestseller books and documentaries that excoriate the economic and social abuses of our industrialized fast-food culture and agricultural systems that support it (e.g., Food, Inc.; Fast Food Nation; *Omnivore's Dilemma*; and *In Defense of Food*). In the aftermath, McDonald's introduced new salad and fruit options for kids' Happy Meals and promoted a balanced lifestyle.

It is unclear, however, if these initiatives are merely what Simon [46] labels "nutriwashing" or represent attempts to cover up what Brownell and Horgen call the epidemic of a "toxic food environment" [47]. The fast-food lobby continues to strenuously counter any government regulation to directly intervene in changing fast-food consumption patterns. We know little about how these initiatives shape and impact the fast-food value chain, particularly because they seem to do little to change the practices of industrialized food production connecting agriculture and processing, which generates wider ripple effects across the entire food system beyond fast food.

The fast-food industry's attempts to counter criticism need to be placed in a global perspective. The rapid expansion of fast-food restaurants abroad, particularly in developing countries, not only brings fast-food menu items to new markets but also changes local food production systems through global-local interactions that facilitate food dependence on a globalized diet. Fast-food companies typically are not altering their menu options and input ingredients in these geographies to meet health-conscious demand. Although in China there is a growth of salad fast-food

markets, fast-food chicken remains dominant. Similarly, there is a growth of "wellness consciousness" for Indian urban middle class adults but not for kids [48]. The youth demographic in these markets is cultivated through a marketing of "cool" and Western brand ideals actively encouraged by global fast-food companies. This has long-term implications for a diversity of healthy food options and the maintenance of cultural food varieties.

Lastly, the public furor over fast-food marketing practices has largely dissipated since it reached a cultural zeitgeist level in the mid-late 2000s, only to be replaced with protests over the working conditions for fast-food retail employees. McDonald's is once again a key target. The Fight for $15 [49] and Fast-Food Forward Movement that began in 2012 was financially supported by the Service Employees International Union (SEIU). The first protest was in New York City and spread throughout the United States. In 2016 the movement won minimum-wage increases in New York, New Jersey, and California and in cities such as Seattle, Pittsburgh, Missoula, and San Marcos [50]. The movement is riding a wave of public discontent about increased income inequality and job prospects in the post-Great Recession of 2008. Thus far, linking poor nutrition options and poor jobs has not been a consistent strategy of organizers of the fast-food debate, but it could be an important coalition-building tactic to exert influence over the fast-food industry. A coalition that linked workers and nutrition throughout the fast-food GVC would be a particularly powerful symbol for change, both in the United States and internationally.

Conclusion

The severity of the global childhood obesity pandemic calls for new theoretical frameworks and research agendas that take into account the broad factors that affect consumption patterns and behavioral choices related to public health crises. The GVC paradigm gives us a foundation to examine how corporate strategies and international processes relating to the production, distribution, and marketing of fast-food companies are linked to childhood obesity as a health problem.

The rise of the fast-food industry has influenced both social conditions and cultural norms in developed as well as developing countries in ways that contribute to childhood obesity. Many fast-food companies have already been compelled to change certain practices within the fast-food GVC, but research is still needed to determine if the health-related initiatives of top firms are merely superficial or if they might have wider impact throughout the agriculture and food value chains. The structural environment that these companies shape, nationally and globally, continues to constrain, induce, and pressure individuals, and especially children, to make food choices that can adversely affect their health.

Editor's Comment and Questions

The legacy of fast food embodies monopolization of food production and distribution, loss of crop diversity, widespread use of toxic pesticides, contamination of the water supply, reductions in the number of small farmers and shop owners, destruction of natural habitat, restrictive and in some cases abusive animal housing, exacerbation of global warming through emission of greenhouse gases, homogenization and impoverishment of global diets, loss of cultural diversity, and a global obesity epidemic. Yet as soaring sales and proliferation of restaurants throughout the world clearly demonstrate, fast food remains powerful and popular because it is highly palatable (being rich in saturated fat, starch, and sugar), readily available at nearly all times of day or night, and delivered at relatively low cost in clean and

child-friendly surroundings. Round-the-clock work demands for most mothers as well as fathers in rapidly urbanizing populations and limited support for childcare make fast food attractive to people of all classes. The vigorous marketing of fast food to children as well as adults appears to promote loyalty to specific foods and brands and, as you point out, increasingly constrains the ability of people to make healthy and "free" choices about food. I am reminded of the blue sweater scene in The Devil Wears Prada, in which the lead character played by Meryl Streep notes that the color "chosen" by millions of people to wear that fall has in reality been selected and thereby "directed" by a few leading figures in the fashion industry. At least wearing chartreuse or mauve is not likely to make you sick!

In any case, major economic and social forces limit our ability to reverse trends that in many ways seem malignant and self-destructive. You argue that a coalition of people concerned about both food quality as well as fast-food employment practices might galvanize a movement to reduce fast-food consumption. Such an appeal might resonate with millennials; indeed a growing locavore movement has taken hold in many cities, but its costs and inconvenience make it less attractive to those with fewer means. Ongoing government action to protect the health of children and prevent the environmental consequences of fast food value chains could prove effective. In what ways could the government act to achieve these goals? Will this be possible in the Trump administration?

Authors' Responses

Efforts to promote healthy choices in eating have been pervasive for decades, and they have been amply justified on multiple levels. The global childhood obesity pandemic is well documented, and the proportion of overweight or obese children in societies across the globe appears to be accelerating. This trend is associated with the extraordinary popularity in the consumption of fast foods, not only in the advanced industrial societies of the Western world, but also in developing regions like Asia, Africa, and Latin America, as well as large emerging economies such as China, India, and Russia, as this chapter has demonstrated. Curbing the trend toward fast-food consumption has proven notoriously difficult. Numerous articles have chronicled the need to adopt multilevel approaches to tackle this problem at the level of individuals, institutions (families, schools, communities), and national as well as international public policies [1, 3, 7]. These measures have been countered, however, by the extensive marketing campaigns of multinational food conglomerates, which combine their 25 global reach with very adept messaging oriented to youth markets that tap into iconic cultural imagery and fast-food identities that are reinforced by popular films, television shows, and social media. In this environment, what can be done? The locavore movement and its "go local" approach to food consumption has devoted adherents, especially in higher-income markets, but it has a limited appeal to lower-income and younger populations, where the nutritional deficiencies and caloric excesses of the fast-food diet are most striking and dangerous. International agencies like the World Health Organization and specialized national food and drug agencies clearly have the expertise and evidence to pitch healthier eating campaigns, but their legitimacy is too remote and abstract to disrupt a fast-food culture that has adapted to diverse global and social settings, fueled by powerful corporate inter-

ests that link the growth of local franchises and jobs to global supply chains. In the United States, the most lucrative fast-food market in the world, there was hope that national policy could make a difference. The 2010 Affordable Care Act mandated that chain restaurants display nutritional and caloric information on all menu items [40] and various states sought to impose higher nutritional standards related to fast-food sales, but the fast-food corporate lobby has sought to block more stringent regulations at the state level [41, 42]. Furthermore, the incoming Trump administration has vowed to limit the regulatory powers of key government agencies, especially in the realm of social services and health. Therefore, national policy will be hotly contested terrain in the near future, and many fear a reversal of hard-fought gains related to health and wellness issues. The main hope for progressive and innovative policies is likely to come from decentralized approaches to twenty-first century governance. Although President-elect Trump appears to be stacking his cabinet with nominees who dispute the science of climate warming, California is poised to continue to be a leader in climate change regulation, not only in the United States but internationally as well (e.g., California's cap-and-trade program is linked with one in Quebec, and state officials have also had discussions with other countries, including Mexico and China, about joining forces on cap-and-trade measures).[a] A similar approach to regional governance might also pay off in efforts to reduce fast-food consumption. In an essay on "what will regional governance look like by 2030," the World Economic Forum suggests that "we're likely to see a 'pop-up culture' of regional governance as cities and ideologically linked groups take centre-stage."[b] The rapid social changes brought about by the Fourth Industrial Revolution are creating pressures that allow production to be decentralized to communities and even households (think about 3D printing). These same trends may prove effective in shaping consumption as well. As "regions" and communities become more virtual in 2030, it could open the door to a new "tribal" form of identity politics oriented around healthy lifestyles. These could scale up far more rapidly than traditional campaigns and also counter the cumbersome and uncertain progress of policy-driven change.

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42 Why We Need Local, State, and National Policy-Based Approaches to Improve Children's Nutrition in the United States

Megan Lott, Marlene Schwartz, Mary Story, and Kelly D. Brownell

Abbreviations

AAP	American Academy of Pediatrics
ACA	The Patient Protection and Affordable Care Act
CACFP	The Child and Adult Care Food Program
CFBAI	The Children's Food and Beverage Advertising Initiative
CHOICES	The Childhood Obesity Intervention Cost-Effectiveness Study
CVV	Cash-Value Vouchers
DGA	Dietary Guidelines for Americans
F2S	Farm to School
FDPIR	The Food Distribution Program on Indian Reservations
FFVP	Fresh Fruit and Vegetable Program
FMNP	The Farmer's Market Nutrition Program
FMNV	Foods of Minimal Nutritional Value
FNS	USDA Food and Nutrition Services
FPL	Federal Poverty Limit
FTC	The Federal Trade Commission
FY	Fiscal Year
HHFKA	The Healthy, Hunger-Free Kids Act of 2010
HUSSC	Healthier U.S. School Challenge
LSWP	Local School Wellness Policies
NSLP	The National School Lunch Program
NSBP	The National School Breakfast Program
QRIS	Quality Rating and Improvement Systems
SFSP	Summer Food Service Program
SNAP	The Supplemental Nutrition Assistance Program
SNDA-III	The 3rd School Nutrition Dietary Assessment study
TANF	Temporary Assistance for Needy Families
TEFAP	The Emergency Food Assistance Program
USDA	U.S. Department of Agriculture
WIC	The Special Suplemental Nutrition Program for Women, Infants, and Children

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Introduction

Local, state, and federal government agencies have the power to improve public health through laws and policies. Examples include mandated car seats for children, child immunizations, smoking bans in public places, and tobacco taxes. Among the most pressing health issues today is childhood obesity. Public health experts are looking to government policies as a means to promote better nutrition for children [1]. Because of the multiple contributors to poor diet and inactivity among children, many policy approaches have been suggested, enacted, and implemented. Some approaches focus on physical activity (e.g., safe routes to school, mandatory recess), and others emphasize nutrition (e.g., improving food in schools and child care, increasing access to healthy foods in low-income communities). The challenge is to identify the policies that will have greatest impact.

This chapter reviews key evidence-based policies to improve children's nutrition and weight. We discuss (a) why policy change may be more cost-effective and impactful than programs aimed at individuals; (b) how to strengthen federal child-feeding programs; and (c) which policies have potential to improve and change food industry practices. While physical activity is important to overall health, including maintaining a healthy weight, this chapter focuses on nutrition and food policies.

Why Nutrition and Food Policies Are Important

A common belief is that eating behavior is predominantly driven by individual factors, such as food preferences, emotional experiences with food, nutrition knowledge, and willpower. Consequently, a primary approach to reducing obesity over the last several decades involved providing education and motivation for people to make dietary changes. However, even the best diets that support individual behavior change have disappointing long-term results in changing weight [2]. Based on the obesity treatment literature to date, it is unlikely that obesity prevalence rates can be reduced through treatment alone, as the small number of successes is offset by the vast number of people in the population that are overweight or obese. Thus there is an urgent need to prevent excess weight gain in the US population as a whole, with efforts starting early in life.

A growing body of evidence supporting the strength of policy, systems, and environmental changes has led to a focus on making the healthy choice an available and easy choice [3, 4]. Public health-focused policies are designed to change the environment, so healthy behaviors become the more likely or even the default action [5]. A striking example is the case of organ donor rates across countries. In some European countries, people must opt in to become organ donors, while in others they are automatically considered donors unless they opt out. Even though the choices are the same in both conditions, about 15% become donors when they have to opt in, compared to approximately 98% with the opposite default [6]. It is unlikely that any amount of education about the importance or desirability of becoming an organ donor could ever approach the impact of simply changing the default. Furthermore, education costs money, and in many cases, changing the default does not. Indeed, it can even raise revenue; one such example is a tax on sugar-sweetened beverages [7, 8].

The default nutrition environment has a substantial impact on children. Educating and motivating children to improve eating behavior is necessary but by itself is insufficient to change body weight. Thus, it is essential to create environmental conditions that make healthy eating an easy behavior for youth and families. The following sections examine the actions that federal, state, and local governments can take to improve children's nutrition.

Strengthening Federal Child-Feeding Programs

The federal government has several programs designed to ensure adequate nutrition for American children (Table 42.1). Three of the largest child-focused programs are (a) The Special Supplemental Nutrition Program for

Table 42.1 Summary of USDA federal feeding programs serving children

USDA program	Program description	Program history	Income eligibility criteria	Enrollment[a]	Recent/current program changes
The Supplemental Nutrition Assistance Program (SNAP)	SNAP, formerly known as Food Stamps, serves low-income individuals and families. It is the largest program in the domestic hunger safety net and provides cash assistance to help families purchase food The Food and Nutrition Service (FNS) works with state agencies, nutrition educators, and neighborhood and faith-based organizations to ensure that those eligible for nutrition assistance can make informed decisions about applying for the program and can access benefits	The First Food Stamp Program began in 1939 and operated over the course of 4 years, during World War II The modern-day Food Stamp Program—focused on food insecurity and hunger—was established as part of the Food Stamp Act of 1964, by President Lyndon Johnson SNAP is included in the Farm Bill, which is reauthorized by Congress ~every 5 years	SNAP eligibility is based on financial and nonfinancial factors and has different requirements based on household type. In most cases, households must have gross incomes below 130% of the federal poverty line (FPL) and total assets less than $2,250 State agencies may choose to apply no asset limits, or higher asset limits, as well as higher gross income eligibility levels	4.6 Million	The program was renamed SNAP as part of the 2008 Farm Bill As part of the 2014 Farm Bill, USDA was directed to update minimum stocking standards for SNAP-approved retailers
The Food Distribution Program on Indian Reservations (FDPIR)	FDPIR is a federal program that provides USDA Foods to income-eligible households living on Indian reservations, as well as those residing in approved areas near reservations or in the state of Oklahoma Many households participate in FDPIR as an alternative to SNAP, as many Indian reservations may not have easy access to SNAP offices or authorized food stores FDPIR provides individual nutrition counseling, cooking demonstrations, nutrition classes, and the dissemination of information on how USDA Foods may be used to contribute to a nutritious diet and on the proper storage of USDA Foods	FDPIR was established in 1977 FDPIR is included in the Farm Bill, which is reauthorized by Congress ~every 5 years	Participating households must contain at least one person who is a member of a federally recognized tribe and that reside on a reservation or live in approved areas near a reservation or in Oklahoma Households are certified based on income standards set by the federal government Households may not participate in FDPIR and SNAP in the same month	Average of 88,600 per month	A recent study conducted by USDA showed that participants would like to see more culturally relevant, local, and fresh foods included in the FDPIR food package[b]

(continued)

Table 42.1 (continued)

USDA program	Program description	Program history	Income eligibility criteria	Enrollment[a]	Recent/current program changes
The Emergency Food Assistance Program (TEFAP)	TEFAP is a federal program that helps supplement the diets of low-income Americans by providing them with emergency food assistance at no cost TEFAP primarily consists of USDA Foods, available via local agencies, such as food banks, food pantries, or soup kitchens Households receiving TEFAP may be eligible for other USDA FNS programs, including SNAP, FDPIR, NSLP, WIC, etc.	TEFAP was first authorized in 1981 as a mechanism to support agriculture markets and surpluses The program was formally named TEFAP under the 1990 Farm Bill TEFAP is included in the Farm Bill, which comes up for reauthorization from Congress ~every 5 years	Public or private nonprofit institutions that provide nutrition assistance to low-income Americans, either through the distribution of food for use at home or the preparation of meals, may receive food as local agencies	–	–
The Special Supplemental Nutrition Program for Women, Infants, and Children (WIC)	WIC provides federal grants to states for supplemental foods, health-care referrals, and nutrition education for low-income pregnant, breastfeeding, and non-breastfeeding postpartum women and to infants and children up to age 5 who are found to be at nutritional risk An applicant must have at least one of the medical or dietary conditions on the state's list of WIC nutrition risk criteria, which can be either a medical-based or a dietary-based condition	WIC started in 1974 WIC is a domestic discretionary program funded annually by Congress WIC is included in the Child Nutrition Act reauthorization, which takes place ~every 5 years	Applicants must have income at or below an income level or standard set by the state agency (between 100% and up to 185% of the FPL guidelines); or applicants can be determined income-eligible based on their participation in certain programs, e.g., SNAP, Medicaid, Temporary Assistance for Needy Families (TANF)	8,024,000	In 2009, changes to the WIC package were gradually introduced to states; these changes were finalized in 2014 WIC packages are required to be reviewed every 10 years. An expert committee convened by the National Academy of Medicine is currently reviewing nutritional needs of the WIC-eligible population and will propose recommended package changes as necessary

