0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(3):1871–1887

doi: 10.1210/jc.2004-1389

CONSENSUS STATEMENT: Childhood Obesity

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In March 2004 a group of 65 physicians and other health professionals representing nine countries on four continents convened in Israel to discuss the widespread public health crisis in childhood obesity. Their aim was to explore the available evidence and develop a consensus on the way forward.

The process was rigorous, although time and resources did not permit the development of formal evidence-based guidelines. In the months before meeting, participants were allocated to seven groups covering prevalence, causes, risks, prevention, diagnosis, treatment, and psychology. Through electronic communication each group selected the key issues for their area, searched the literature, and developed a draft document. Over the 3-d meeting, these papers were debated and finalized by each group before presenting to the full group for further discussion and agreement.

In developing a consensus statement, this international group has presented the evidence, developed recommendations, and provided a platform aimed toward future corrective action and ongoing debate in the international community. (*J Clin Endocrinol Metab* 90: 1871–1887, 2005)

Prevalence

What is the scope of the problem?

There has been a worldwide increase in obesity among people of all ages. The definition of obesity varies but is based on body mass index (BMI) cutoffs described below. As many as 250 million people, or about 7% of the current world population, are obese. Two to three times more people are overweight. In one of the most extreme examples, the prevalence of overweight doubled among children 6–11 yr of age and tripled among those 12–17 yr of age in the United States between the second National Health and Nutrition Examination Survey, conducted between 1976 and 1980, and the most recent such survey, conducted in 1999 and 2000. Approximately 14–15% of all 15 yr olds in the United States can be classified as obese (1). African-Americans, Hispanics (predominantly Mexican and Puerto Rican), Pima Indians, and other Native Americans have a particularly high predisposition to obesity. There are national differences in prevalence rates for obesity (2). Comparison of cross-sectional data from school-based surveys conducted in 1997 and 1998 describing body size among adolescents in 13 European countries, Israel, and the United States showed that the United States, Ireland, Greece, and Portugal had the highest prevalence of overweight (Table 1) (3). A review of 21 surveys conducted in various European countries indicated a higher prevalence of overweight in western and southern Europe. The countries surrounding the Mediterranean showed prevalence rates for overweight children in the range of

First Published Online December 14, 2004

Abbreviations: AHI, Apnea-hypopnea index; BBS, Bardet-Biedl syndrome; BIA, bioelectric impedance assay; BMI, body mass index; BWS, Beckwith-Wiedemann syndrome; DEXA, dual-energy x-ray absorptiometry; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; IOTF, International Obesity Task Force; LDL, low-density lipoprotein; MCR, melanocortin receptor; MS, metabolic syndrome; OGTT, oral glucose tolerance test; OSA, obstructive sleep apnea; POMC, proopiomelanocortin; PWS, Prader-Willi syndrome; RYGB, Roux-en-Y gastric bypass; SES, socioeconomic status; T2DM, type 2 diabetes mellitus.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

TABLE 1. Prevalence of BMI ≥85th and ≥95th percentiles of adolescents 15 yr of age by gender

Country	Boys (%)		Girls (%)	
	≥85th	≥95th	≥85th	≥95th
Austria	11.6	5.1	10.9	4.4
Belgium	13.1	5.2	15.4	5.8
Czech Republic	8.1	1.9	9.3	3.5
Denmark	10.4	3.2	18.2	6.5
Finland	15.6	4.9	14.5	5.1
France	9.8	2.7	12.8	4
Germany	14.2	5.4	14.8	5.1
Greece	28.9	10.8	16.4	5.5
Ireland	19.3	2.8	14.2	4.7
Israel	20.1	6.8	16.4	6.2
Lithuania	5.2	0.8	8.1	2.1
Portugal	14.3	5.2	20.8	6.7
Slovakia	16.5	4.4	11.3	1.1
Sweden	12.3	4	12.3	3.4
United States	28.2	13.9	31	15.1
Total	15	5.3	15.3	5.5

20–40%, whereas those in northern areas showed lower rates, in the range of 10–20% (4).