The Child and Adult Care Food Program (CACFP)	CACFP provides aid to child and adult care institutions and family or group day care homes for the provision of nutritious foods that contribute to the wellness, healthy growth, and development of young children and the health and wellness of older adults and chronically impaired disabled persons CACFP reimburses day care centers and family day care homes for meals and snacks provided to infants and children as a regular part of their day care CACFP also reimburses meals provided to children residing in emergency shelters and snacks and suppers to youth participating in eligible after-school programs	CACFP was established as a small pilot program in 1968 CACFP is included in the Child Nutrition Act reauthorization, which takes place ~every 5 years	CACFP uses standard income eligibility guidelines for all USDA child nutrition programs, which are updated annually. These guidelines are based on the FPL and are stated by household size but generally range from 130 to 185%	3.3 million children	The 2010 HHFKA directed USDA to update meal patterns for CACFP. A final rule was published in April 2016 and must be implemented by October 1, 2017
The National School Lunch Program (NSLP)	The National School Lunch Program is a federally assisted meal program operating in public and nonprofit private schools and residential child care institutions. It provides nutritionally balanced, low-cost, or free lunches to children each school day Participating programs receive cash reimbursements and USDA Foods for each meal served. In return, they must serve lunches that meet federal nutrition requirements, and they must offer free or reduced-price lunches to eligible children	NSLP was established in 1946 by the National School Lunch Act In 1998, the program was expanded to include reimbursement for snacks served to children (through 18 years) in after-school educational and enrichment programs NSLP is included in the Child Nutrition Act reauthorization, which takes place ~every 5 years	Any child at a participating school may purchase a meal through the NSLP. Meals are free for students from households with income at or below 130% FPL; those from households with incomes between 130 and 185% FPL are eligible for reduced-price meals, for which students can be charged no more than 40 cents After-school snacks are provided to children using this same income eligibility criteria	Average of 30.5 million per day	The 2010 HHFKA resulted in a number of improvements for the NSLP, including updated nutrition standards, increased meal reimbursements, improvements to program access (e.g., direct certification, community eligibility), and improving the management and integrity of the program Many of these provisions are still in the process of being implemented

(continued)

Table 42.1 (continued)

USDA program	Program description	Program history	Income eligibility criteria	Enrollment[a]	Recent/current program changes
The National School Breakfast Program (NSBP)	The NSBP is a federally assisted meal program operating in public and nonprofit private schools and residential child care institutions Participating programs receive cash assistance to operate nonprofit breakfast programs in schools and residential child care institutions. In return, they must serve breakfasts that meet federal nutrition requirements, and they must offer free or reduced-price breakfasts to eligible children	NSBP started as a pilot program in 1966 under the Child Nutrition Act, was extended several times, and received permanent authorization as a nationwide program in 1975 NSBP is included in the Child Nutrition Act reauthorization, which takes place ~every 5 years	Any child at a participating school may purchase a meal through the NSBP. Meals are free for students from households with income at or below 130% FPL; those from households with incomes between 130 and 185% FPL are eligible for reduced-price meals, for which students can be charged no more than 30 cents	Average of 14.09 million per day	The 2010 HHFKA resulted in a number of improvements for the NSBP, including updated nutrition standards, grants for expansion of school breakfast programs, improvements to program access (e.g., direct certification, community eligibility), and improving the management and integrity of the program Many of these provisions are still in the process of being implemented
Special Milk Program	The Special Milk Program provides milk to children in schools and child care institutions that do not participate in other federal meal service programs. The program reimburses schools for the milk they serve. In return, programs must agree to serve milk meeting specific nutrient standards and use the reimbursement to reduce the selling price of milk to all children Schools in the NSLP or NSBP may also participate in the Special Milk Program to provide milk to children in half-day prekindergarten and kindergarten programs where children do not have access to the school meal programs	In 1946, a milk provision was included in the NSLP In 1966, the Special Milk Program was established in the Child Nutrition Act The Special Milk Program is included in the Child Nutrition Act reauthorization, which takes place ~every 5 years	The Special Milk Program uses standard income eligibility guidelines for all USDA child nutrition programs, which are updated annually. These guidelines are based on the federal income poverty levels and are stated by household size but generally range from 130% to 185%	46.9 million half-pints served at 4000 sites	–

The Fresh Fruit and Vegetable Snack Program (FFVP)	FFVP is a federally assisted program providing free fresh fruit and vegetable snacks to students in participating elementary schools during the school day The goal of the FFVP is to improve children's overall diet and create healthier eating habits, as well as to help schools create healthier environments by providing healthier food choices and expanding access to a variety of fruits and vegetables	FFVP was originally authorized as a small pilot program in the 2002 Farm Bill The pilot was expanded by Congress in the 2004 Child Nutrition reauthorization and again via the 2006 Agriculture Appropriations bill The 2008 Farm Bill authorized FFVP as a permanent program and expanded it to include all 50 states, DC, Guam, Puerto Rico, and the Virgin Islands	The FFVP is targeted to elementary schools with the highest free and reduced-price enrollment State agencies determine which elementary schools will receive the program each school year based on school meal participation data from the previous academic year	–	Due to the success of the program, industry has tried in recent years to expand the scope to include items such as dried fruits, trail mix, and beef jerky. To date, these efforts have been unsuccessful
Afterschool Snacks and Supper	USDA provides after-school snacks to school children through either the NSLP or the CACFP. In addition to serving NSLP lunches, schools can offer nutritious snacks as part of after-care educational programs or enrichment activities In return, schools must serve nutritionally balanced meals and snacks that meet USDA's nutrition standards	Program first authorized by Congress in 1998 Beginning in 2000, some state CACFP programs were given the option to offer after-school suppers through community programs in at-risk areas The Afterschool Snacks and Supper Program is included in the Child Nutrition Act reauthorization, which takes place ~every 5 years	In order for a site to participate, a school district must run the NSLP and sponsor or operate an after-school care program, which must provide children with regularly scheduled educational or enrichment activities in a supervised environment Schools in which at least 50% of students qualify for free or reduced-price meals are "area eligible" and subsidized at the free rate for all participating students	Average of 1.4 million snacks served daily[c]	In December 2010, the program was expanded to all 50 states. Through this option, community programs may also serve breakfast or lunch on weekends, holidays, and school breaks, addressing gaps that may occur when at-risk children are not in school

(continued)

Table 42.1 (continued)

USDA program	Program description	Program history	Income eligibility criteria	Enrollment[a]	Recent/current program changes
Summer Food Service Program (SFSP)	SFSP is a federally funded, state-administered program, which reimburses providers who serve free healthy meals to children and teens in low-income areas during the summer months when school is not in session SFSP sites include schools, camps, parks, playgrounds, housing projects, community centers, churches, and other public sites where children gather in the summer	SFSP was authorized in 1975 The SFSP is included in the Child Nutrition Act reauthorization, which takes place ~every 5 years	Sites are eligible to offer free meals and snacks to participating children (18 years and younger) if they operate in areas where at least 50% of the children come from families with incomes at or below 185% FPL or if more than half of the children served by the site meet this income criterion	Average of 2.6 million meals per day[d]	The 2010 HHFKA removed limits on the number of sites that private nonprofit organizations may operate in the SFSP, in an effort to increase program access Advocates are currently pushing for additional opportunities to improve food access during the summer months including a pilot program to provide low-income families with children an electronic benefit transfer card to purchase additional food during the summer months
Farm to School (F2S)	USDA's F2S program helps child nutrition program operators incorporate local foods into school meal programs, including the SFSP and CACFP. This is accomplished through grant making, training and technical assistance, and research The term "farm to school" represents a suite of activities centered on connecting local farmers and food producers to schools, teaching children where their food comes from, and expanding market opportunities for agricultural producers of all kinds	A F2S grant program was authorized under the 2004 WIC and Child Nutrition Act reauthorization; however, it never received funding F2S was included in the 2010 HHFKA and funded at $5 million per year	USDA awards grants annually to help schools connect with local producers and teach children where their food comes from. Eligible entities include schools and districts (large and small, rural and urban), Indian tribal organizations, agricultural producers or groups of agricultural producers, nonprofit entities, and state and local agencies	42% of school districts participate in F2S activities[e]	Due to large demand, efforts are currently underway by advocates to expand funding of the F2S grant program

Team Nutrition	Team Nutrition is an initiative of the USDA FNS to support child nutrition programs through training and technical assistance for food service, nutrition education for children and their caregivers, and school and community support for healthy eating and physical activity	Team Nutrition was established in 1993 as part of an effort to improve the nutritional content of school meals	All schools participating in the NSLP are eligible. They must designate a Team Nutrition leader and have the support of their school nutrition director and principal	–	Following the 2010 HHFKA, USDA offers more than $5 million in training grants and resources to support healthy meals and snacks in schools
Healthier US School Challenge: Smarter Lunchrooms (HUSSC:SL)	The HUSSC:SL is a voluntary certification initiative recognizing those schools enrolled in Team Nutrition that have created healthier school environments through promotion of nutrition and physical activity Schools earning HUSSC:SL designation receive a financial reward, ranging from $500 (Bronze) to $2,000 (Gold Award of Distinction), based on the level of achievement	In 2010, First Lady Michelle Obama introduced the Let's Move! Initiative, incorporating HUSSC:SL into this campaign To date, HUSSC: SL awards have been given to schools in 50 states and DC	All schools participating in the NSLP or NSBP are eligible to participate in HUSSC	4,661 Schools[f]	Following the 2010 HHFKA, USDA offers more than $5 Million in training grants and resources to support healthy meals and snacks in schools through Team Nutrition, including money to support HUSSC:SL

[a]Participation data from FY 2015
[b]Pindus, NM, et.al. Study of the Food Distribution Program on Indian Reservations (FDPIR). Prepared by Urban Institute for the US Department of Agriculture, Food and Nutrition Service, 2016. Available at: http://www.fns.usda.gov/research-and-analysis
[c]Participation data from FY 2014, as 2015 data were not yet available
[d]SFSP provided meals to 2.6 million children each day at 47,585 sites during the program's peak month of July in FY 2015
[e]According to the 2015 Farm to School Census, 42% of school districts surveyed by the USDA participate in farm to school activities (5,254 districts and 42,587 schools serving 23.6 million students)
[f]As of August 31, 2016, there are 4,661 schools certified (3,234 Bronze, 908 Silver, 330 Gold, and 189 Gold Award of Distinction)
Data from: USDA, Food and Nutrition Services Programs; Available at: http://www.fns.usda.gov. Accessed September 15, 2016

Women, Infants, and Children (WIC), (b) The Child and Adult Care Food Program (CACFP), and (c) The National School Lunch (NSLP) and Breakfast Programs (NSBP). These programs have national standards and requirements but typically are administered through the state departments of health or education. Depending on the assignment of regulatory authority within a state, some state or city agencies will have license to further strengthen the nutrition standards of each program as described below.

The Special Supplemental Nutrition Program for Women, Infants, and Children (WIC)

For more than 40 years, WIC has provided nutritious foods, nutrition education, breastfeeding promotion and support, and referrals to other health and social services. The program serves low-income pregnant women, breastfeeding and postpartum mothers, infants, and young children up to the age of 5 who are found to be nutritionally at risk [9]. WIC has tremendous reach, currently serving 53% of all infants born in the United States [9]. Established in the early 1970s, the WIC food package was designed to supplement participants' diets with foods rich in five target nutrients found to otherwise be lacking: vitamins A and C, calcium, iron, and protein. Therefore, the specific foods included in the original WIC food packages were infant formula, juice, cereal, milk, cheese, eggs, dried beans/peas and/or peanut butter, tuna, and carrots.

Research has shown WIC to be successful in meeting its initial goals. Participation improves children's health status, decreases the likelihood of anemia, and improves diet [10, 11]. Yet, in the early 2000s, obesity rates among young children, including those eligible for WIC, were alarmingly high [12]. In 2003, at USDA's request, the National Academy of Medicine[1] reviewed nutritional needs of the WIC population and developed scientifically based, cost-neutral recommendations for modifying WIC food packages [13]. The primary goal of these changes was to reduce excessive and inadequate nutrient intakes among WIC participants and improve overall diet to be consistent with the Dietary Guidelines for Americans (DGA) and the infant feeding practice guidelines of the American Academy of Pediatrics (AAP). In 2009, USDA implemented the proposed revisions—updating WIC-provided foods—and in March 2014 these revisions were finalized [14]. Only 2% or lower-fat milk is authorized for children 2 and older, and a number of foods have been added, including more fruits and vegetables, whole grains, and milk alternatives (e.g., soy-based beverages). Whole grain options now include a variety of nutritious foods, such as whole wheat bread, corn and whole grain tortillas, and brown rice. Fruits and vegetables are encouraged through cash value vouchers ($6, $8, or $10 per month) that can be used to purchase a wide variety of fresh, canned, or frozen products [14].

Since implementation began in 2009, both individual and community-level changes have occurred. WIC participants have changed their purchasing patterns in several product categories, including increased purchases of whole grain bread and rice products [15] and decreased purchases of whole milk and cheese [16]. Additionally, the WIC food package revisions appear to have improved access to healthier foods in low-income communities overall. For example, a study examining availability, variety, quality, and prices of WIC-approved foods in Connecticut stores before and after implementation of the WIC package changes found improved availability and variety of healthy foods in both WIC-authorized and non-WIC convenience and grocery stores [17]. Another study in Illinois found that overall availability and selection of commonly consumed fresh fruits and vegetables, as well as availability of culturally specific fruits and vegetables, improved after implementation of the WIC package changes [18]. These changes suggest that policies requiring participating stores to stock healthier foods are an effective way to improve access to these items for entire neighborhoods.

[1]Formerly, the Institute of Medicine

States have piloted innovative strategies in the WIC program that later inspired federal policy change. In the late 1980s, for example, New York state conducted a pilot program to allow WIC coupons to be used at farmer's markets. The program was successful, and by 1992 Congress had established and funded a USDA farmer's market nutrition program (FMNP) that today funds 48 state agencies, US territories, and federally recognized Indian Tribal Organizations to allow WIC coupons at farmer's markets [19]. In addition, the revised food package now provides cash value vouchers (CVV) for the purchase of fruits and vegetables. While the CVV can be redeemed at any WIC-approved retailer, state agencies are responsible for determining if they can also be used at farmer's markets or roadside stands. As of June 2015, many states, US territories, and tribal nations had not yet chosen to allow redemption of the CVV at farmer's markets, creating an opportunity for WIC package policy improvements at the state and local levels [20].

The reformulation of the WIC food package represents a significant step in improving participants' diets. To ensure the continued success of WIC, Congress mandated that USDA reevaluate the program's food packages every 10 years. The most recent review was completed by the National Academies of Sciences, Engineering, and Medicine, and recommendations were released in January 2017 to better align the WIC package with the DGA and to promote and support breastfeeding [21]. The food choices allowed in the 2009 package revisions are retained, and additional choices are added. The committee recommended cost-neutral changes including adding fish, increasing the amount of whole grains, and increasing fruits and vegetables as a trade-off for decreasing juice, milk, legumes, peanut butter, infant fruits and vegetables, and infant meats. The committee also recommended allowing women to receive the quantity of formula needed to support any level of breastfeeding. Finally, the committee developed a set of criteria for inclusion of foods in the food package, with the goal that these criteria would also guide future WIC package revisions [21].

The Child and Adult Care Food Program (CACFP)

The CACFP was established as a small pilot program in 1968 with the purpose of providing funding for meals to low-income children when schools were not in session [22]. The program has evolved and expanded over the years and today serves more than 3.3 million children, providing cash reimbursements to food service operations for child care centers with at least 25% enrollment of children from low-income families [23]. CACFP also reimburses meals provided to children residing in emergency shelters and snacks and suppers to youth participating in eligible after-school programs [23]. USDA administers the CACFP through grants to states, where an agency handles the administrative and financial management of the program. Child care centers work directly with the state agency; family and group care homes enter into agreements with sponsoring organizations, which then interact with the state [23].

Many low-income children who participate in all-day child care receive a majority of their daily food and nutrient intake through CACFP. Historically, the CACFP nutrition standards consisted of four food groups or components—(a) meat/meat alternate, (b) fluid milk, (c) fruit/vegetable, and (d) grain/bread—with different combinations and amounts required by age group and meal type (e.g., breakfast required serving three components, lunch/supper required four, and snacks two) [22]. While these standards ensured dietary variety in children's meals and snacks, they were not specific enough to guarantee that menus met current dietary guideline recommendations.

In an effort to better align nutrition standards with the DGA, the 2010 Healthy, Hunger-Free Kids Act (HHFKA) directed USDA to update meal pattern requirements for CACFP. The final rule, published in April 2016, requires participating centers and home day cares to serve more whole grains, a greater variety of fruits and vegetables, and reduce the amount of added sugars and saturated fats in meals [24]. Participating sites are also required to follow new beverage

requirements, specifically: 100% fruit/vegetable juice may only be served once per day, flavored milk is prohibited for children ages 1 through 5,[2] and potable drinking water is required to be offered and made available upon request throughout the day [24]. The beverage policy changes are of particular importance given the growing body of evidence linking sweetened beverage consumption with poor overall dietary quality and excess weight gain in children [25–27]. All changes were designed to be cost neutral and implemented by October 1, 2017 [24].

The CACFP infant meal pattern changes are noteworthy. Early life is a critical period for the development of childhood obesity, especially among racial and ethnic minority children [28]. To develop these new requirements, USDA relied on recommendations from the AAP, as the DGA do not currently address children under 2 years old.[3] There are now two age groups in the infant meal pattern (0–5 and 6–11 months). Breast milk and/or infant formula are the only foods permitted through 5 months of age, and providers are now reimbursed for meals when a mother breastfeeds her child on-site [24]. Additional meal components may be introduced at 6 months, as developmentally appropriate, although no fruit juice is allowed for infants under 1 year of age. All snacks must include a vegetable or fruit.

The final regulations also highlight voluntary best practices to guide day care centers and homes that wish to further improve the nutritional value of meals and snacks [24]. For example, while snacks are now required to include a fruit or vegetable for children under 1 year of age, doing so is a best practice recommendation for children ages 1 and older. CACFP providers still have the flexibility to serve foods or beverages that are not reimbursable, such as on special occasions; however, USDA encourages discretion as these items are often higher in added sugar, saturated fats, and sodium and can compete with healthier options.

While federal nutrition standards are an effective means to impact children's health, state and local regulations, commonly known as licensing standards, provide another opportunity to set nutrition policy. Child care licensing standards exist in every state, most large cities, and some counties. Licensing regulations commonly address several areas such as health and safety, facility capacity, and caregiver qualifications, but many lack strong nutrition standards, which would be an effective and politically feasible avenue for improving nutrition and weight [29].

Several states now supplement regulatory approaches to address childhood obesity prevention with voluntary, incentive programs, such as Quality Rating and Improvement Systems (QRIS). A recent report from Nemours Children's Health System noted that as of fall 2016, 40 states and the District of Columbia have statewide QRIS implementation [30]. Nemours conducted a survey of these states and noted that a majority of respondents (24 out of 31, or 77% of states) indicated having practices related to healthy eating, breastfeeding, physical activity, and/or screen time that their state wanted to promote via QRIS [30]. This signals states' commitment to childhood obesity prevention and serves as an additional policy lever for affecting change.

The School Food Environment

The school food environment plays an important role in the diets of children and adolescents, as up to 50% of their total daily calories are consumed at school. There is strong evidence that children's diets are influenced by the foods served and sold in school cafeterias and vending machines, the schools' nutrition policies, and the availability of unhealthy snacks in the areas surrounding schools [31–33]. As noted with CACFP above, the 2010 HHFKA also directed USDA to make significant changes to school food programs for the first time in over 30 years (Table 42.2) [34].

The National School Lunch Program (NSLP) established in 1946 and the National School

[2]Updated CACFP meal patterns recommend serving only unflavored milk to all participants; however, if flavored milk is to be served to children 6 years and older, it should be limited to no more than 22g of sugar per 8 fl oz.

[3]Dietary recommendations for children under age 2 will be included in the 2020 Dietary Guidelines for Americans.

Table 42.2 Summary of changes to school food programs discussed in this chapter resulting from the 2010 HHFKA

	Nutrition requirements/standards pre-2010 HHFKA	Nutrition requirements/standards post-2010 HHFKA
School meals—NSLP) AND NSBP)	Nutrition standards were in existence, with a requirement to align with the most current version of the Dietary Guidelines for Americans; however, they had not been updated since the mid-1990s	USDA updated school meal standards requiring schools to serve more fruits, vegetables, and whole grains and less sugar, salt, and fat beginning in the 2012–2013 school year. These standards also redefine portion sizes and apply calorie counts (by grade level) designed to maintain a healthy weight. Schools are provided an additional 6 cents per lunch for meeting these updated standards
Water access	No requirements	Schools participating in the NSLP are required to make free potable water available where lunch meals are served during the meal service. Schools are encouraged, but not required, to provide water at breakfast
Competitive foods and beverages—i.e., Smart Snacks	No national nutrition standards; rather there was a patchwork of state and local policies addressing this issue The only foods excluded from sale during the lunch period were those defined as Foods of Minimal Nutritional Value (FMNV), which were identified over 30 years ago and were limited to four categories: soda water, water ices, chewing gum, and certain candies[a]	Effective July 1, 2014, schools are required to meet the Smart Snack requirements for all foods sold on campus during the school day, including those sold a la carte, in the school store and in vending machines. Special exemptions are allowed for infrequent school-sponsored fundraisers
USDA Foods	No nutrition requirements	USDA was required to develop model product specifications and practices for all USDA Foods offered in school programs and to provide nutrition information to schools
Farm to School (F2S)	Prior to 2010, a competitive F2S grant program did exist, but no funding was ever made available. An allowance for giving local products a priority was included in the 2008 Farm Bill ("geographic preference")	USDA was required to provide training and technical assistance, and $5 million per year was made available for competitive grants to schools, states, and local agencies for farm to school activities
Local School Wellness Policies (LSWP)	Required by the 2004 Child Nutrition and WIC Reauthorization Act, all schools were required to develop a LSWP by the 2006–2007 school year	USDA was required to update LSWP requirements to focus on nutrition and obesity, increase the transparency and accountability, and provide training and technical assistance to schools. A proposed rule was released in February 2014; a final rule has not yet been released

[a]School Meals: Foods of Minimal Nutrition Value (Accessed 16 Sept 2009, at http://www.fns.usda.gov/cnd/menu/fmnv.htm.)

Adapted with permission of Springer Science+Business Media from Welker E, Lott M, Story M. The School Food Environment and Obesity Prevention: Progress Over the Last Decade. Curr Obes Rep 2016;5(2):145–155

Breakfast Program (NSBP), established in 1975,[4] are two federal programs which provide foods and beverages in schools during the school day. In 2015, 30.5 million children per day participated in the NSLP [35] and 14.09 million in the NSBP [36]. These programs are especially critical for the 21.5 million youth from low-income households who receive free or reduced-price school meals.

The meals served in each of these programs have been required to meet federal nutrition standards since their inception, and since 1995 both

[4]The National School Breakfast Program began as a pilot program in 1966; it received permanent authorization as a nationwide program in 1975.

programs were required to be consistent with the DGA. However, the third School Nutrition Dietary Assessment (SNDA-III), which collected data in the 2004–2005 school year, indicated that meals provided by the NSLP and NSBP were too high in sodium and saturated fat and too low in important nutrients and food groups like fiber and whole grains [37]. In fact, only 6% of schools met all of the nutrition standards for lunch in 2005 and only 14% in 2010 [33, 37].

Since 2012, following the most recent updates to nutrition standards for meals, schools are now required to offer larger servings and greater varieties of fruits and vegetables, more whole grains, and less saturated and trans fats and sodium [38]. Schools are also now required to make free, potable water available to all students where meals are served [38]. Recent research has shown that these changes have led to significant improvements in the nutritional quality of foods chosen by students, without negative impacts on meal participation or increased plate waste [39, 40]. Moreover, according to data from USDA, 98.5% of all school food authorities in the nation participating in the NSLP were meeting these updated standards as of December 2015 [41].

Nearly all schools also sell additional foods and beverages—termed "competitive foods"—via a la carte lines, vending machines, school stores, and fundraisers. Until recently, competitive foods were virtually unregulated, allowing items like ice cream, potato chips, baked goods, and sports drinks to contribute to excess caloric intake and compete with the school lunch. The 2010 HHFKA, however, gave USDA the authority to regulate these items—now referred to as Smart Snacks—for the first time [42].

USDA's Smart Snacks nutrition standards went into effect in 2014; these limit the calories, fat, sodium, and sugar found in competitive foods and encourage the inclusion of fruits, vegetables, and whole grains. Because of the recency of these changes, there is little in the published literature evaluating their impact; however, there is reason to be optimistic. A systematic review published in 2014 examined the effects of competitive food and beverage state laws and/or school district policies and found that, in most cases, having a nutrition policy was positively associated with improvements in the quality of the snacks available and student diets [43]. Additionally, more rigorous policies have been associated with decreased consumption of sugar, fat, and calories and increased consumption of vegetables, fruits, and whole grains [44, 45].

Smart Snacks has driven many manufacturers to reformulate products to meet nutrition standards; however, one challenge is that these "healthier" versions are only available in schools. A recent study from the Rudd Center for Food Policy and Obesity found that this created confusion among consumers as packaging of Smart Snack compliant items sold in schools often looks very similar to the less healthy versions still available in most grocery and convenience stores [46]. Moreover, the companies continue to advertise unhealthy versions of the same products, raising concerns among the public health community that this will undermine the schools' ability to teach good nutrition and improve children's overall diet [46].

While the aforementioned changes are significant, several opportunities for federal policy improvement remain [47]. There is an ongoing need for technical assistance and training to assist schools in their implementation of updated nutrition standards. For example, several concerns have been raised from school districts related to finding innovative, cost-efficient means of meeting updated standards for both meals and Smart Snacks. Specific to school meals, updated guidelines were initially accompanied by anecdotal reports of increased food waste in school cafeterias due to new requirements that students take a fruit or vegetable at lunch. While research has shown that students are responding positively to the new lunches and policies resulting from the HHFKA appear to have actually lowered plate waste [40], it is important for USDA to continue to provide guidance and circulate best practices centered on encouraging kids to select and consume meal components and ensuring that schools provide enough time for young children to eat at meal times. Specific to the Smart Snacks standards, additional technical assistance has also been requested related to fundraisers as well as

the "look-alike" snack issue mentioned previously. The need for staff training on updated standards, cooking, and food safety has also been raised, as has the need to prioritize federal funding for new/updated kitchen equipment.

The new requirement to provide free, potable water to students where meals are served is important for increasing water access and consumption; however, the recent water crisis in Flint, Michigan, has raised concerns regarding the safety of water, especially in older school buildings. Ensuring that children are served safe and appealing water in place of unhealthy beverages requires a clear set of enforceable policies for water quality monitoring and adequate access, as well as plans for remediation, should problems be found. This issue will require action at the local, state, and federal levels as it often involves the public water supply, which is governed by food safety codes, sanitation and plumbing codes, and state and federal water treatment and quality laws. These policies span government agencies including state departments of health, environment, education, and human services and can involve multiple departments within these agencies.

The 2010 HHFKA also made significant improvements to other federal child nutrition programs (Table 42.2), such as USDA Foods (an additional benefit to help offset the costs of meals in programs serving low-income children) and Farm to School; however, other programs, such as out-of-school time and summer meals were largely unaddressed. For example, the Summer Food Service Program ensures that low-income children continue to receive nutritious meals when schools are not in session; programs can operate in a variety of ways and in a multitude of locations, not just schools [48]. Nutrition standards for summer programs were not updated as part of the HHFKA [38]. Additionally, many child nutrition programs have individualized operating guidelines and procedures, including separate application processes. Program access would be improved by one streamlined application process for families, allowing eligible children to more easily participate in a variety of federal programs.

In the decade before the federal government updated nutrition standards for school foods, many states took the initiative to create stronger regulations on their own. Prior to the 2010 HHFKA, 19 states had stricter NSLP and NSBP standards than the USDA, and 27 states had set standards for competitive foods and beverages [49]. Many of these policies now require updating following the new federal standards; however, this provides additional opportunities to strengthen policies at the state level. For example, practices to support implementation of the standards or to address the challenges mentioned above could also be adopted at the state or local policy level.

Beyond state regulation, a unique opportunity to use local policies to improve the school environment emerged with the 2004 Child Nutrition and WIC Reauthorization Act, with the requirement that all school districts participating in federally funded school meal programs create a Local School Wellness Policy (LSWP) to support healthy eating and physical activity. LSWPs were required to have five features and to be implemented by the start of the 2006–2007 school year. Some research suggests that LSWPs may be associated with improved implementation of health-promoting practices in the school environment [50] and increased consumption of healthier items among students [51]. However, other studies have shown that school wellness policies have been weakly worded and that schools may have been simply adopting standard wellness policy templates lacking strong nutrition standards [52].

The 2010 HHFKA strengthened the LSWP requirement by expanding the scope to promote health and prevent childhood obesity and increasing the accountability and transparency of policies. USDA released a final rule in July 2016, which establishes a framework for policy content, ensures stakeholder participation in policy development, and requires periodic compliance assessment and reporting on progress toward achieving the LSWP goals [53]. This final rule requires school districts to begin developing a revised LSWP during the 2016–2017 school year, and all must be in full compliance with updated requirements by June 30, 2017 [53].

At a minimum, policies are now required to include:

1. Specific goals for nutrition promotion and education, physical activity, and other school-based activities that promote student wellness
2. Standards and nutrition guidelines for all foods and beverages sold to students on the school campus during the school day that are (at a minimum) consistent with the federal regulations for school meals and Smart Snacks
3. Standards for all foods and beverages provided—not sold—to students during the school day (e.g., classroom snacks, parties, incentives)
4. Policies that only allow the marketing and advertising of those foods and beverages that meet the Smart Snacks nutrition standards
5. A description of plans for public involvement, public updates, policy leadership, and evaluation [53]

To improve accountability, school districts must establish wellness policy leadership to include individuals who will have the authority and responsibility to ensure compliance, which must be assessed every 3 years. And, to improve transparency, school districts must provide a mechanism for public involvement, including by parents, teachers, students, and others in the community. Additionally, the state agency will now examine records during the administrative review process, including a copy of the current wellness policy and documentation of assessments and implementation, in an attempt to ensure they are not collecting dust in a drawer.

USDA is working with partners to ensure that school districts have the technical assistance needed to implement these changes. In doing so, special attention should be paid to rural schools, which have previously demonstrated weaker LSWPs and practices [54]. The major benefit of placing the responsibility on school districts to establish their own policies is the involvement of representatives from many stakeholder groups, including parents, students, public school administrators, the board of education, and school food service. This sets the stage for each district to hear viewpoints from relevant parties and achieve buy-in, cooperation, and better compliance with implementation [55]. This also provides a substantial opportunity for local districts to strengthen existing policies and for states to require such action.

Policy Approaches Designed to Improve Food Industry Practices

While the term food industry can encompass the entire collection of enterprises involved in the global production and consumption of food and beverages from farmers to processors to retailers, we use this term to refer to the companies that produce, process, manufacture, sell or serve, and market foods and beverages [56]. These companies play a large role in controlling the products in the food supply and consequently the foods and beverages many people consume on a daily basis. Thus, in order to change the dietary patterns of individuals, it is also important to improve and change food industry practices. Two examples discussed below are menu labeling and food marketing to children.

Menu Labeling

The issue of chain restaurant menu labeling has received substantial attention by policymakers and the restaurant industry over the last decade. In 2006, New York City broke new ground by requiring chain restaurants to provide calories on menus and menu boards. Litigation followed, with the restaurant industry twice suing the city to block the regulation, but a revised version was successfully implemented in January 2008 [57]. Other states and localities followed, with menu labeling enacted in California, Massachusetts, Maine, and Oregon, as well as four New York counties (Ulster, Suffolk, Westchester, and Albany), Nashville, Philadelphia, and King County (Seattle), Washington [58].

The restaurant industry was quick to note that different menu labeling laws throughout the country—with different requirements for menus

and menu boards—would lead to confusion and increased expense for consumers and suppliers. In early 2009, the industry worked with federal legislators to create a unified federal law which was incorporated into the 2010 Patient Protection and Affordable Care Act (ACA) and requires chain restaurants with 20 or more outlets to list calories and other nutrition information on menus and menu boards [59].

Shortly after passage of the ACA, the Food and Drug Administration, which is responsible for oversight and implementation of the menu labeling provision, opened a docket in the federal register to solicit comments, data, and other information necessary to inform implementation. Yet, final guidance on the topic was not released until April 2016, setting an implementation date of May 2017 [59]. Despite pushing for a national menu labeling law to be included in the ACA, much of this delay has been driven by members of the food industry—primarily some restaurant chains, convenience stores, and supermarkets—working with Congress to attach policy riders to appropriation bills to delay implementation [60].

The ACA menu labeling law preempts states and localities from enacting stricter policies, bringing progress at the state and local level on this issue to a halt since 2010. In the meantime, research has emerged supporting the theory that providing nutrition information at the point of purchase reduces consumer's intentions to purchase items high in calories and fat and, in some populations, increases selection of healthier items [61, 62]. With strong evidence that sodium in restaurant meals poses a significant public health concern [63], New York City is now requiring chain food service establishments (with 15 or more locations nationwide) to post a warning label on menu items that contain 2300 mg or more of sodium—the daily recommended limit [64].[5] The proposal was passed unanimously by the Board of Health in September, 2015; however, the National Restaurant Association quickly appealed the decision, claiming that the science regarding sodium's health effects is unsettled and that the rule is invalid. In May 2016 the Appellate Division of the New York State Supreme Court upheld the proposal, allowing the New York City Health Department to enforce the rule beginning June 6, 2016 [64]. The city has moved forward with implementation; unfortunately, the legal case will continue as the National Restaurant Association is now appealing the merits of the case [65]. New York City is the first location to enact such a requirement, and if the law is upheld, other municipalities and states may be motivated to adopt similar public health measures.

[5]This NYC sodium warning label was permitted under the preemption law because it was marking a set of items that exceeded a limit, but not actually providing the number of mg of sodium in the item.

Food Marketing to Youth

The food industry spends enormous sums to market its products to children. A 2012 industry-monitoring report from the Federal Trade Commission (FTC) documented that 48 food, beverage, and restaurant companies spent $1.8 billion on marketing to US children in 2009 [66]. Food marketing is often cited as a contributing factor to childhood obesity, with many of the foods and beverages marketed of poor dietary quality [67, 68]. Marketing has evolved with the growing digital presence of web-based entertainment, social networking, and smart phones [69]. There is more food marketing than ever through media that parents do not monitor or control (such as website game sites) and subtle methods that individuals may not recognize as marketing (such as product placements in popular television shows, movies, and video games). For example, half of all marketing dollars targeting children ages 2–11 ($531 million) in 2009 involved cross-promotions, including media-character merchandising and tie-ins (i.e., product placements) with movies, TV programs, video games, and social media [66]. From 2009 to 2014, brands from 954 different companies appeared on US prime-time TV programming [70]. Appearances peaked in 2011 and have been declining since; however, this is still a concern with beverages, savory snacks, candy, and other sweets being the most

common foods featured and reality TV shows being the most popular vehicle [70].

Industry has responded in a number of ways to increasing public disapproval of marketing unhealthy foods to children. Initially, food companies focused on the importance of physical activity and invested in promoting more activity for children by sponsoring events and putting branded playgrounds in schools. But in 2006, following a call to action from the National Academy of Medicine, the Council of Better Business Bureaus launched a voluntary self-regulation program to shift the mix of foods advertised to children under age 12 in an attempt to encourage healthier dietary choices. Today this initiative is known as the Children's Food and Beverage Advertising Initiative (CFBAI) and consists of 18 of the nation's leading food and beverage companies and quick-serve restaurants. In 2013, CFBAI established a uniform set of voluntary category-specific nutrition standards for participating companies, which took effect in January 2014 [67]. The focus on establishing nutrition standards has resulted in nutrition improvements of products marketed to children, such as reduced sugar, salt, and saturated and trans fats, as well as increased whole grain content [67].