Evaluation of Australian children from surveys taken 10 yr apart also showed an increase of overweight and obesity. By 1995 15% of boys and 15.8% of girls were overweight, and 4.5% of boys and 5.3% of girls were classified as obese (5). In other Asian populations, Polynesians, Micronesians, Anurans, and Maoris are at high risk for obesity.

There has also been a trend toward increasing prevalence of overweight and obesity as well as metabolic complications in developing countries. Regions with the highest prevalence of overweight were: the Middle East, 7%; North Africa, 8%; and Latin America and the Caribbean, 4.5–7% (6).

Overweight children often become overweight adolescents and adults (7), and overweight in adulthood is a serious health risk (8). Obesity is associated with the development of a number of serious medical complications and increased mortality in children and adults. Thus, monitoring trends in the prevalence of obesity in populations worldwide is important for epidemiological assessment.

Why is obesity so prevalent?

Man has evolved under conditions of stress in which it was advantageous to be able to store fat (9). It is this genetic propensity to store fat in response to insulin, paired with our lifestyles with too much sedentary activity and processed energy-dense foods, that has contributed to the problem of overweight. Numerous genetic markers have been linked with obesity and its metabolic consequences (10), yet identifiable hormonal, syndromic, or molecular genetic abnormalities can presently account for less than 5% of obese individuals (11). This is discussed in greater detail in *Causes*.

Diagnosis

Clinical evaluation: How do we evaluate overweight and obesity in childhood?

Basic evaluation: history and anthropometrics. The definition of overweight and obesity in childhood is still a matter of debate for two main reasons: the lack of a simple, low-cost, accurate, and reproducible method to measure fat mass in infants, children, or adolescents and the lack of cutoffs of fat mass for children to identify individuals at moderate or high cardiovascular and metabolic risk in childhood and adulthood. Whitaker *et al.* (12) demonstrated that the prognostic importance of obesity in infancy and childhood depends on the presence or absence of obesity in one or both parents.

It is important to distinguish between primary or idiopathic obesity and the rarer situation of secondary obesity owing to genetic disorders, endocrine disease, central nervous system lesions, or iatrogenic causes. Detailed medical history, physical examination, and laboratory tests are helpful.

In the initial assessment of the overweight or obese child, nutritional history should include breast-feeding or formula; age at introducing solids; and assessment of caloric intake, including dietary quality in terms of the balance of nutrients and food groups. The clinician should ask about the child's level of physical activity; limitations due to weight; and respiratory difficulties including snoring and somnolence, potential signs of sleep apnea.

Physical examination should first be directed to overall body proportions and the presence or absence of any distinctive or dysmorphic features that could guide the diagnosis to rare obesity syndromes. Recording and graphical plotting of height, weight, BMI, and waist circumference should be done at each visit.

Quantitation of body fat in childhood and adolescence. Overweight and obesity occur with excessive accumulation of body fat. Because increasing body fat is associated with increasing morbidity, the definition of overweight and obesity should be linked to health risks. Due to difficulties in direct measurement of body fat, obesity can be simply and inexpensively estimated using the BMI. BMI correlates with the amount of body fat in both children and adults (13). The World Health Organization (WHO) classification and U.S. dietary guidelines for obesity in adults define overweight based on health risk as a BMI of 25–30 kg/m^2 and obesity as a BMI of 30 kg/m^2 or greater.

Country-specific growth charts have been developed based on cross-sectional and longitudinal data. For example, the U.S. Centers for Disease Control and Prevention (CDC) 2000 growth charts include gender-specific BMI for age growth charts for ages 2–19 yr (14). These charts were developed from five national data sets in the United States. Overweight and obesity among individuals 2–19 yr old are defined as the 95th percentile or greater of BMI for age; those with BMI between the 85th and 95th percentiles are considered at risk for overweight. In a separate report from the National Heart, Lung, and Blood Institute, overweight is defined in adolescents as the 85th percentile or greater of BMI for age (15). A recent review concluded that the evidence for use of national BMI reference data is sufficiently strong for its adoption in clinical practice and screening (16). An advantage of these charts is that a child can be followed up over time with graphical plotting of serial BMI measures. A disadvantage is that the charts are based on arbitrary statistical measures and not on biological data related to the risk of later morbidity. Moreover, the CDC reference data are based on American children and may not be applicable to other populations. Another problem with this approach is that as the population becomes heavier, these percentiles define changing thresholds for overweight and obesity.

To have an absolute and internationally relevant definition of child overweight and obesity, Cole *et al.* (2) developed age- and sex-specific cutoff lines from data derived from six countries across several continents using BMI. These charts extrapolate risk from the adult experience to children. The International Obesity Task Force (IOTF) has recommended this approach for the comparison of populations (17). IOTF currently defines overweight as approximately 91% or greater and obesity as approximately 99% or greater. The charts of Cole *et al.* are recommended for epidemiologic purposes and may underestimate the prevalence of obesity if applied to cross-sectional charts. Owing to the lack of precise percentiles, these charts are not useful for longitudinal follow-up of individual patients.

Quantitation of body fat in infancy. Weight for length is usually used in the under 2-yr age group. In the United States, overweight in this age group is defined as greater than the 95th percentile of the weight for length. The definition is purely statistical, and the percentile values are age and gender specific. It is important to measure head circumference because a very large head may alter weight-for-length ratio.

Laboratory tests for body fat

What are the most reliable methods of assessment of body fat and its distribution? As discussed, BMI, an indirect estimate of total adiposity, does not necessarily predict health risk for children. There are some situations in which BMI gives an inaccurate picture, *e.g.* in short muscular people. Furthermore, BMI does not distinguish between sc and visceral fat. It is therefore useful to employ adjunctive measures of total and regional body fat.

Skinfold thickness. This is a quick, simple, inexpensive method, which is useful for community pediatrics and large studies and gives information on fat distribution because it is done at several body sites. It does not require a high degree of technical skill, although the technique requires a trained person to standardize the measurements; otherwise it is poorly reproducible, especially at the highest BMIs. Triceps skinfold is correlated with fat mass and, combined with BMI, increases the sensitivity for the determination of percent body fat (18).

Bioelectric impedance assay (BIA). BIA is a method of body composition assessment that is simple, quick, relatively inexpensive, and noninvasive. However, BIA measurements are highly variable because they are affected by meals; physical activity; and other variables that change the subject's hydration state, such as menstrual phase, acute illness, kidney disease, and water and electrolyte disturbances (19).

Hydrodensitometry. Underwater weighing requires special equipment and is used primarily for research purposes; it is not available for routine clinical care. It is useful for validation of other methods of measuring body fat.

Dual-energy x-ray absorptiometry (DEXA). This is a relatively expensive but safe method for assessing total body fat that has high precision and simplicity for the subject. X-ray exposure is minimal. DEXA also is limited by the inability to distinguish between sc and visceral fat. The method is most useful for research.

Imaging. Computed tomography and magnetic resonance imaging of the abdomen are accurate methods that can be used to measure visceral fat (20). However, the disadvantages are high cost and radiation exposure with computed tomography. These methods require more time to perform and specialists for interpretation. Therefore, these methods are also recommended only for research purposes.

Anthropometrics. Waist circumference or waist to hip ratios are used as indirect markers of intraabdominal adipose tissue. As with BMI, there is some controversy as to appropriate cutoffs for adults. Waist circumferences above 95 cm indicate elevated mortality rates (21). This parameter is also a predictor of cardiovascular and metabolic risk factors in obese children (22). Visceral or intraabdominal adiposity is also associated with the metabolic syndrome (see definitions in *Risks*) in adults and children. Methodologies such as DEXA, skinfolds, and BIA do not assess visceral fat. Thus, waist circumference should be included in clinical practice as the least invasive and least costly tool to help identify obese children at higher metabolic risk. Currently there are limited pediatric reference values for waist circumference (24, 25), and these should be developed.

Causes

Genetic: which genes are important determinants of obesity?