Despite these improvements, major loopholes still exist that allow companies to continue marketing unhealthy foods and beverages to children. To address this gap, Healthy Eating Research—a national program of the Robert Wood Johnson Foundation—released a comprehensive set of evidence-based model definitions for food marketing practices directed to children in 2015. The recommendations were developed by a national panel of experts and are intended to provide guidance to a broad range of stakeholders, including food and beverage manufacturers, retailers, restaurants, government agencies, and other policymakers, advocates, and researchers. Key recommendations include expanding the child audience from 0–12 to 0–14 years of age, to consider any media and venues child-directed if children constitute 25% or more of the audience (the current industry standard is 35%), and brands marketed to children should contain only products meeting nutrition criteria, as most companies primarily focus on promoting a corporate or family brand when marketing to children [67].

Experts argue that closing these loopholes is critical to further reducing the amount of unhealthy foods marketed to children. For example, though many children watch popular reality shows such as "American Idol" or "America's Got Talent," these programs are not subject to following guidelines around child-directed marketing because youth (under 12) are less than 35% of the total viewing audience. And, yet, research discussed previously highlights these programs as the primary vehicles for unhealthy product placements [70].

Local, state, and federal governments can and must take action to protect children from food marketing. The vast branded marketing that occurs inside school buildings and on school grounds (e.g., branded scoreboards, nutrition education materials, and "free" book covers that contain food company logos) has also been documented [71]. At the state or city level, school-based policies, such as LSWP and, specifically, the inclusion of marketing practices as now required by the 2010 HHFKA, may be established as law. States may also broaden marketing regulations to apply to other sites that serve children and receive government funding, such as child care programs, after-school programs, and community centers. Some other ideas that have been put forward include local ordinances to restrict mobile vending of unhealthy foods near playgrounds and schools, zoning regulations to limit the density of fast-food restaurants, and incentive programs to encourage retail outlets to reduce point-of-sale marketing of unhealthy foods (e.g., candy-free checkout aisles).

Another area that may be ripe for consideration is the marketing of infant and toddler foods. This issue has largely been unaddressed to date, but examples of its pervasiveness are more and more prevalent. A Rudd Center report released in 2016 documents that much of this marketing promotes products that should not be served to young children, such as nutritionally poor snacks, toddler milk, and energy-dense nutritional supplements. Moreover, the marketing messages targeting this population often

imply that commercially prepared baby and toddler foods and drinks are nutritionally superior and/or provide developmental advantages as compared with breast milk or whole milk and table food [72]. The companies marketing these foods portray themselves as "experts" on children's nutrition and often present their products as "solutions" for common issues such as crying, not sleeping through the night, or picky eating. However, these claims are not typically backed up with scientific evidence.

Conclusions

The early history of using public policy for the prevention of obesity is being written now. Until recently, the nation focused decades of effort on treating obesity and on various approaches to individual behavior change. Funding went to basic research on genetics, pathophysiology, and pharmacology as well as treatment research, with little attention paid to changing the conditions that drive obesity.

This picture began to change as prevalence statistics soared and realization set in that existing approaches were not working. Neither biological abnormalities nor failure of personal will can fully explain the rising prevalence of obesity in every corner of the world. Over the past century, food and physical activity environments have changed dramatically with rampant obesity as an understandable consequence. Changing these environments must be the top priority if obesity prevalence is to decrease. Public policy must be placed at the heart of a national (and global) effort to prevent obesity, and policies should strive to create healthier defaults. A number of public policy options have been discussed in this chapter, and our coverage is not exhaustive. A key question is which approaches will be the most effective and produce the greatest benefit at the lowest cost. More data are needed in this area, but the Childhood Obesity Intervention Cost-Effectiveness Study (CHOICES), a research project out of Harvard, has generated cost-effectiveness estimates for more than 40 of the most widely promoted or implemented childhood obesity prevention interventions in five sectors—school, early and out-of-school care, community and government, transportation, and clinical [73]. There are additional gaps in knowledge that must be addressed with an aggressive funding strategy on the factors contributing to obesity at the population level, models for policies that change these factors, and immediate and thorough evaluation of policies once implemented.

It is essential that science and policy work together. Demanding perfect science before implementing policy change, and yielding to arguments that many factors contribute to obesity and hence no single policy will solve the problem, will permit paralysis to prevail over invention, lock in the status quo, and let death and disability continue unabated. Rather, science should be an ally to policy, and stronger connections between the scientific community and elected leaders will be necessary. Over the past decade, there have been encouraging signs that this is beginning to happen.

Editor's Comments and Questions

1. It may be valuable to view the role of government in the regulation of childhood nutrition from a historical and international perspective. Having spent two sabbaticals in Paris, where my children attended French schools, I was interested in the French approach to school lunches. Rates of childhood (and adult) obesity are far lower in France than in the United States and UK.

   Following rapid industrialization at the beginning of the twentieth century, many of the rural French poor migrated to cities; life in squalor increased dramatically the rates of infant mortality, and in 1904 the French government instituted a number of laws and policies designed to improve child health. Based in part on the recommendations of Augusta Moll-Weiss, founder of the Paris School for Mothers, the government

established nationwide clinics to teach breastfeeding, guaranteed time for women to breastfeed at work, and counseled mothers not to overfeed their children; to that end, school reports of students' heights and weights were provided to parents, and plans for healthy school lunches were developed. All meals (at home and at school) were to be supervised and snacking was discouraged. The child's preferences were unimportant, she said. "The essential thing is that the quality and the quantity of the diet correspond to the exertion of the young human being." Nearly all school children were raised according to her advice. Consequently, the rates of obesity in French children were very low until very recently, when the tentacles of the global food industries began to take hold.

Standardization of school lunches in France has a number of important advantages: food is generally of high quality, junk food and snacking are eliminated, and there is no stigma attached to a child who gets "free lunch." On the other hand, the costs to the society are high, and the child and family lack the ability to choose their meals. Moreover, the selection of school food can become a source of national political controversy, as demonstrated by current disputes in France over serving ham in schools.

2. As discussed in the initial chapter of this book, the nutritional determinants of childhood obesity include concentrated sugars, high-density starches, fried foods, and saturated fats. Some have argued strenuously for a tax on sugar-sweetened beverages in order to reduce the rates of childhood and adult obesity and type 2 diabetes. Indeed, some localities have adopted such taxes, in part to raise revenue for community infrastructure and programs. Others consider a tax on a single macronutrient unlikely to alter the course of childhood weight gain at the population level, particularly if the tax is relatively low.

What are your views about the power of a tax on sugary drinks to reduce population obesity rates?

How effective have sugar taxes been thus far in reducing rates of obesity and its complications?

Authors' Responses

1. The prevalence of childhood overweight and obesity has risen substantially worldwide in less than one generation. This is occurring not only in the United States and other high- and middle-income countries but also in low-income countries where they continue to experience high levels of child undernutrition [a]. Nutrition policies to curb child obesity need to promote healthy growth and development, support food security, and protect children from marketing and high availability of food and beverage products that are energy-rich and of poor nutritional quality and lead to excess weight gain [a]. To meet this challenge, governments play a critical role in passing and implementing policies to protect and promote children's health.

We agree with you that schools can play an important role in national efforts to prevent childhood obesity in all countries through governmental policies. Indeed, schools can become one of every nation's most effective weapons in preventing child obesity by creating environments that are conducive to healthful eating and physical activity through providing healthful school meals and foods, physical education programs and recess, classroom health education, and school health services. Health and success in school are interrelated. Schools cannot

achieve their primary educational mission if their students and staff are not healthy and physically, mentally, and socially fit.

2. As of 2009, 40 states had small taxes on sugared beverages and snack foods primarily via a sales tax [b]. While this sales tax was a vehicle for generating revenue, the tax was not significant enough to alter consumer consumption. Over the past 15 years, the idea of taxing foods at a rate large enough to make a difference in consumption has transitioned from a radical idea that no one thought was feasible to a mainstream concept that has now been considered seriously in many states and cities around the country. For several years, campaigns to pass sugary drink taxes in several states and cities were defeated; however, in 2015, a ballot initiative in Berkeley, California, passed. A year later in 2016, another tax passed in Philadelphia, Pennsylvania [c], and then subsequently in November 2016, taxes passed in three cities in California, Boulder, Colorado, and Cook County, Illinois [d, e].

   Prior to any large soda taxes being in effect in the United States, economists used both actual and simulated experiments to test whether increasing sugary drink prices would reliably decrease consumption and found that consumption and demand for sugary drinks is generally price elastic [f–h]. The research on the implementation and impact of the aforementioned taxes is being conducted now. So far, we know that the tax in Berkeley was passed on to the consumer, which alleviates the concern that the beverage industry or retailers would undermine the effect of the tax by absorbing it and keeping the sugary drinks at the same price as they were before [i]. Another recent study suggests that low-income individuals in Berkeley have decreased their consumption of the taxed products by 21%, while consumption increased by 4% in comparison cities [j].

   Time will reveal the long-term impact of this policy change. Similar taxes on tobacco products were highly effective at reducing consumption [b]. It is also possible that the earned media exposure associated with the tax campaigns is its own public health initiative because it is educating the public about the harm associated with sugary drinks. The benefit of this type of policy is that it will have a broad reach as the tax applies to all sales of sugary beverages, and research shows that it is a cost-saving policy—in other words, implementing such a tax would save more in projected health-care costs over the course of 10 years than it would cost to implement [k].

   While taxes have the potential to reduce consumption of sugar-sweetened beverages, it is important to emphasize that a broad spectrum of multilevel and multi-sector strategies is needed to reduce obesity at the population level. There is no single strategy that will accomplish this on its own. Thus, a soda tax must be paired with other policy, systems, and environment changes, such as the implementation of nutrition standards in schools and child care settings, the addition of added sugars to the nutrition facts label, and the elimination of tax subsidies for advertising unhealthy foods to children.

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Appendix A: Valuable Reference Sites

CDC Growth Charts

http://www.cdc.gov/growthcharts/

Childhood Obesity Rates US

https://www.cdc.gov/obesity/data/childhood.html

BMI and BMI z Calculations

https://www.cdc.gov/growthcharts/percentile_data_files.htm
http://www.who.int/childgrowth/standards/en/
http://stokes.chop.edu/web/zscore/

Obesity Gene Databases

http://www.ncbi.nlm.nih.gov/projects/mapview/map_search.cgi?taxid=9606&query=obesity&qchr=&strain=All
https://www.ncbi.nlm.nih.gov/omim/?term=obesity

Jagannadham J, Jaiswal HK, Agrawal S, Rawal K. Comprehensive map of molecules implicated in obesity. PLoS One. 2016;11(2):e0146759.

Tables of Glycemic Index and Glycemic Load of Foods

Atkinson FS et al. International tables of glycemic index and glycemic load values: 2008. Diabetes Care. 2008;31(12):2281–3.

M.S. Freemark (ed.), *Pediatric Obesity*, Contemporary Endocrinology,
https://doi.org/10.1007/978-3-319-68192-4

Appendix B

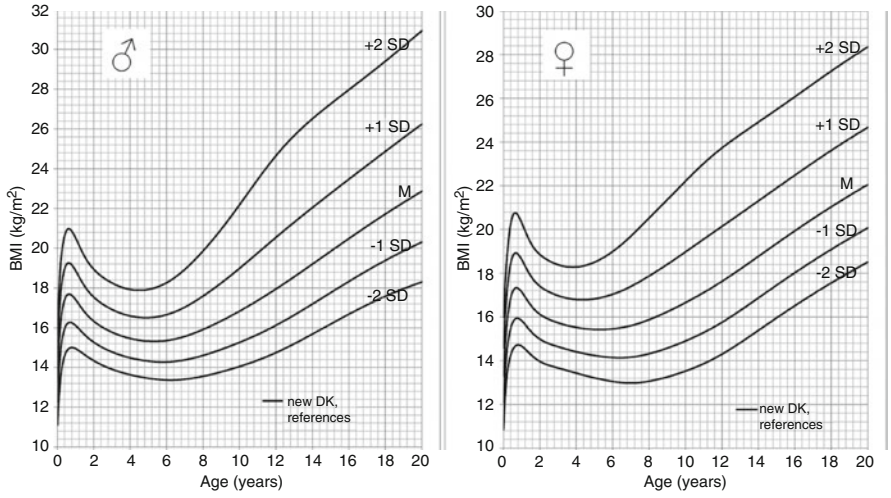

Fig. B.1 Representative changes in BMI during childhood and adolescence. Danish reference data are from Tinggaard J et al. The 2014 Danish references from birth to 20 years for height, weight, and body mass index. (Used with permission of John Wiley and Sons from Tinggaard J, Aksglaede L, Sørensen K, Mouritsen A, Wohlfahrt-Veje C, Hagen CP et al. The 2014 Danish references from birth to 20 years for height, weight, and body mass index. Acta Paediatr. 2014;103(2):214–24.)

Appendix C

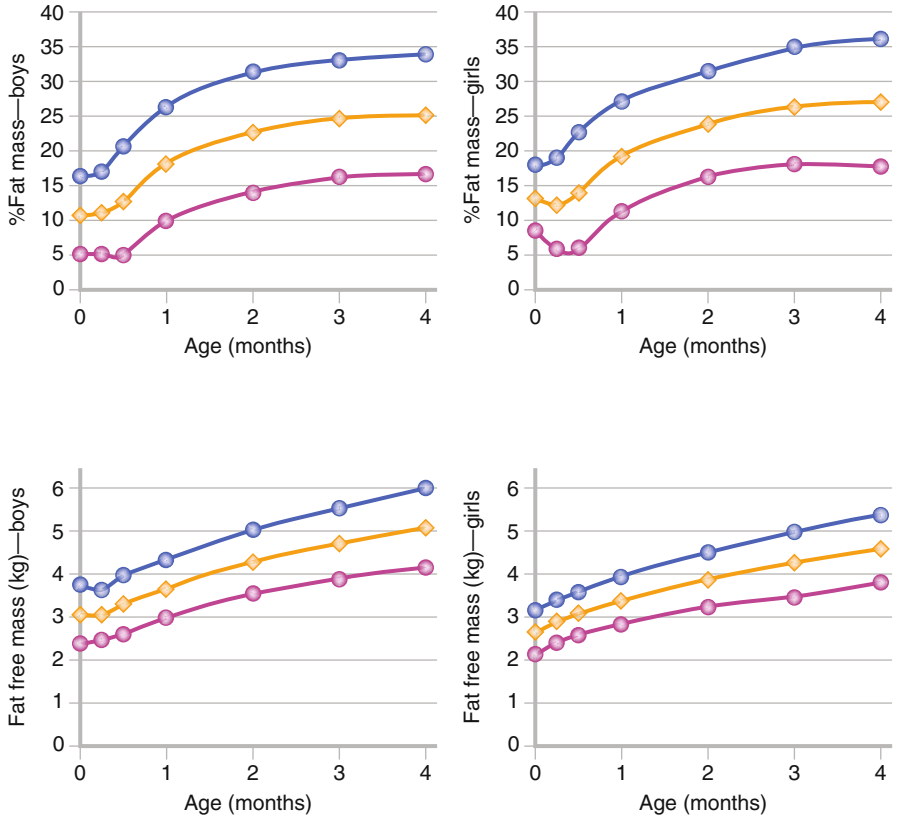

Fig. C.1 Body composition in breast fed infants. *Top*: Mean (*diamond*) and ± 2 s.d. (*circle*) % fat mass values for boys and girls from birth to 4 months of age. *Bottom*: Mean (*diamond*) and ± 2 s.d. (*circle*) fat-free mass values for boys and girls from birth to 4 months of age. (Used with permission of John Wiley and Sons from Fields DA, Gilchrist JM, Catalano PM, Giannì ML, Roggero PM, Mosca F. Longitudinal body composition data in exclusively breast-fed infants: a multicenter study. Obesity (Silver Spring). 2011;19(9):1887–91.)

Appendix D

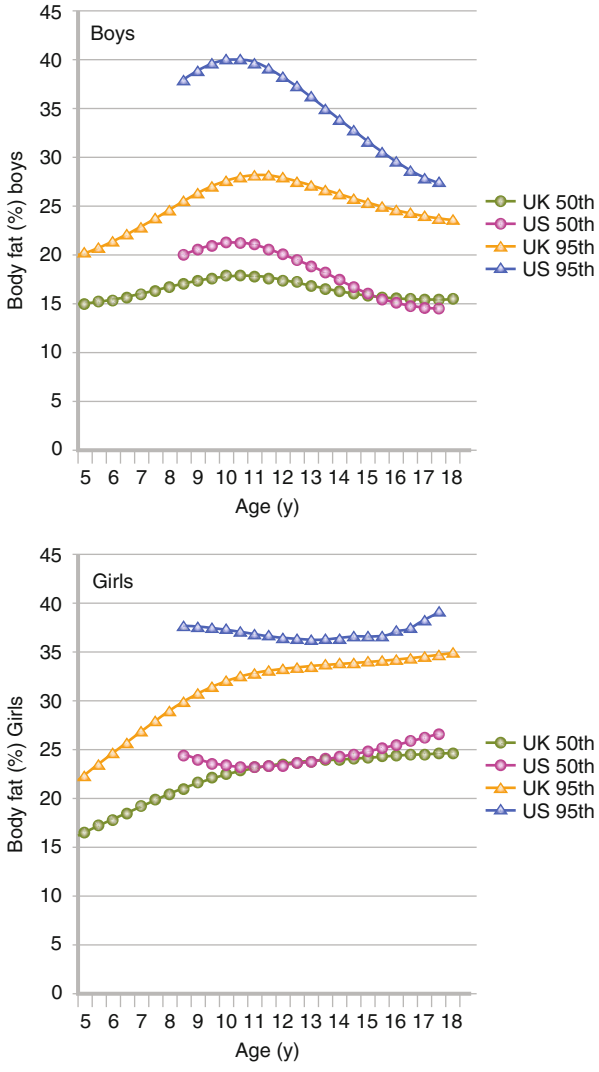

Fig. D.1 Body fat percentage in Caucasian children. *Top*: Boys. *Bottom*: Girls. (Used with permission of Nature Publishing Group from McCarthy HD, Cole TJ, Fry T, Jebb SA, Prentice AM. Body fat reference curves for children. Int J Obes (Lond). 2006;30(4):598–602.)