Monogenic obesity. Leptin was the first specific gene recognized as important in human body weight control. This adipocyte hormone is involved in a complex circuit of hormones and neurotransmitters to control appetite (Table 2). To date, several monogenic obesity syndromes have been identified, and most involve the leptin-melanocortin regulation pathway (26, 27). The known genes include leptin, the leptin receptor proopiomelanocortin (POMC), prohormone convertase 1, melanocortin receptors 3 and 4, and the transcription factor single-minded 1; the list will continue to expand. Severe and early-onset obesity, common findings in monogenic cases, parallels the phenotype in the corresponding knockout mice and supports the central role of these genes in body weight regulation. There have been conflicting reports about the association between obesity and human polymorphisms in genes involved in the regulation of peripheral metabolic control, *e.g.* mitochondrial uncoupling genes, perhaps attributable to ethnic or gender-specific variations (28).

Homozygous mutations of the leptin-melanocortin genes are extremely rare causes of severe obesity and are often associated with other features, *e.g.* hypogonadotropic hypogonadism in leptin deficiency (26) and red hair and hypocortisolism in POMC deficiency (29) resulting in phenotypes that exclude these genes as likely candidates for common obesity. In the case of leptin, leptin receptor, and POMC genes, heterozygous mutation carriers have a minimally abnormal phenotype. Heterozygous mutations causing significant obesity are found only in the melanocortin receptor (MCR) 4 and are not associated with an otherwise distinctive

TABLE 2. Factors critical in the regulation of appetite and energy balance

Central nervous system-appetite regulation command: Ventro-medial-hypothalamus, paraventricular nucleus, lateral hypothalamus area	
Appetite stimulation pathway	Appetite suppressing pathway
Agouti-related protein	Cocaine and amphetamine reg. transcript (CART)
GABA	Corticotropin-releasing hormone (CRH)
Galanin	Dopamine
Glutamate	Melanocortin receptors (MC3R, MC4R)
MCH	α-Melanocyte-stim.-hormone (MSH)
Neuropeptide Y	POMC
Norepinephrine	Neurotensin
Opioids (β-endorphin, dynorphin, met-enkephalin)	Serotonin (5-hydroxy-tryptamine)
Orexins, hypocretins	

Peripheral incoming signals		Central nervous system outgoing signals
Suppressing	Stimulating	
Amylin	Cortisol	Parasympathetic nervous system: vagus nerve
Bombesin	Ghrelin	Energy storage by glucose-stimulated insulin secretion
GLP1	Glucose (low)	Sympathetic nervous system: α-adrenergic activation
Glucagon		Stress, cold (lipolysis, heat production, thyroid activation)
Leptin		
Protein		
Insulin		

phenotype. To date, MC4R mutations are the most frequent known cause of monogenic human obesity, occurring in up to 4% of early-onset and severe childhood obesity (30).

Other candidate genes involved in human obesity. Because insulin plays a crucial role in energy metabolism, the insulin gene has been examined. There is an association between variable nucleotide tandem repeat polymorphisms upstream of the insulin gene, increased fasting insulin levels, and childhood obesity in individuals of European descent (31).

The human obesity gene map continues to expand as more genes and chromosomal regions are linked with human obesity. In the most recent published update, there were more than 430 genes, markers, and chromosomal regions associated or linked with human obesity phenotypes. There are 35 genomic regions with quantitative trait loci that have been replicated in two or more studies of obesity phenotypes (32). Every chromosome, except the Y chromosome, has had loci linked with the phenotype of obesity. Some genes have been identified that are specific to visceral obesity. Most of the specific genes involved are as yet unknown. In view of these data, it is highly probable that childhood obesity is polygenic with susceptibility conferred via complex genetic factors. It is estimated that 30–50% of the tendency toward excess adiposity can be explained by genetic variations (33).

Which syndromes are associated with early childhood obesity? Obesity is a component of several rare human genetic syndromes that present with characteristic phenotypes; two of these are described here. Prader-Willi syndrome (PWS; OMIM no. 176270) is characterized by intrauterine hypotonia, mental retardation, and hypogonadotropic hypogonadism. The obesity of PWS that occurs in early childhood is resistant to diet and associated with early mortality. PWS is caused by the loss of paternally expressed genes, including small nuclear ribonucleoprotein, within the PWS critical region on chromosome 15q; however, the precise metabolic functions of the missing gene products remain unknown. One major difference in the obesity associated with PWS is the presence of elevated ghrelin levels contrasting with decreased levels in other forms of obesity. Ghrelin, an orexigenic protein, may be responsible, at least in part, for the hyperphagia observed in PWS (34).