Appendix E

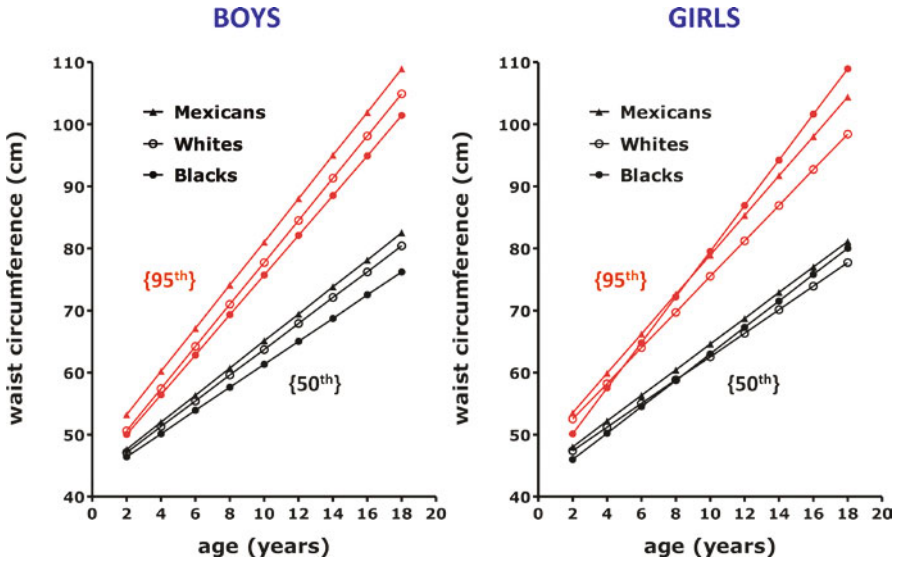

Fig. E.1 Waist circumference standards in US children. *Left*: Boys. *Right*: Girls. (Data from Fernández JR, Redden DT, Pietrobelli A, Allison DB. Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. J Pediatr. 2004;145(4):439–44.)

Appendix F

Energy expenditure associated with daily physical activity. 1 MET (Metabolic Equivalent) = multiple of resting metabolic rate [~ 1 kcal (4.184 kJ)/kg/h]

Code	METS	Major heading	Specific activities
01003	14.0	Bicycling	Bicycling, mountain, uphill, vigorous bicycling
01004	16.0	Bicycling	Mountain, competitive, racing bicycling, BMX
01008	*8.5*	Bicycling	Bicycling, mountain, general
01009	*8.5*	Bicycling	Bicycling, <10 mph, leisure, to work or for pleasure (Taylor Code 115)
01010	4.0	Bicycling	Bicycling, to/from work, self-selected pace
01011	6.8	Bicycling	Bicycling, on dirt or farm road, moderate pace
01013	5.8	Bicycling	Bicycling, general
01015	7.5	Bicycling	Bicycling, leisure, 5.5 mph
01018	3.5	Bicycling	Bicycling, leisure, 9.4 mph
01019	5.8	Bicycling	Bicycling, 10–11.9 mph, leisure, slow, light effort
01020	6.8	Bicycling	Bicycling, 12–13.9 mph, leisure, moderate effort
01030	8.0	Bicycling	Bicycling, 14–15.9 mph, racing or leisure, fast, vigorous effort
01040	10.0	Bicycling	Bicycling, 16–19 mph, racing/not drafting or > 19 mph drafting, very fast, racing general
01050	*12.0*	Bicycling	Bicycling, >20 mph, racing, not drafting
01060	15.8	Bicycling	Bicycling, 12 mph, seated, hands on brake hoods or bar drops, 80 rpm
01065	8.5	Bicycling	Bicycling, 12 mph, standing, hands on brake hoods, 60 rpm
01066	9.0	Bicycling	Unicycling
01070	*5.0*	Bicycling	Activity-promoting video game (e.g., Wii Fit), light effort (e.g., balance, yoga)
02001	2.3	Conditioning exercise	Activity-promoting video game (e.g., Wii Fit), moderate effort (e.g., aerobic, resistance)
02003	3.8	Conditioning exercise	Activity-promoting video/arcade game (e.g., Exergaming, Dance Revolution), vigorous effort
02005	7.2	Conditioning exercise	Army type obstacle course exercise, boot camp training program
02008	5.0	Conditioning exercise	Bicycling, stationary, general
02010	*7.0*	Conditioning exercise	Bicycling, stationary, 30–50 watts, very light to light effort
02011	3.5	Conditioning exercise	Bicycling, stationary, 90–100 watts, moderate to vigorous effort
02012	6.8	Conditioning exercise	Bicycling, stationary, 101–160 watts, vigorous effort
02013	8.8	Conditioning exercise	Bicycling, stationary, 161–200 watts, vigorous effort
02014	11.0	Conditioning exercise	Bicycling, stationary, 201–270 watts, very vigorous effort
02015	14.0	Conditioning exercise	Bicycling, stationary, 51–89 watts, light-to-moderate effort
02017	4.8	Conditioning exercise	Bicycling, stationary, RPM/Spin bike class
02019	8.5	Conditioning exercise	Calisthenics (e.g., push-ups, sit-ups, pull-ups, jumping jacks), vigorous effort

(continued)

Appendix F (continued)

Code	METS	Major heading	Specific activities
02020	*8.0*	Conditioning exercise	Calisthenics (e.g., push-ups, sit-ups, pull-ups, lunges), moderate effort
02022	3.8	Conditioning exercise	Calisthenics (e.g., sit-ups, abdominal crunches), light effort
02024	2.8	Conditioning exercise	Calisthenics, light or moderate effort, general (e.g., back exercises), going up and down from floor (Taylor Code 150)
02030	3.5	Conditioning exercise	Circuit training, moderate effort
02035	4.3	Conditioning exercise	Circuit training, including kettlebells, some aerobic movement with minimal rest, general, vigorous intensity
02040	8.0	Conditioning exercise	Curves™ exercise routines in women
02045	3.5	Conditioning exercise	Elliptical trainer, moderate effort
02048	5.0	Conditioning exercise	Resistance training (weight lifting, free weight, nautilus or universal), power lifting or body building, vigorous effort (Taylor Code 210)
02050	6.0	Conditioning exercise	Resistance (weight) training, squats , slow or explosive effort
02052	5.0	Conditioning exercise	Resistance (weight) training, multiple exercises, 8–15 repetitions at varied resistance
02054	3.5	Conditioning exercise	Health club exercise, general (Taylor Code 160)
02060	5.5	Conditioning exercise	Health club exercise classes, general, gym/weight training combined in one visit
02061	5.0	Conditioning exercise	Health club exercise, conditioning classes
02062	7.8	Conditioning exercise	Home exercise, general
02064	3.8	Conditioning exercise	Stair-treadmill ergometer, general
02065	*9.0*	Conditioning exercise	Rope skipping, general
02068	12.3	Conditioning exercise	Rowing, stationary ergometer, general, vigorous effort
02070	*6.0*	Conditioning exercise	Rowing, stationary, general, moderate effort
02071	4.8	Conditioning exercise	
02072	*7.0*	Conditioning exercise	Rowing, stationary, 100 watts, moderate effort
02073	*8.5*	Conditioning exercise	Rowing, stationary, 150 watts, vigorous effort
02074	*12.0*	Conditioning exercise	Rowing, stationary, 200 watts, very vigorous effort
02080	6.8	Conditioning exercise	Ski machine, general
02085	11.0	Conditioning exercise	Slide board exercise, general
02090	*6.0*	Conditioning exercise	Slimnastics, jazzercise
02101	2.3	Conditioning exercise	Stretching, mild
02105	3.0	Conditioning exercise	Pilates, general
02110	6.8	Conditioning exercise	Teaching exercise class (e.g., aerobic, water)
02112	2.8	Conditioning exercise	Therapeutic exercise ball, Fitball exercise
02115	2.8	Conditioning exercise	Upper body exercise, arm ergometer
02117	4.3	Conditioning exercise	Upper body exercise, stationary bicycle—Airdyne (arms only) 40 rpm, moderate

02120	5.3	Conditioning exercise	Water aerobics, water calisthenics, water exercise
02135	*1.3*	Conditioning exercise	Whirlpool, sitting
02140	*2.3*	Conditioning exercise	Video exercise workouts, TV conditioning programs (e.g., yoga, stretching), light effort
02143	*4.0*	Conditioning exercise	Video exercise workouts, TV conditioning programs (e.g., cardio-resistance), moderate effort
02146	6.0	Conditioning exercise	Video exercise workouts, TV conditioning programs (e.g., cardio-resistance), vigorous effort
02150	2.5	Conditioning exercise	Yoga, Hatha
02160	*4.0*	Conditioning exercise	Yoga, Power
02170	2.0	Conditioning exercise	Yoga, Nadisodhana
02180	3.3	Conditioning exercise	Yoga, Surya Namaskar
02200	5.3	Conditioning exercise	Native New Zealander physical activities (e.g., Haka Powhiri, Moteatea, Waita Tira, Whakawatea, etc.), general, moderate effort
02205	6.8	Conditioning exercise	Native New Zealander physical activities (e.g., Haka, Taiahab), general, vigorous effort
03010	5.0	Dancing	Ballet, modern, or jazz, general, rehearsal or class
03012	6.8	Dancing	Ballet, modern, or jazz, performance, vigorous effort
03014	4.8	Dancing	Tap
03015	7.3	Dancing	Aerobic, general
03016	7.5	Dancing	Aerobic, step, with 6–8 inch step
03017	9.5	Dancing	Aerobic, step, with 10–12 inch step
03018	5.5	Dancing	Aerobic, step, with 4-inch step
03019	8.5	Dancing	Bench step class, general
03020	*5.0*	Dancing	Aerobic, low impact
03021	7.3	Dancing	Aerobic, high impact
03022	10.0	Dancing	Aerobic dance wearing 10–15 lb weights
03025	*4.5*	Dancing	Ethnic or cultural dancing (e.g., Greek, Middle Eastern, hula, salsa, merengue, bamba y plena, flamenco, belly, and swing)
03030	5.5	Dancing	Ballroom, fast (Taylor Code 125)
03031	7.8	Dancing	General dancing (e.g., disco, folk, Irish step dancing, line dancing, polka, contra, country)
03038	11.3	Dancing	Ballroom dancing, competitive, general
03040	*3.0*	Dancing	Ballroom, slow (e.g., waltz, foxtrot, slow dancing, samba, tango, nineteenth century dance, mambo, cha cha)
03050	5.5	Dancing	Anishinaabe Jingle Dancing
03060	3.5	Dancing	Caribbean dance (Abakua, Beguine, Bellair, Bongo, Brukins, Caribbean Quadrills, Dinki Mini, Gere, Gumbay, Ibo, Jonkonnu, Kumina, Oreisha, Jambu)
04001	3.5	Fishing and hunting	Fishing, general
04005	4.5	Fishing and hunting	Fishing, crab fishing

(continued)

Appendix F (continued)

Code	METS	Major heading	Specific activities
04007	4.0	Fishing and hunting	Fishing, catching fish with hands
04010	4.3	Fishing and hunting	Fishing related, digging worms with shovel
04020	*4.0*	Fishing and hunting	Fishing from river bank and walking
04030	*2.0*	Fishing and hunting	Fishing from boat or canoe, sitting
04040	*3.5*	Fishing and hunting	Fishing from river bank, standing (Taylor Code 660)
04050	*6.0*	Fishing and hunting	Fishing in stream, in waders (Taylor Code 670)
04060	*2.0*	Fishing and hunting	Fishing, ice, sitting
04061	1.8	Fishing and hunting	Fishing, jog or line, standing, general
04062	*3.5*	Fishing and hunting	Fishing, dip net, setting net and retrieving fish, general
04063	3.8	Fishing and hunting	Fishing, set net, setting net and retrieving fish, general
04064	*3.0*	Fishing and hunting	Fishing, fishing wheel, setting net and retrieving fish, general
04065	2.3	Fishing and hunting	Fishing with a spear, standing
04070	*2.5*	Fishing and hunting	Hunting, bow and arrow, or crossbow
04080	6.0	Fishing and hunting	Hunting, deer, elk, large game (Taylor Code 170)
04081	11.3	Fishing and hunting	Hunting large game, dragging carcass
04083	*4.0*	Fishing and hunting	Hunting large marine animals
04085	*2.5*	Fishing and hunting	Hunting large game, from a hunting stand, limited walking
04086	*2.0*	Fishing and hunting	Hunting large game from a car, plane, or boat
04090	*2.5*	Fishing and hunting	Hunting, duck, wading
04095	3.0	Fishing and hunting	Hunting, flying fox, squirrel
04100	*5.0*	Fishing and hunting	Hunting, general
04110	6.0	Fishing and hunting	Hunting, pheasants or grouse (Taylor Code 680)
04115	3.3	Fishing and hunting	Hunting, birds
04120	5.0	Fishing and hunting	Hunting, rabbit, squirrel, prairie chick, raccoon, small game (Taylor Code 690)
04123	3.3	Fishing and hunting	Hunting, pigs, wild
04124	*2.0*	Fishing and hunting	Trapping game, general
04125	9.5	Fishing and hunting	Hunting, hiking with hunting gear
04130	*2.5*	Fishing and hunting	Pistol shooting or trap shooting, standing
04140	2.3	Fishing and hunting	Rifle exercises, shooting, lying down
04145	2.5	Fishing and hunting	Rifle exercises, shooting, kneeling or standing
05010	3.3	Home activities	Cleaning, sweeping carpet or floors, general
05011	2.3	Home activities	Cleaning, sweeping, slow, light effort

05012	3.8	Home activities	Cleaning, sweeping, slow, moderate effort
05020	*3.5*	Home activities	Cleaning, heavy or major (e.g. wash car, wash windows, clean garage), moderate effort
05021	3.5	Home activities	Cleaning, mopping, standing, moderate effort
05022	3.2	Home activities	Cleaning windows, washing windows, general
05023	2.5	Home activities	Mopping, standing, light effort
05024	4.5	Home activities	Polishing floors, standing, walking slowly, using electric polishing machine
05025	2.8	Home activities	Multiple household tasks all at once, light effort
05026	*3.5*	Home activities	Multiple household tasks all at once, moderate effort
05027	4.3	Home activities	Multiple household tasks all at once, vigorous effort
05030	3.3	Home activities	Cleaning, house or cabin, general, moderate effort
05032	2.3	Home activities	Dusting or polishing furniture, general
05035	3.3	Home activities	Kitchen activity, general, (e.g., cooking, washing dishes, cleaning up), moderate effort
05040	2.5	Home activities	Cleaning, general (straightening up, changing linen, carrying out trash, light effort
05041	1.8	Home activities	Wash dishes, standing or in general (not broken into stand/walk components)
05042	*2.5*	Home activities	Wash dishes, clearing dishes from table, walking, light effort
05043	3.3	Home activities	Vacuuming, general, moderate effort
05044	*3.0*	Home activities	Butchering animals, small
05045	*6.0*	Home activities	Butchering animal, large, vigorous effort
05046	*2.3*	Home activities	Cutting and smoking fish, drying fish or meat
05048	*4.0*	Home activities	Tanning hides, general
05049	3.5	Home activities	Cooking or food preparation, moderate effort
05050	2.0	Home activities	Cooking or food preparation – standing or sitting or in general (not broken into stand/walk components), manual appliances, light effort
05051	*2.5*	Home activities	Serving food, setting table, implied walking or standing
05052	*2.5*	Home activities	Cooking or food preparation, walking
05053	*2.5*	Home activities	Feeding household animals
05055	*2.5*	Home activities	Putting away groceries (e.g. carrying groceries, shopping without a grocery cart), carrying packages
05056	*7.5*	Home activities	Carrying groceries upstairs
05057	*3.0*	Home activities	Cooking Indian bread on an outside stove
05060	2.3	Home activities	Food shopping with or without a grocery cart, standing or walking
05065	*2.3*	Home activities	Nonfood shopping, with or without a cart, standing or walking
05070	1.8	Home activities	Ironing
05080	1.3	Home activities	Knitting, sewing, light effort, wrapping presents, sitting
05082	2.8	Home activities	Sewing with a machine

(continued)

Appendix F (continued)

Code	METS	Major heading	Specific activities
05090	2.0	Home activities	Laundry, fold or hang clothes, put clothes in washer or dryer, packing suitcase, washing clothes by hand, implied standing, light effort
05092	4.0	Home activities	Laundry, hanging wash, washing clothes by hand, moderate effort
05095	*2.3*	Home activities	Laundry, putting away clothes, gathering clothes to pack, putting away laundry, implied walking
05100	3.3	Home activities	Making bed, changing linens
05110	5.0	Home activities	Maple syruping/sugar bushing (including carrying buckets, carrying wood)
05120	5.8	Home activities	Moving furniture, household items, carrying boxes
05121	5.0	Home activities	Moving, lifting light loads
05125	4.8	Home activities	Organizing room
05130	3.5	Home activities	Scrubbing floors, on hands and knees, scrubbing bathroom, bathtub, moderate effort
05131	2.0	Home activities	Scrubbing floors, on hands and knees, scrubbing bathroom, bathtub, light effort
05132	6.5	Home activities	Scrubbing floors, on hands and knees, scrubbing bathroom, bathtub, vigorous effort
05140	*4.0*	Home activities	Sweeping garage, sidewalk or outside of house
05146	*3.5*	Home activities	Standing, packing/unpacking boxes, occasional lifting of lightweight household items, loading or unloading items in car, moderate effort
05147	*3.0*	Home activities	Implied walking, putting away household items, moderate effort
05148	*2.5*	Home activities	Watering plants
05149	*2.5*	Home activities	Building a fire inside
05150	*9.0*	Home activities	Moving household items upstairs, carrying boxes or furniture
05160	*2.0*	Home activities	Standing, light effort tasks (pump gas, change light bulb, etc.)
05165	3.5	Home activities	Walking, moderate effort tasks, non-cleaning (readying to leave, shut/lock doors, close windows, etc.)
05170	2.2	Home activities	Sitting, playing with child(ren), light effort, only active periods
05171	*2.8*	Home activities	Standing, playing with child(ren) light effort, only active periods
05175	3.5	Home activities	Walking/running, playing with child(ren), moderate effort, only active periods
05180	5.8	Home activities	Walking/running, playing with child(ren), vigorous effort, only active periods
05181	*3.0*	Home activities	Walking and carrying small child, child weighing 15 lbs or more
05182	2.3	Home activities	Walking and carrying small child, child weighing less than 15 lbs
05183	2.0	Home activities	Standing, holding child
05184	2.5	Home activities	Child care, infant, general
05185	2.0	Home activities	Child care, sitting/kneeling (e.g., dressing, bathing, grooming, feeding, occasional lifting of child), light effort, general
05186	*3.0*	Home activities	Child care, standing (e.g., dressing, bathing, grooming, feeding, occasional lifting of child), moderate effort

05188	*1.5*	Home activities	Reclining with baby
05189	2.0	Home activities	Breastfeeding, sitting or reclining
05190	*2.5*	Home activities	Sit, playing with animals, light effort, only active periods
05191	*2.8*	Home activities	Stand, playing with animals, light effort, only active periods
05192	3.0	Home activities	Walk/run, playing with animals, general, light effort, only active periods
05193	*4.0*	Home activities	Walk/run, playing with animals, moderate effort, only active periods
05194	*5.0*	Home activities	Walk/run, playing with animals, vigorous effort, only active periods
05195	*3.5*	Home activities	Standing, bathing dog
05197	*2.3*	Home activities	Animal care, household animals, general
05200	*4.0*	Home activities	Elder care, disabled adult, bathing, dressing, moving into and out of bed, only active periods
05205	*2.3*	Home activities	Elder care, disabled adult, feeding, combing hair, light effort, only active periods
06010	*3.0*	Home repair	Airplane repair
06020	*4.0*	Home repair	Automobile body work
06030	3.3	Home repair	Automobile repair, light or moderate effort
06040	3.0	Home repair	Carpentry, general, workshop (Taylor Code 620)
06050	6.0	Home repair	Carpentry, outside house, installing rain gutters (Taylor Code 640), carpentry, outside house, building a fence
06052	3.8	Home repair	Carpentry, outside house, building a fence
06060	3.3	Home repair	Carpentry, finishing or refinishing cabinets or furniture
06070	6.0	Home repair	Carpentry, sawing hardwood
06072	4.0	Home repair	Carpentry, home remodeling tasks, moderate effort
06074	2.3	Home repair	Carpentry, home remodeling tasks, light effort
06080	*5.0*	Home repair	Caulking, chinking log cabin
06090	*4.5*	Home repair	Caulking, except log cabin
06100	*5.0*	Home repair	Cleaning gutters
06110	*5.0*	Home repair	Excavating garage
06120	*5.0*	Home repair	Hanging storm windows
06122	*5.0*	Home repair	Hanging sheet rock inside house
06124	3.0	Home repair	Hammering nails
06126	*2.5*	Home repair	Home repair, general, light effort
06127	*4.5*	Home repair	Home repair, general, moderate effort
06128	*6.0*	Home repair	Home repair, general, vigorous effort
06130	*4.5*	Home repair	Laying or removing carpet
06140	3.8	Home repair	Laying tile or linoleum, repairing appliances
06144	*3.0*	Home repair	Repairing appliances

(continued)

Appendix F (continued)

Code	METS	Major heading	Specific activities
06150	5.0	Home repair	Painting, outside home (Taylor Code 650)
06160	3.3	Home repair	Painting inside house, wallpapering, scraping paint
06165	4.5	Home repair	Painting, (Taylor Code 630)
06167	*3.0*	Home repair	Plumbing, general
06170	*3.0*	Home repair	Put on and removal of tarp - sailboat
06180	*6.0*	Home repair	Roofing
06190	*4.5*	Home repair	Sanding floors with a power sander
06200	*4.5*	Home repair	Scraping and painting sailboat or powerboat
06205	2.0	Home repair	Sharpening tools
06210	*5.0*	Home repair	Spreading dirt with a shovel
06220	*4.5*	Home repair	Washing and waxing hull of sailboat or airplane
06225	2.0	Home repair	Washing and waxing car
06230	*4.5*	Home repair	Washing fence, painting fence, moderate effort
06240	3.3	Home repair	Wiring, tapping-splicing
07010	*1.0*	Inactivity quiet/light	Lying quietly and watching television
07011	1.3	Inactivity quiet/light	Lying quietly, doing nothing, lying in bed awake, listening to music (not talking or reading)
07020	1.3	Inactivity quiet/light	Sitting quietly and watching television
07021	1.3	Inactivity quiet/light	Sitting quietly, general
07022	1.5	Inactivity quiet/light	Sitting quietly, fidgeting, general, fidgeting hands
07023	1.8	Inactivity quiet/light	Sitting, fidgeting feet
07024	*1.3*	Inactivity quiet/light	Sitting, smoking
07025	1.5	Inactivity quiet/light	Sitting, listening to music (not talking or reading) or watching a movie in a theater
07026	1.3	Inactivity quiet/light	Sitting at a desk, resting head in hands
07030	1.0	Inactivity quiet/light	Sleeping
07040	1.3	Inactivity quiet/light	Standing quietly, standing in a line
07041	1.8	Inactivity quiet/light	Standing, fidgeting
07050	*1.3*	Inactivity quiet/light	Reclining, writing
07060	*1.3*	Inactivity quiet/light	Reclining, talking or talking on phone
07070	1.3	Inactivity quiet/light	Reclining, reading
07075	*1.0*	Inactivity quiet/light	Meditating
08009	3.3	Lawn and garden	Carrying, loading or stacking wood, loading/unloading or carrying lumber, light-to-moderate effort
08010	5.5	Lawn and garden	Carrying, loading or stacking wood, loading/unloading or carrying lumber

08019	4.5	Lawn and garden	Chopping wood, splitting logs, moderate effort
08020	6.3	Lawn and garden	Chopping wood, splitting logs, vigorous effort
08025	3.5	Lawn and garden	Clearing light brush, thinning garden, moderate effort
08030	6.3	Lawn and garden	Clearing brush/land, undergrowth, or ground, hauling branches, wheelbarrow chores, vigorous effort
08040	5.0	Lawn and garden	Digging sandbox, shoveling sand
08045	3.5	Lawn and garden	Digging, spading, filling garden, composting, light-to-moderate effort
08050	5.0	Lawn and garden	Digging, spading, filling garden, compositing, (Taylor Code 590)
08052	7.8	Lawn and garden	Digging, spading, filling garden, composting, vigorous effort
08055	2.8	Lawn and garden	Driving tractor
08057	8.3	Lawn and garden	Felling trees, large size
08058	5.3	Lawn and garden	Felling trees, small–medium size
08060	5.8	Lawn and garden	Gardening with heavy power tools, tilling a garden, chain saw
08065	2.3	Lawn and garden	Gardening, using containers, older adults > 60 years
08070	4.0	Lawn and garden	Irrigation channels, opening and closing ports
08080	6.3	Lawn and garden	Laying crushed rock
08090	*5.0*	Lawn and garden	Laying sod
08095	5.5	Lawn and garden	Mowing lawn, general
08100	2.5	Lawn and garden	Mowing lawn, riding mower (Taylor Code 550)
08110	6.0	Lawn and garden	Mowing lawn, walk, hand mower (Taylor Code 570)
08120	5.0	Lawn and garden	Mowing lawn, walk, power mower, moderate or vigorous effort
08125	4.5	Lawn and garden	Mowing lawn, power mower, light or moderate effort (Taylor Code 590)
08130	2.5	Lawn and garden	Operating snow blower, walking
08135	2.0	Lawn and garden	Planting, potting, transplanting seedlings or plants, light effort
08140	4.3	Lawn and garden	Planting seedlings, shrub, stooping, moderate effort
08145	4.3	Lawn and garden	Planting crops or garden, stooping, moderate effort
08150	*4.5*	Lawn and garden	Planting trees
08160	3.8	Lawn and garden	Raking lawn or leaves, moderate effort
08165	4.0	Lawn and garden	Raking lawn (Taylor Code 600)
08170	*4.0*	Lawn and garden	Raking roof with snow rake
08180	*3.0*	Lawn and garden	Riding snow blower
08190	*4.0*	Lawn and garden	Sacking grass, leaves
08192	5.5	Lawn and garden	Shoveling dirt or mud
08195	5.3	Lawn and garden	Shoveling snow, by hand, moderate effort
08200	6.0	Lawn and garden	Shoveling snow, by hand (Taylor Code 610)

(continued)

Appendix F (continued)

Code	METS	Major heading	Specific activities
08202	7.5	Lawn and garden	Shoveling snow, by hand, vigorous effort
08210	4.0	Lawn and garden	Trimming shrubs or trees, manual cutter
08215	3.5	Lawn and garden	Trimming shrubs or trees, power cutter, using leaf blower, edge, moderate effort
08220	3.0	Lawn and garden	Walking, applying fertilizer or seeding a lawn, push applicator
08230	*1.5*	Lawn and garden	Watering lawn or garden, standing or walking
08239	3.5	Lawn and garden	Weeding, cultivating garden, light-to-moderate effort
08240	4.5	Lawn and garden	Weeding, cultivating garden (Taylor Code 580)
08241	5.0	Lawn and garden	Weeding, cultivating garden, using a hoe, moderate-to-vigorous effort
08245	3.8	Lawn and garden	Gardening, general, moderate effort
08246	3.5	Lawn and garden	Picking fruit off trees, picking fruits/vegetables, moderate effort
08248	4.5	Lawn and garden	Picking fruit off trees, gleaning fruits, picking fruits/vegetables, climbing ladder to pick fruit, vigorous effort
08250	3.3	Lawn and garden	Implied walking/standing – picking up yard, light, picking flowers or vegetables
08251	*3.0*	Lawn and garden	Walking, gathering gardening tools
08255	5.5	Lawn and garden	Wheelbarrow, pushing garden cart or wheelbarrow
08260	3.0	Lawn and garden	Yard work, general, light effort
08261	4.0	Lawn and garden	Yard work, general, moderate effort
08262	6.0	Lawn and garden	Yard work, general, vigorous effort
09000	*1.5*	Miscellaneous	Board game playing, sitting
09005	*2.5*	Miscellaneous	Casino gambling, standing
09010	1.5	Miscellaneous	Card playing, sitting
09013	1.5	Miscellaneous	Chess game, sitting
09015	1.5	Miscellaneous	Copying documents, standing
09020	1.8	Miscellaneous	Drawing, writing, painting, standing
09025	1.0	Miscellaneous	Laughing, sitting
09030	1.3	Miscellaneous	Sitting, reading, book, newspaper, etc.
09040	1.3	Miscellaneous	Sitting, writing, desk work, typing
09045	1.0	Miscellaneous	Sitting, playing traditional video game, computer game
09050	*1.8*	Miscellaneous	Standing, talking in person, on the phone, computer, or text messaging, light effort
09055	*1.5*	Miscellaneous	Sitting, talking in person, on the phone, computer, or text messaging, light effort
09060	1.3	Miscellaneous	Sitting, studying, general, including reading and/or writing, light effort
09065	1.8	Miscellaneous	Sitting, in class, general, including note-taking or class discussion
09070	*1.8*	Miscellaneous	Standing, reading

09071	2.5	Miscellaneous	Standing, miscellaneous
09075	1.8	Miscellaneous	Sitting, arts and crafts, carving wood, weaving, spinning wool, light effort
09080	*3.0*	Miscellaneous	Sitting, arts and crafts, carving wood, weaving, spinning wool, moderate effort
09085	2.5	Miscellaneous	Standing, arts and crafts, sand painting, carving, weaving, light effort
09090	*3.3*	Miscellaneous	Standing, arts and crafts, sand painting, carving, weaving, moderate effort
09095	*3.5*	Miscellaneous	Standing, arts and crafts, sand painting, carving, weaving, vigorous effort
09100	1.8	Miscellaneous	Retreat/family reunion activities involving sitting, relaxing, talking, eating
09101	3.0	Miscellaneous	Retreat/family reunion activities involving playing games with children
09105	*2.0*	Miscellaneous	Touring/traveling/vacation involving riding in a vehicle
09106	*3.5*	Miscellaneous	Touring/traveling/vacation involving walking
09110	*2.5*	Miscellaneous	Camping involving standing, walking, sitting, light-to-moderate effort
09115	*1.5*	Miscellaneous	Sitting at a sporting event, spectator
10010	1.8	Music playing	Accordion, sitting
10020	2.3	Music playing	Cello, sitting
10030	2.3	Music playing	Conducting orchestra, standing
10035	2.5	Music playing	Double bass, standing
10040	3.8	Music playing	Drums, sitting
10045	3.0	Music playing	Drumming (e.g., bongo, conga, benbe), moderate, sitting
10050	2.0	Music playing	Flute, sitting
10060	1.8	Music playing	Horn, standing
10070	2.3	Music playing	Piano, sitting
10074	2.0	Music playing	Playing musical instruments, general
10077	2.0	Music playing	Organ, sitting
10080	3.5	Music playing	Trombone, standing
10090	1.8	Music playing	Trumpet, standing
10100	2.5	Music playing	Violin, sitting
10110	1.8	Music playing	Woodwind, sitting
10120	*2.0*	Music playing	Guitar, classical, folk, sitting
10125	*3.0*	Music playing	Guitar, rock and roll band, standing
10130	*4.0*	Music playing	Marching band, baton twirling, walking, moderate pace, general
10131	5.5	Music playing	Marching band, playing an instrument, walking, brisk pace, general
10135	*3.5*	Music playing	Marching band, drum major, walking
11003	2.3	Occupation	Active workstation, treadmill desk, walking
11006	3.0	Occupation	Airline flight attendant

(continued)

Appendix F (continued)

Code	METS	Major heading	Specific activities
11010	*4.0*	Occupation	Bakery, general, moderate effort
11015	2.0	Occupation	Bakery, light effort
11020	2.3	Occupation	Bookbinding
11030	*6.0*	Occupation	Building road, driving heavy machinery
11035	*2.0*	Occupation	Building road, directing traffic, standing
11038	2.5	Occupation	Carpentry, general, light effort
11040	4.3	Occupation	Carpentry, general, moderate effort
11042	7.0	Occupation	Carpentry, general, heavy or vigorous effort
11050	*8.0*	Occupation	Carrying heavy loads (e.g., bricks, tools)
11060	*8.0*	Occupation	Carrying moderate loads upstairs, moving boxes 25–49 lbs
11070	4.0	Occupation	Chambermaid, hotel housekeeper, making bed, cleaning bathroom, pushing cart
11080	5.3	Occupation	Coal mining, drilling coal, rock
11090	5.0	Occupation	Coal mining, erecting supports
11100	5.5	Occupation	Coal mining, general
11110	6.3	Occupation	Coal mining, shoveling coal
11115	2.5	Occupation	Cook, chef
11120	4.0	Occupation	Construction, outside, remodeling, new structures (e.g., roof repair, miscellaneous)
11125	2.3	Occupation	Custodial work, light effort (e.g., cleaning sink and toilet, dusting, vacuuming, light cleaning)
11126	3.8	Occupation	Custodial work, moderate effort (e.g., electric buffer, feathering arena floors, mopping, taking out trash, vacuuming)
11130	3.3	Occupation	Electrical work (e.g., hook up wire, tapping-splicing)
11135	1.8	Occupation	Engineer (e.g., mechanical or electrical)
11145	7.8	Occupation	Farming, vigorous effort (e.g., baling hay, cleaning barn)
11146	4.8	Occupation	Farming, moderate effort (e.g., feeding animals, chasing cattle by walking and/or horseback, spreading manure, harvesting crops)
11147	2.0	Occupation	Farming, light effort (e.g., cleaning animal sheds, preparing animal feed)
11170	2.8	Occupation	Farming, driving tasks (e.g., driving tractor or harvester)
11180	3.5	Occupation	Farming, feeding small animals
11190	4.3	Occupation	Farming, feeding cattle, horses
11191	4.3	Occupation	Farming, hauling water for animals, general hauling water, farming, general hauling water
11192	4.5	Occupation	Farming, taking care of animals (e.g., grooming, brushing, shearing sheep, assisting with birthing, medical care, branding), general
11195	3.8	Occupation	Farming, rice, planting, grain milling activities