Bardet-Biedl syndrome (BBS; OMIM no. 209900) is characterized by a variable degree of obesity; mental retardation; and pigmentary retinopathy, polydactyly, and renal abnormalities (35). Based on several large pedigrees with mainly recessive inheritance of the BBS phenotype, several chromosomal regions, including genes involved in cilial and centriole function, have been identified (36).

Beckwith-Wiedemann syndrome (BWS; OMIM no. 130650) is principally characterized as a syndrome of generalized fetal overgrowth and visceromegaly with tall stature but not specifically obesity in childhood.

Endocrine: are endocrine disorders a common cause of obesity?

Although rare among children and adolescents with obesity, GH deficiency, thyroid hormone deficiency, and cortisol excess are characterized by a combination of decreased energy expenditure and decreased growth resulting in prominent central adiposity in a short, slowly growing child. GH therapy in individuals with GH or IGF-I deficiency reverses these changes in body composition, reducing fat mass while increasing muscle mass (37). Thyroid hormone replacement increases resting metabolic rate and improves impaired secretion of GH and IGF-I production that accompany thyroid hormone deficiency. Patients with excessive cortisol levels often have hypertension, glucose intolerance, dyslipidemia, moon facies, decreased muscle mass, and broad violaceous striae in addition to visceral obesity and poor growth. Removing the glucocorticoid source ameliorates these problems (38). Insulin and leptin are produced in the periphery, circulate at levels proportional to body fat content, and enter the central nervous system in proportion to their plasma level. Receptors for leptin and insulin are expressed in brain neurons involved in regulating energy intake; administration of either peptide directly into the brain induces satiety (39). Hyperinsulinism, relative insulin resistance, and to a lesser extent type 2 diabetes mellitus (T2DM) are recognized comorbidities of obesity in the young (40). Insulinomas are rarely diagnosed in children. With hyperinsulinism and normal insulin sensitivity, symptoms of hypoglycemia would herald the diagnosis before the onset of obesity in most cases. Most obese individuals have elevated circulating insulin and leptin levels and are relatively resistant to the satiety-inducing effects of both hormones.

Pseudohypoparathyroidism is a rare cause of childhood obesity, also associated with PTH resistance with hypocalcemia and hyperphosphatemia, short stature, round face, short metacarpals, basal ganglia calcification, and developmental delay.

Laboratory investigations directed at identifying comorbidities of obesity may include thyroid functions, lipid profile, complete chemistries and hepatic profile, and fasting glucose and insulin. An oral glucose tolerance test (OGTT) should be considered to exclude impaired glucose tolerance or T2DM in individuals at high risk, *e.g.* family history of T2DM and/or metabolic syndrome, after 10 yr of age. Determination of serum or urinary cortisol levels should be reserved to exclude the presence of Cushing's syndrome in obese individuals who have appropriate historical information and/or physical findings.

Infants who are hypoglycemic or require very frequent feedings as well as infants with dysmorphic features require further evaluation. Examples include persistent hyperinsulinemic hypoglycemia of infancy (OMIM no. 601820) and BWS with hypoglycemia, or PWS and BBS with dysmorphism.

Neurologic: how can central nervous system lesions cause obesity?

Obesity is a frequent complication in children surviving serious brain injury, brain tumors, and/or cranial irradiation. Significant increases in weight are noted to occur in the early postoperative period. These children often have reduced physical activity more than increased energy intake. The pattern of decreased physical activity may be secondary to suboptimal hormonal replacement and decreased sympathetic nervous system function. The exact mechanisms responsible for this phenomenon are still unknown, although alterations in hypothalamic neuropeptides (41) and enhanced activity of 11-β hydroxysteroid dehydrogenase, converting cortisone to cortisol (42), have been implicated. These individuals often have autonomic dysregulation of the β-cell, with insulin hypersecretion in response to oral glucose tolerance testing (41).