11210	3.5	Occupation	Farming, milking by hand, cleaning pails, moderate effort
11220	1.3	Occupation	Farming, milking by machine, light effort
11240	8.0	Occupation	Firefighter, general
11244	6.8	Occupation	Firefighter, rescue victim, automobile accident, using pike pole
11245	8.0	Occupation	Firefighter, raising and climbing ladder with full gear, simulated fire suppression
11246	9.0	Occupation	Firefighter, hauling hoses on ground, carrying/hoisting equipment, breaking down walls etc., wearing full gear
11247	*3.5*	Occupation	Fishing, commercial, light effort
11248	*5.0*	Occupation	Fishing, commercial, moderate effort
11249	*7.0*	Occupation	Fishing, commercial, vigorous effort
11250	17.5	Occupation	Forestry, ax chopping, very fast, 1.25 kg ax 51 blows/min, extremely vigorous effort
11260	5.0	Occupation	Forestry, ax chopping, slow, 1.25 kg ax 19 blows/min, moderate effort
11262	8.0	Occupation	Forestry, ax chopping, fast, 1.25 kg ax 35 blows/min, vigorous effort
11264	4.5	Occupation	Forestry, moderate effort (e.g., sawing wood with power saw, weeding, hoeing)
11266	8.0	Occupation	Forestry, vigorous effort (e.g., barking, felling, or trimming trees, carrying or stacking logs, planting seeds, sawing lumber by hand)
11370	4.5	Occupation	Furriery
11375	4.0	Occupation	Garbage collector, walking, dumping bins into truck
11378	1.8	Occupation	Hairstylist (e.g., plaiting hair, manicure, makeup artist)
11380	7.3	Occupation	Horse grooming, including feeding, cleaning stalls, bathing, brushing, clipping, longeing and exercising horses
11381	*4.3*	Occupation	Horse, feeding, watering, cleaning stalls, implied walking and lifting loads
11390	7.3	Occupation	Horse racing, galloping
11400	5.8	Occupation	Horse racing, trotting
11410	3.8	Occupation	Horse racing, walking
11413	3.0	Occupation	Kitchen maid
11415	4.0	Occupation	Lawn keeper, yard work, general
11418	3.3	Occupation	Laundry worker
11420	3.0	Occupation	Locksmith
11430	3.0	Occupation	Machine tooling (e.g., machining, working sheet metal, machine fitter, operating lathe, welding) light-to-moderate effort
11450	5.0	Occupation	Machine tooling, operating punch press, moderate effort
11472	1.8	Occupation	Manager, property
11475	*2.8*	Occupation	Manual or unskilled labor, general, light effort
11476	*4.5*	Occupation	Manual or unskilled labor, general, moderate effort
11477	*6.5*	Occupation	Manual or unskilled labor, general, vigorous effort

(continued)

Appendix F (continued)

Code	METS	Major heading	Specific activities
11480	4.3	Occupation	Masonry, concrete, moderate effort
11482	2.5	Occupation	Masonry, concrete, light effort
11485	*4.0*	Occupation	Massage therapist, standing
11490	*7.5*	Occupation	Moving, carrying or pushing heavy objects, 75 lbs or more, only active time (e.g., desks, moving van work)
11495	*12.0*	Occupation	Skindiving or SCUBA diving as a frogman, Navy Seal
11500	*2.5*	Occupation	Operating heavy duty equipment, automated, not driving
11510	4.5	Occupation	Orange grove work, picking fruit
11514	3.3	Occupation	Painting, house, furniture, moderate effort
11516	*3.0*	Occupation	Plumbing activities
11520	2.0	Occupation	Printing, paper industry worker, standing
11525	*2.5*	Occupation	Police, directing traffic, standing
11526	2.5	Occupation	Police, driving a squad car, sitting
11527	1.3	Occupation	Police, riding in a squad car, sitting
11528	*4.0*	Occupation	Police, making an arrest, standing
11529	2.3	Occupation	Postal carrier, walking to deliver mail
11530	2.0	Occupation	Shoe repair, general
11540	7.8	Occupation	Shoveling, digging ditches
11550	8.8	Occupation	Shoveling, more than 16 lbs/minute, deep digging, vigorous effort
11560	5.0	Occupation	Shoveling, less than 10 lbs/minute, moderate effort
11570	6.5	Occupation	Shoveling, 10–15 lbs/minute, vigorous effort
11580	1.5	Occupation	Sitting tasks, light effort (e.g., office work, chemistry lab work, computer work, light assembly repair, watch repair, reading, desk work)
11585	1.5	Occupation	Sitting meetings, light effort, general, and/or with talking involved (e.g., eating at a business meeting)
11590	*2.5*	Occupation	Sitting tasks, moderate effort (e.g., pushing heavy levers, riding mower/forklift, crane operation)
11593	*2.8*	Occupation	Sitting, teaching stretching or yoga, or light effort exercise class
11600	3.0	Occupation	Standing tasks, light effort (e.g., bartending, store clerk, assembling, filing, duplicating, librarian, putting up a Christmas tree, standing and talking at work,
			changing clothes when teaching physical education, standing)
11610	*3.0*	Occupation	Standing, light/moderate effort (e.g., assemble/repair heavy parts, welding, stocking parts, auto repair, standing, packing boxes, nursing patient care)
11615	4.5	Occupation	Standing, moderate effort, lifting items continuously, 10–20 lbs, with limited walking or resting
11620	3.5	Occupation	Standing, moderate effort, intermittent lifting 50 lbs, hitch/twisting ropes

11630	4.5	Occupation	Standing, moderate/heavy tasks (e.g., lifting more than 50 lbs, masonry, painting, paper hanging)
11708	5.3	Occupation	Steel mill, moderate effort (e.g., fettling, forging, tipping molds)
11710	8.3	Occupation	Steel mill, vigorous effort (e.g., hand rolling, merchant mill rolling, removing slag, tending furnace)
11720	2.3	Occupation	Tailoring, cutting fabric
11730	2.5	Occupation	Tailoring, general
11740	1.8	Occupation	Tailoring, hand sewing
11750	2.5	Occupation	Tailoring, machine sewing
11760	3.5	Occupation	Tailoring, pressing
11763	2.0	Occupation	Tailoring, weaving, light effort (e.g., finishing operations, washing, dyeing, inspecting cloth, counting yards, paperwork)
11765	4.0	Occupation	Tailoring, weaving, moderate effort (e.g., spinning and weaving operations, delivering boxes of yam to spinners, loading of warp bean, pinwinding,
			conewinding, warping, cloth cutting)
11766	*6.5*	Occupation	Truck driving, loading and unloading truck, tying down load, standing, walking and carrying heavy loads
11767	2.0	Occupation	Truck driving delivery truck, taxi, shuttlebus, school bus
11770	1.3	Occupation	Typing, electric, manual or computer
11780	6.3	Occupation	Using heavy power tools such as pneumatic tools (e.g., jackhammers, drills)
11790	8.0	Occupation	Using heavy tools (not power) such as shovel, pick, tunnel bar, spade
11791	2.0	Occupation	Walking on job, less than 2.0 mph, very slow speed, in office or lab area
11792	3.5	Occupation	Walking on job, 3.0 mph, in office, moderate speed, not carrying anything
11793	4.3	Occupation	Walking on job, 3.5 mph, in office, brisk speed, not carrying anything
11795	3.5	Occupation	Walking on job, 2.5 mph, slow speed and carrying light objects less than 25 lbs
11796	*3.0*	Occupation	Walking, gathering things at work, ready to leave
11797	3.8	Occupation	Walking, 2.5 mph, slow speed, carrying heavy objects more than 25 lbs
11800	4.5	Occupation	Walking, 3.0 mph, moderately and carrying light objects less than 25 lbs
11805	3.5	Occupation	Walking, pushing a wheelchair
11810	*4.8*	Occupation	Walking, 3.5 mph, briskly and carrying objects less than 25 lbs
11820	*5.0*	Occupation	Walking or walk downstairs or standing, carrying objects about 25 to 49 lbs
11830	*6.5*	Occupation	Walking or walk downstairs or standing, carrying objects about 50 to 74 lbs
11840	*7.5*	Occupation	Walking or walk downstairs or standing, carrying objects about 75 to 99 lbs
11850	*8.5*	Occupation	Walking or walk downstairs or standing, carrying objects about 100 lbs or more
11870	*3.0*	Occupation	Working in scene shop, theater actor, backstage employee
12010	6.0	Running	Jog/walk combination (jogging component of less than 10 minutes) (Taylor Code 180)
12020	*7.0*	Running	Jogging, general

(continued)

Appendix F (continued)

Code	METS	Major heading	Specific activities
12025	*8.0*	Running	Jogging, in place
12027	*4.5*	Running	Jogging, on a mini-tramp
12029	6.0	Running	Running, 4 mph (13 min/mile)
12030	8.3	Running	Running, 5 mph (12 min/mile)
12040	*9.0*	Running	Running, 5.2 mph (11.5 min/mile)
12050	9.8	Running	Running, 6 mph (10 min/mile)
12060	10.5	Running	Running, 6.7 mph (9 min/mile)
12070	11.0	Running	Running, 7 mph (8.5 min/mile)
12080	11.5	Running	Running, 7.5 mph (8 min/mile)
12090	11.8	Running	Running, 8 mph (7.5 min/mile)
12100	*12.3*	Running	Running, 8.6 mph (7 min/mile)
12110	12.8	Running	Running, 9 mph (6.5 min/mile)
12120	14.5	Running	Running, 10 mph (6 min/mile)
12130	16.0	Running	Running, 11 mph (5.5 min/mile)
12132	19.0	Running	Running, 12 mph (5 min/mile)
12134	19.8	Running	Running, 13 mph (4.6 min/mile)
12135	23.0	Running	Running, 14 mph (4.3 min/mile)
12140	9.0	Running	Running, cross country
12150	8.0	Running	Running, (Taylor code 200)
12170	*15.0*	Running	Running, stairs, up
12180	*10.0*	Running	Running, on a track, team practice
12190	*8.0*	Running	Running, training, pushing a wheelchair or baby carrier
12200	13.3	Running	Running, marathon
13000	2.3	Self-care	Getting ready for bed, general, standing
13009	1.8	Self-care	Sitting on toilet, eliminating while standing or squating
13010	*1.5*	Self-care	Bathing, sitting
13020	2.5	Self-care	Dressing, undressing, standing or sitting
13030	1.5	Self-care	Eating, sitting
13035	*2.0*	Self-care	Talking and eating or eating only, standing
13036	*1.5*	Self-care	Taking medication, sitting or standing
13040	2.0	Self-care	Grooming, washing hands, shaving, brushing teeth, putting on make-up, sitting or standing
13045	*2.5*	Self-care	Hairstyling, standing

13046	*1.3*	Self-care	Having hair or nails done by someone else, sitting
13050	*2.0*	Self-care	Showering, toweling off, standing
14010	2.8	Sexual activity	Active, vigorous effort
14020	1.8	Sexual activity	General, moderate effort
14030	1.3	Sexual activity	Passive, light effort, kissing, hugging
15000	*5.5*	Sports	Alaska Native Games, Eskimo Olympics, general
15010	4.3	Sports	Archery, nonhunting
15020	7.0	Sports	Badminton, competitive (Taylor Code 450)
15030	5.5	Sports	Badminton, social singles and doubles, general
15040	8.0	Sports	Basketball, game (Taylor Code 490)
15050	6.0	Sports	Basketball, nongame, general (Taylor Code 480)
15055	6.5	Sports	Basketball, general
15060	7.0	Sports	Basketball, officiating (Taylor Code 500)
15070	*4.5*	Sports	Basketball, shooting baskets
15072	9.3	Sports	Basketball, drills, practice
15075	7.8	Sports	Basketball, wheelchair
15080	2.5	Sports	Billiards
15090	3.0	Sports	Bowling (Taylor Code 390)
15092	3.8	Sports	Bowling, indoor, bowling alley
15100	12.8	Sports	Boxing, in ring, general
15110	5.5	Sports	Boxing, punching bag
15120	7.8	Sports	Boxing, sparring
15130	*7.0*	Sports	Broomball
15135	5.8	Sports	Children's games, adults playing (e.g., hopscotch, 4-square, dodgeball, playground apparatus, t-ball, tetherball, marbles, arcade games), moderate effort
15138	*6.0*	Sports	Cheerleading, gymnastic moves, competitive
15140	*4.0*	Sports	Coaching, football, soccer, basketball, baseball, swimming, etc.
15142	8.0	Sports	Coaching, actively playing sport with players
15150	4.8	Sports	Cricket, batting, bowling, fielding
15160	3.3	Sports	Croquet
15170	*4.0*	Sports	Curling
15180	*2.5*	Sports	Darts, wall or lawn
15190	*6.0*	Sports	Drag racing, pushing or driving a car
15192	8.5	Sports	Auto racing, open wheel

(continued)

Appendix F (continued)

Code	METS	Major heading	Specific activities
15200	*6.0*	Sports	Fencing
15210	8.0	Sports	Football, competitive
15230	8.0	Sports	Football, touch, flag, general (Taylor Code 510)
15232	*4.0*	Sports	Football, touch, flag, light effort
15235	*2.5*	Sports	Football or baseball, playing catch
15240	*3.0*	Sports	Frisbee playing, general
15250	*8.0*	Sports	Frisbee, ultimate
15255	4.8	Sports	Golf, general
15265	4.3	Sports	Golf, walking, carrying clubs
15270	*3.0*	Sports	Golf, miniature, driving range
15285	5.3	Sports	Golf, walking, pulling clubs
15290	3.5	Sports	Golf, using power cart (Taylor Code 070)
15300	3.8	Sports	Gymnastics, general
15310	*4.0*	Sports	Hacky sack
15320	12.0	Sports	Handball, general (Taylor Code 520)
15330	*8.0*	Sports	Handball, team
15335	4.0	Sports	High ropes course, multiple elements
15340	*3.5*	Sports	Hang gliding
15350	7.8	Sports	Hockey, field
15360	*8.0*	Sports	Hockey, ice, general
15362	*10.0*	Sports	Hockey, ice, competitive
15370	5.5	Sports	Horseback riding, general
15375	*4.3*	Sports	Horse chores, feeding, watering, cleaning stalls, implied walking and lifting loads
15380	4.5	Sports	Saddling, cleaning, grooming, harnessing and unharnessing horse
15390	5.8	Sports	Horseback riding, trotting
15395	7.3	Sports	Horseback riding, canter or gallop
15400	3.8	Sports	Horseback riding, walking
15402	9.0	Sports	Horseback riding, jumping
15408	1.8	Sports	Horse cart, driving, standing or sitting
15410	*3.0*	Sports	Horseshoe pitching, quoits
15420	*12.0*	Sports	Jai alai
15425	5.3	Sports	Martial arts, different types, slower pace, novice performers, practice

15430	10.3	Sports	Martial arts, different types, moderate pace (e.g., judo, jujitsu, karate, kickboxing, tae kwon do, tae-bo, Muay Thai boxing)
15440	*4.0*	Sports	Juggling
15450	*7.0*	Sports	Kickball
15460	*8.0*	Sports	Lacrosse
15465	3.3	Sports	Lawn bowling, bocce ball, outdoor
15470	*4.0*	Sports	Motocross, off-road motor sports, all-terrain vehicle, general
15480	*9.0*	Sports	Orienteering
15490	*10.0*	Sports	Paddleball, competitive
15500	6.0	Sports	Paddleball, casual, general (Taylor Code 460)
15510	*8.0*	Sports	Polo, on horseback
15520	*10.0*	Sports	Racquetball, competitive
15530	7.0	Sports	Racquetball, general (Taylor Code 470)
15533	8.0	Sports	Rock or mountain climbing (Taylor Code 470) *(Formerly code = 17120)*
15535	7.5	Sports	Rock climbing, ascending rock, high difficulty
15537	5.8	Sports	Rock climbing, ascending or traversing rock, low-to-moderate difficulty
15540	*5.0*	Sports	Rock climbing, rappelling
15542	*4.0*	Sports	Rodeo sports, general, light effort
15544	*5.5*	Sports	Rodeo sports, general, moderate effort
15546	*7.0*	Sports	Rodeo sports, general, vigorous effort
15550	12.3	Sports	Rope jumping, fast pace, 120–160 skips/min
15551	11.8	Sports	Rope jumping, moderate pace, 100–120 skips/min, general, 2 foot skip, plain bounce
15552	8.8	Sports	Rope jumping, slow pace, < 100 skips/min, 2 foot skip, rhythm bounce
15560	8.3	Sports	Rugby, union, team, competitive
15562	6.3	Sports	Rugby, touch, noncompetitive
15570	*3.0*	Sports	Shuffleboard
15580	*5.0*	Sports	Skateboarding, general, moderate effort
15582	*6.0*	Sports	Skateboarding, competitive, vigorous effort
15590	7.0	Sports	Skating, roller (Taylor Code 360)
15591	7.5	Sports	Rollerblading, in-line skating, 14.4 km/h (9.0 mph), recreational pace
15592	9.8	Sports	Rollerblading, in-line skating, 17.7 km/h (11.0 mph), moderate pace, exercise training
15593	12.3	Sports	Rollerblading, in-line skating, 21.0 to 21.7 km/h (13.0 to 13.6 mph), fast pace, exercise training
15594	14.0	Sports	Rollerblading, in-line skating, 24.0 km/h (15.0 mph), maximal effort
15600	*3.5*	Sports	Skydiving, base jumping, bungee jumping

(continued)

Appendix F (continued)