Medications: do medications cause obesity?

High-dose, chronic glucocorticoid treatment is well known to be associated with a distinctive pattern of centripetal weight gain with visceral fat accumulation predisposing to cardiovascular risk. Other drugs used in children and adolescents that may predispose to weight gain include cyproheptadine, valproate, and progestins.

There is considerable evidence that treatment with some newer antipsychotic drugs can cause a rapid increase in body weight. There is, however, considerable variability among the various drugs in their effect on weight gain, lipid profile, and risk of diabetes. The prevalence of both diabetes and hyperlipidemia among individuals with schizophrenia and affective disorders is 1.5–2 times higher than the general population (43). Among the second-generation drugs, which have generally replaced first generation, clozapine and olanzapine, have a marked effect on weight gain, with increased risks for developing diabetes and hyperlipidemia. Risperidone and quetiapine have a moderate effect on weight gain and possible effects on development of diabetes and hyperlipidemia. Aripiprazole and ziprasidone are associated with less weight gain and better glucose: insulin and lipid profiles; however, there is less long-term experience with the latter drugs (44).

Environment: how does environment contribute to the genetic predisposition to obesity?

Genes play a permissive role and interact with environmental factors to promote obesity. Studies of energy balance among pairs of monozygotic twins have shown that subjects with the same genotype are more alike in response to energy surplus and deprivation than are subjects with different genotypes for changes in circulating lipid levels, sc fat, fat mass, and visceral fat in response to dietary changes. Advances in the ability to generate genotypic information, in combination with precise phenotypic markers, will improve our capacity to better determine gene-environment interactions (45).

Does the in utero milieu contribute to obesity? Epidemiological studies of the impact of maternal gestational diabetes mellitus (GDM) on adolescent obesity demonstrate conflicting results. Infants of Pima Indians with GDM had an increased risk of obesity, compared with siblings born before their mothers developed GDM. This study supports the role of *in utero* exposure to hyperglycemia as a risk factor for subsequent obesity (36). Other studies (37, 38) demonstrated an increased risk of adolescent overweight associated with increased birth weight and maternal GDM, yet the association was attenuated or lost completely after adjustment for maternal BMI. Thus, the effect of fetal hyperinsulinemia on body composition and size at birth may set the stage for the future development of obesity.

Psychosocial factors

What is the impact of socioeconomic status (SES), race, ethnicity, and gender? Most of the data in this area are derived from the adult population in the United States (46). In general, those with lower income and education levels are more likely to become obese than those with higher income levels and higher education levels, who may have greater awareness of and access to health care, healthy foods, and fitness facilities.

The prevalence of obesity is higher in racial and ethnic minorities, perhaps attributable to greater poverty among these groups. Selective weight gain in certain populations may also indicate that the interaction between people and their environment varies according to genetic background. Clearly some populations are at greater risk of obesity-related morbidity. Therefore, effective prevention and treatment may require racial and ethnic-specific strategies.

Gender influences the impact of SES and ethnicity on the development of obesity in that a poor woman is twice as likely to become obese as a poor man. Conversely, a wealthy woman is less likely to become obese than a wealthy man. However, a wealthy man is significantly more likely to be overweight than a man with low SES. Overall, women are more likely to be obese than men. In view of the influence of maternal BMI on their children, this is especially concerning. According to the American Obesity Association, among women between the ages of 20 and 74 yr, 34% are obese (BMI $\geq$ 30) and 6.3% are severely obese (BMI $\geq$ 40), compared with 28 and 3.1%, respectively, for men (47).

What is the role of lifestyle and diet? Studies using motion sensors have shown that children who spend less time in moderately vigorous activity are at higher risk to become obese during childhood and adolescence (48). In the United States, only about 25% of adolescents report regular exercise, and an alarming 14% say they do not exercise at all. Television and video games have contributed to more sedentary leisure activities as well as increased snacking and inappropriate food choices due to television advertising. There is a positive correlation between hours of television viewing and overweight, especially in older children and adolescents (49).