Code	METS	Major heading	Specific activities
15605	10.0	Sports	Soccer, competitive
15610	7.0	Sports	Soccer, casual, general (Taylor Code 540)
15620	5.0	Sports	Softball or baseball, fast or slow pitch, general (Taylor Code 440)
15625	4.0	Sports	Softball, practice
15630	*4.0*	Sports	Softball, officiating
15640	*6.0*	Sports	Softball, pitching
15645	3.3	Sports	Sports spectator, very excited, emotional, physically moving
15650	12.0	Sports	Squash (Taylor Code 530)
15652	7.3	Sports	Squash, general
15660	4.0	Sports	Table tennis, ping pong (Taylor Code 410)
15670	3.0	Sports	Tai chi, Qi Gong, general
15672	1.5	Sports	Tai chi, Qi Gong, sitting, light effort
15675	7.3	Sports	Tennis, general
15680	6.0	Sports	Tennis, doubles (Taylor Code 430)
15685	4.5	Sports	Tennis, doubles
15690	8.0	Sports	Tennis, singles (Taylor Code 420)
15695	*5.0*	Sports	Tennis, hitting balls, non-game play, moderate effort
15700	*3.5*	Sports	Trampoline, recreational
15702	*4.5*	Sports	Trampoline, competitive
15710	4.0	Sports	Volleyball (Taylor Code 400)
15711	6.0	Sports	Volleyball, competitive, in gymnasium
15720	3.0	Sports	Volleyball, noncompetitive, 6–9 member team, general
15725	*8.0*	Sports	Volleyball, beach, in sand
15730	*6.0*	Sports	Wrestling (one match = 5 minutes)
15731	*7.0*	Sports	Volleyball, general
15732	*4.0*	Sports	Track and field (e.g., shot, discus, hammer throw)
15733	*6.0*	Sports	Track and field (e.g., high jump, long jump, triple jump, javelin, pole vault)
15734	*10.0*	Sports	Track and field (e.g., steeplechase, hurdles)
16010	2.5	Transportation	Automobile or light truck (not a semi) driving
16015	1.3	Transportation	Riding in a car or truck
16016	1.3	Transportation	Riding in a bus or train
16020	1.8	Transportation	Flying airplane or helicopter

16030	3.5	Transportation	Motor scooter, motorcycle
16035	6.3	Transportation	Pulling rickshaw
16040	*6.0*	Transportation	Pushing plane in and out of hangar
16050	2.5	Transportation	Truck, semi, tractor, > 1 ton, or bus, driving
16060	3.5	Transportation	Walking for transportation, 2.8–3.2 mph, level, moderate pace, firm surface
17010	7.0	Walking	Backpacking (Taylor Code 050)
17012	7.8	Walking	Backpacking, hiking or organized walking with a daypack
17020	5.0	Walking	Carrying 15 lb load (e.g. suitcase), level ground or downstairs
17021	2.3	Walking	Carrying 15 lb child, slow walking
17025	*8.3*	Walking	Carrying load upstairs, general
17026	*5.0*	Walking	Carrying 1–15 lb load, upstairs
17027	*6.0*	Walking	Carrying 16–24 lb load, upstairs
17028	*8.0*	Walking	Carrying 25–49 lb load, upstairs
17029	*10.0*	Walking	Carrying 50–74 lb load, upstairs
17030	*12.0*	Walking	Carrying >74 lb load, upstairs
17031	*3.5*	Walking	Loading /unloading a car, implied walking
17033	6.3	Walking	Climbing hills, no load
17035	6.5	Walking	Climbing hills with 0–9 lb load
17040	7.3	Walking	Climbing hills with 10–20 lb load
17050	8.3	Walking	Climbing hills with 21–42 lb load
17060	*9.0*	Walking	Climbing hills with 42+ lb load
17070	3.5	Walking	Descending stairs
17080	6.0	Walking	Hiking, cross country (Taylor Code 040)
17082	5.3	Walking	Hiking or walking at a normal pace through fields and hillsides
17085	*2.5*	Walking	Bird watching, slow walk
17088	4.5	Walking	Marching, moderate speed, military, no pack
17090	8.0	Walking	Marching rapidly, military, no pack
17100	4.0	Walking	Pushing or pulling stroller with child or walking with children, 2.5–3.1 mph
17105	3.8	Walking	Pushing a wheelchair, nonoccupational
17110	*6.5*	Walking	Race walking
17130	8.0	Walking	Stair climbing, using or climbing up ladder (Taylor Code 030)
17133	4.0	Walking	Stair climbing, slow pace
17134	8.8	Walking	Stair climbing, fast pace
17140	5.0	Walking	Using crutches

(continued)

Appendix F (continued)

Code	METS	Major heading	Specific activities
17150	*2.0*	Walking	Walking, household
17151	2.0	Walking	Walking, less than 2.0 mph, level, strolling, very slow
17152	2.8	Walking	Walking, 2.0 mph, level, slow pace, firm surface
17160	3.5	Walking	Walking for pleasure (Taylor Code 010)
17161	*2.5*	Walking	Walking from house to car or bus, from car or bus to go places, from car or bus to and from the worksite
17162	*2.5*	Walking	Walking to neighbor's house or family's house for social reasons
17165	*3.0*	Walking	Walking the dog
17170	3.0	Walking	Walking, 2.5 mph, level, firm surface
17180	3.3	Walking	Walking, 2.5 mph, downhill
17190	3.5	Walking	Walking, 2.8 to 3.2 mph, level, moderate pace, firm surface
17200	4.3	Walking	Walking, 3.5 mph, level, brisk, firm surface, walking for exercise
17210	5.3	Walking	Walking, 2.9–3.5 mph, uphill, 1–5% grade
17211	8.0	Walking	Walking, 2.9–3.5 mph, uphill, 6–15% grade
17220	5.0	Walking	Walking, 4.0 mph, level, firm surface, very brisk pace
17230	7.0	Walking	Walking, 4.5 mph, level, firm surface, very, very brisk
17231	8.3	Walking	Walking, 5.0 mph, level, firm surface
17235	9.8	Walking	Walking, 5.0 mph, uphill, 3% grade
17250	3.5	Walking	Walking, for pleasure, work break
17260	4.8	Walking	Walking, grass track
17262	4.5	Walking	Walking, normal pace, plowed field or sand
17270	4.0	Walking	Walking, to work or class (Taylor Code 015)
17280	*2.5*	Walking	Walking, to and from an outhouse
17302	4.8	Walking	Walking, for exercise, 3.5–4 mph, with ski poles, Nordic walking, level, moderate pace
17305	9.5	Walking	Walking, for exercise, 5.0 mph, with ski poles, Nordic walking, level, fast pace
17310	*6.8*	Walking	Walking, for exercise, with ski poles, Nordic walking, uphill
17320	6.0	Walking	Walking, backwards, 3.5 mph, level
17325	8.0	Walking	Walking, backwards, 3.5 mph, uphill, 5% grade
18010	*2.5*	Water activities	Boating, power, driving
18012	*1.3*	Water activities	Boating, power, passenger, light
18020	4.0	Water activities	Canoeing, on camping trip (Taylor Code 270)
18025	3.3	Water activities	Canoeing, harvesting wild rice, knocking rice off the stalks
18030	*7.0*	Water activities	Canoeing, portaging

18040	2.8	Water activities	Canoeing, rowing, 2.0–3.9 mph, light effort
18050	5.8	Water activities	Canoeing, rowing, 4.0–5.9 mph, moderate effort
18060	12.5	Water activities	Canoeing, rowing, kayaking, competition, >6 mph, vigorous effort
18070	3.5	Water activities	Canoeing, rowing, for pleasure, general (Taylor Code 250)
18080	12.0	Water activities	Canoeing, rowing, in competition, or crew or sculling (Taylor Code 260)
18090	*3.0*	Water activities	Diving, springboard or platform
18100	5.0	Water activities	Kayaking, moderate effort
18110	4.0	Water activities	Paddle boat
18120	3.0	Water activities	Sailing, boat and board sailing, windsurfing, ice sailing, general (Taylor Code 235)
18130	4.5	Water activities	Sailing, in competition
18140	3.3	Water activities	Sailing, Sunfish/Laser/Hobie Cat, Keel boats, ocean sailing, yachting, leisure
18150	6.0	Water activities	Skiing, water or wakeboarding (Taylor Code 220)
18160	7.0	Water activities	Jet skiing, driving, in water
18180	15.8	Water activities	Skindiving, fast
18190	11.8	Water activities	Skindiving, moderate
18200	7.0	Water activities	Skindiving, scuba diving, general (Taylor Code 310)
18210	5.0	Water activities	Snorkeling (Taylor Code 310)
18220	*3.0*	Water activities	Surfing, body or board, general
18222	*5.0*	Water activities	Surfing, body or board, competitive
18225	*6.0*	Water activities	Paddle boarding, standing
18230	9.8	Water activities	Swimming laps, freestyle, fast, vigorous effort
18240	5.8	Water activities	Swimming laps, freestyle, front crawl, slow, light or moderate effort
18250	9.5	Water activities	Swimming, backstroke, general, training or competition
18255	4.8	Water activities	Swimming, backstroke, recreational
18260	10.3	Water activities	Swimming, breaststroke, general, training or competition
18265	5.3	Water activities	Swimming, breaststroke, recreational
18270	13.8	Water activities	Swimming, butterfly, general
18280	10.0	Water activities	Swimming, crawl, fast speed, ~75 yards/minute, vigorous effort
18290	8.3	Water activities	Swimming, crawl, medium speed, ~50 yards/minute, vigorous effort
18300	6.0	Water activities	Swimming, lake, ocean, river (Taylor Codes 280, 295)
18310	*6.0*	Water activities	Swimming, leisurely, not lap swimming, general
18320	7.0	Water activities	Swimming, sidestroke, general
18330	*8.0*	Water activities	Swimming, synchronized
18340	9.8	Water activities	Swimming, treading water, fast, vigorous effort

(continued)

Appendix F (continued)

Code	METS	Major heading	Specific activities
18350	3.5	Water activities	Swimming, treading water, moderate effort, general
18352	*2.3*	Water activities	Tubing, floating on a river, general
18355	5.5	Water activities	Water aerobics, water calisthenics
18360	*10.0*	Water activities	Water polo
18365	*3.0*	Water activities	Water volleyball
18366	9.8	Water activities	Water jogging
18367	2.5	Water activities	Water walking, light effort, slow pace
18368	4.5	Water activities	Water walking, moderate effort, moderate pace
18369	6.8	Water activities	Water walking, vigorous effort, brisk pace
18370	*5.0*	Water activities	Whitewater rafting, kayaking, or canoeing
18380	5.0	Water activities	Windsurfing, not pumping for speed
18385	11.0	Water activities	Windsurfing or kitesurfing, crossing trial
18390	13.5	Water activities	Windsurfing, competition, pumping for speed
19005	*7.5*	Winter activities	Dog sledding, mushing
19006	*2.5*	Winter activities	Dog sledding, passenger
19010	*6.0*	Winter activities	Moving ice house, set up/drill holes
19011	*2.0*	Winter activities	Ice fishing, sitting
19018	14.0	Winter activities	Skating, ice dancing
19020	*5.5*	Winter activities	Skating, ice, 9 mph or less
19030	7.0	Winter activities	Skating, ice, general (Taylor Code 360)
19040	*9.0*	Winter activities	Skating, ice, rapidly, more than 9 mph, not competitive
19050	13.3	Winter activities	Skating, speed, competitive
19060	*7.0*	Winter activities	Ski jumping, climb up carrying skis
19075	*7.0*	Winter activities	Skiing, general
19080	6.8	Winter activities	Skiing, cross country, 2.5 mph, slow or light effort, ski walking
19090	9.0	Winter activities	Skiing, cross country, 4.0–4.9 mph, moderate speed and effort, general
19100	12.5	Winter activities	Skiing, cross country, 5.0–7.9 mph, brisk speed, vigorous effort
19110	15.0	Winter activities	Skiing, cross country, >8.0 mph, elite skier, racing
19130	15.5	Winter activities	Skiing, cross country, hard snow, uphill, maximum, snow mountaineering
19135	13.3	Winter activities	Skiing, cross-country, skating
19140	13.5	Winter activities	Skiing, cross-country, biathlon, skating technique
19150	4.3	Winter activities	Skiing, downhill, alpine or snowboarding, light effort, active time only

19160	5.3	Winter activities	Skiing, downhill, alpine or snowboarding, moderate effort, general, active time only
19170	*8.0*	Winter activities	Skiing, downhill, vigorous effort, racing
19175	12.5	Winter activities	Skiing, roller, elite racers
19180	7.0	Winter activities	Sledding, tobogganing, bobsledding, luge (Taylor Code 370)
19190	5.3	Winter activities	Snow shoeing, moderate effort
19192	10.0	Winter activities	Snow shoeing, vigorous effort
19200	*3.5*	Winter activities	Snowmobiling, driving, moderate
19202	*2.0*	Winter activities	Snowmobiling, passenger
19252	5.3	Winter activities	Snow shoveling, by hand, moderate effort
19254	7.5	Winter activities	Snow shoveling, by hand, vigorous effort
19260	2.5	Winter activities	Snow blower, walking and pushing
20000	1.3	Religious activities	Sitting in church, in service, attending a ceremony, sitting quietly
20001	2.0	Religious activities	Sitting, playing an instrument at church
20005	1.8	Religious activities	Sitting in church, talking or singing, attending a ceremony, sitting, active participation
20010	1.3	Religious activities	Sitting, reading religious materials at home
20015	1.3	Religious activities	Standing quietly in church, attending a ceremony
20020	*2.0*	Religious activities	Standing, singing in church, attending a ceremony, standing, active participation
20025	*1.3*	Religious activities	Kneeling in church or at home, praying
20030	1.8	Religious activities	Standing, talking in church
20035	2.0	Religious activities	Walking in church
20036	2.0	Religious activities	Walking, less than 2.0 mph, very slow
20037	3.5	Religious activities	Walking, 3.0 mph, moderate speed, not carrying anything
20038	4.3	Religious activities	Walking, 3.5 mph, brisk speed, not carrying anything
20039	*2.0*	Religious activities	Walk/stand combination for religious purposes, usher
20040	*5.0*	Religious activities	Praise with dance or run, spiritual dancing in church
20045	2.5	Religious activities	Serving food at church
20046	2.0	Religious activities	Preparing food at church
20047	3.3	Religious activities	Washing dishes, cleaning kitchen at church
20050	1.5	Religious activities	Eating at church
20055	2.0	Religious activities	Eating/talking at church or standing eating, American Indian Feast days
20060	3.3	Religious activities	Cleaning church
20061	4.0	Religious activities	General yard work at church
20065	3.5	Religious activities	Standing, moderate effort (e.g., lifting heavy objects, assembling at fast rate)
20095	4.5	Religious activities	Standing, moderate-to-heavy effort, manual labor, lifting ≥ 50 lbs, heavy maintenance

(continued)

Appendix F (continued)

Code	METS	Major heading	Specific activities
20100	1.3	Religious activities	Typing, electric, manual, or computer
21000	1.5	Volunteer activities	Sitting, meeting, general, and/or with talking involved
21005	1.5	Volunteer activities	Sitting, light office work, in general
21010	2.5	Volunteer activities	Sitting, moderate work
21015	2.3	Volunteer activities	Standing, light work (filing, talking, assembling)
21016	2.0	Volunteer activities	Sitting, child care, only active periods
21017	3.0	Volunteer activities	Standing, child care, only active periods
21018	3.5	Volunteer activities	Walk/run play with children, moderate, only active periods
21019	5.8	Volunteer activities	Walk/run play with children, vigorous, only active periods
21020	3.0	Volunteer activities	Standing, light/moderate work (e.g., pack boxes, assemble/repair, set up chairs/furniture)
21025	3.5	Volunteer activities	Standing, moderate (lifting 50 lbs., assembling at fast rate)
21030	4.5	Volunteer activities	Standing, moderate/heavy work
21035	1.3	Volunteer activities	Typing, electric, manual, or computer
21040	2.0	Volunteer activities	Walking, less than 2.0 mph, very slow
21045	3.5	Volunteer activities	Walking, 3.0 mph, moderate speed, not carrying anything
21050	4.3	Volunteer activities	Walking, 3.5 mph, brisk speed, not carrying anything
21055	3.5	Volunteer activities	Walking, 2.5 mph slowly and carrying objects less than 25 lbs
21060	4.5	Volunteer activities	Walking, 3.0 mph moderately and carrying objects less than 25 lbs, pushing something
21065	4.8	Volunteer activities	Walking, 3.5 mph, briskly and carrying objects less than 25 lbs
21070	3.0	Volunteer activities	Walk/stand combination, for volunteer purposes

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Appendix G

Medications that Promote Weight Gain

- Atypical antipsychotics
- Glucocorticoids
- Synthetic progestins
- Hypoglycemic agents: insulin, sulfonylureas, thiazolidinediones
- Beta-blockers
- Antidepressants: tricyclics, paroxetine, trazodone
- Antiepileptics: valproate, gabapentin

Appendix H

Effects of medications on lipid levels

Medication	Cholesterol	TG	HDL
Estrogens		Increased	Increased
Androgens		Increased	Decreased
Progestins		Decreased	Decreased
Glucocorticoids	Increased	Increased	Increased
Thiazides (high dose)	Increased	Increased	Decreased
Beta-blockers		Increased	Decreased
Valproic acid		Increased	Decreased
Isotretinoin		Increased	Decreased
Cyclosporin[a]	Increased	Increased	Decreased
Protease inhibitors		Increased	
PEG-asparaginase	Increased	Increased	
Atypical antipsychotics		Increased	Decreased
Bile acid-binding resins	Decreased	Increased	
Omega-3 fatty acids	Increased	Decreased	
Diphenylhydantoin			Increased
Phenobarbital			Increased

[a]Similar but less severe effects with tacrolimus

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