Aside from these lifestyle issues, eating patterns of children and adolescents have changed dramatically in the past few decades (50). Dietary factors that place children at risk for obesity include high fat and excess calorie intake. Obese children tend to skip breakfast but consume a large amount of food at dinner (51).

In terms of dietary content, there is an inverse relationship between calcium intake and adiposity (52). The consumption of high-carbohydrate soft drinks is a major contributing factor to high calorie counts (53), especially because these fluids tend to replace milk and calcium intake for adolescents. Additionally, fast food consumption now accounts for 10% of food intake in children in U.S. schools, compared with 2% in the 1970s. Children who frequently eat fast food consume more total energy, more energy per gram of food, more total fat, more total carbohydrate, more added sugars, less fiber, less milk (calcium), and fewer fruits and vegetables than children who eat fast food infrequently (50, 54). Those who are overweight are particularly vulnerable to the adverse health effects of consuming fast foods (55).

It appears that neonatal nutrition has an impact on childhood and adolescent obesity. In particular, breast-feeding has been shown to have at least some protective effect in some populations (56, 57), although this has been refuted in other reports (58).

Is binge eating a major cause of obesity? Twenty to 40% of severely obese adults (59) and adolescents (60) suffer from binge eating. Obese binge eaters show weight and shape concern as well as symptoms of depression and anxiety with lower self-esteem when compared with nonbingeing obese individuals. Apparently binge eating disorder in youngsters does not develop into bulimia nervosa in later life (61).

What is the psychological profile of obese children and adolescents? A causal relationship between obesity and psychological factors remains unclear. Adiposity is very visible, and children tend to rate disease and minor deformities as preferable to obesity at 6 yr of age. Children's perceptions of obesity emphasize laziness, selfishness, lower intelligence, social isolation, poor social functioning, and academic success as well as low levels of perceived health, healthy eating, and activity (62). Thus, children share the overall negative societal perceptions toward those who are overweight or obese. This is regardless of the child's own weight status or gender. Children as young as 5 yr are aware of their own fatness, which impacts their perceptions of appearance, athletic ability, social competence, and self-worth. Quality of life is poor among obese youngsters by parental and self-report (63). Self-esteem in obese children varies with gender and age. Females are at greater risk for self-esteem problems (64). Parental acceptance or lack of concern may be a protective factor for self-esteem.

Among severely obese adolescents, 48% have moderate to severe depressive symptoms and 35% report high levels of anxiety. Obese girls are more likely to have attempted suicide than nonobese girls. Overweight adolescents reported engaging in significantly more unhealthy behaviors and experiencing more psychosocial distress than their nonoverweight peers. Overweight adolescents were found to be more isolated and peripheral to social networks than were their normal-weight peers (65).

Risks

Why is obesity of such concern?

Childhood obesity is now recognized as a major medical and public health problem. Obesity in adults is strongly associated with many serious medical complications that impair quality of life and lead to increased morbidity. Obese children are at high risk for adult obesity, but there are as yet insufficient data to assign specific risk levels in childhood. However, obesity in childhood provides an independent contribution to the development of adult morbidity. Without proper intervention, adult morbidities will likely begin to appear in the young. There are strong epidemiologic and causal links between obesity in the young and earlier-onset T2DM (40).

Diabetes

Over the past decade, there has been an alarming increase in the appearance of T2DM in children, a disease that formerly occurred almost exclusively in adults. T2DM in youth represents the most rapidly growing form of diabetes in America, Europe, Japan, and Australasia, now responsible for up to about one fifth of new diagnoses of diabetes in pubertal children. Although universal screening is not recommended, the American Academy of Pediatrics and American Diabetes Association recommend that all youngsters who are overweight and have at least two other risk factors should be tested for T2DM beginning at age 10 yr or at the onset of puberty and every 2 yr thereafter (66). The risk factors include family history of T2DM in first- or second-degree relatives; belonging to certain ethnic groups (*i.e.* Native American, African-American, Hispanic, Japanese, or other Asian/Pacific Islander); or having signs associated with insulin resistance (hypertension, dyslipidemia, acanthosis nigricans, or polycystic ovarian syndrome). Fasting plasma glucose is the primary screen to test for T2DM in young people. The 2-h blood glucose concentration after a standard OGTT is more sensitive than plasma glucose in assessing impaired glucose tolerance in youngsters, but it is also more invasive, inconvenient, and expensive. Insulin resistance is considered the greatest risk factor for the development of T2DM. The homeostatic model assessment, which estimates insulin resistance, and the quantitative insulin-sensitivity check index, based on solely on fasting insulin and glucose, provide a crude, and not always reproducible, measure of indices that are most accurately derived from the more invasive euglycemic and hyperglycemic clamp studies (67).

Metabolic syndrome (MS)

Metabolic changes seen in obese adults have been summarized under the so-called MS. The MS is defined differently according to different authorities. The U.S. National Cholesterol Education Program's Adult Treatment Panel III (68) requires three of five characteristics: 1) abdominal obesity given as waist circumference greater than 102 cm in men and greater than 88 cm in women; 2) hypertriglyceridemia with triglyceride concentration (≥150 mg/dl or 1.7 mmol/liter); 3) abnormal cholesterol profile with high-density lipoprotein (HDL) cholesterol less than 40 mg/dl or 1 mmol/liter in men and less than 50 mg/dl or 1.3 mmol/liter in women; 4) blood pressure: 130/85 mm Hg or more; 5) impaired glucose tolerance, *i.e.* elevated fasting plasma glucose 100 mg/dl or 5.5 mmol/liter or more (69). The National Cholesterol Education Program guidelines for adults have been modified for adolescents such that triglycerides 110 mg/dl or 1.2 mmol/liter or more are considered abnormal, and the HDL threshold is set at 40 or less. Waist circumferences 90% or more (from National Health and Nutrition Examination Surveys III) are considered abnormal, as are blood pressures 90% or more (70). There is as yet no definition of the MS for the pediatric age group, but using adult criteria, the overall prevalence of MS among 12- to 19-yr-olds in the United States was found to be 4.2% (70). Using modified criteria, Weiss *et al.* (71) found that the risk of MS was nearly 50% in severely obese youngsters, and risk increased with every 0.5-U increment in BMI.

The WHO (72) and American Association of Clinical Endocrinologists (73) criteria overlap the above but differ by requiring impaired fasting glucose, impaired glucose tolerance, or frank T2DM as defined on an OGTT. An added diagnostic criterion of urinary albumin excretion rate greater than 20 μg/min has been included in the WHO/American Association of Clinical Endocrinologists criteria.

Hyperandrogenism

In adolescent girls and young women, excess central or abdominal body fat is associated with hyperandrogenemia (74). Sex hormone-producing enzymes are expressed in adipose tissue, and up to 50% of circulating testosterone may be derived from fat in young women (75). There is also a causal relationship between high androgen activity and hyperinsulinemia in women. To complete the circle, insulin resistance correlates strongly with the abdominal fat in obese adolescent girls. Insulin resistance stimulates ovarian as well as adrenal androgen and estrogen production. Obese females also have lower concentrations of SHBG with consequent further increase in the (free) biologically active fraction of the sex hormones. These hormonal perturbations place the obese adolescent girl at a high risk of menstrual disorders and early onset of polycystic ovarian syndrome. Weight loss induces a decrease in insulin resistance and androgenic activity, particularly in adolescent girls with the abdominal pattern (76).

Cardiovascular factors

Heart disease. Obesity produces a variety of cardiac structural changes and hemodynamic alterations. Excessive adipose accumulation induces increased blood volume and cardiac output. Sleep apnea and obesity-related hypoventilation may contribute to pulmonary arterial hypertension. In morbid obesity these abnormalities may lead to a cardiomyopathy. Studies involving obese children and cardiovascular risk are limited. The Bogalusa Heart Study indicated that increased insulin and glucose levels in heavier children and adolescents might be risk factors for increased left ventricular mass corrected for growth (77). Childhood obesity does predispose to endothelial dysfunction, carotid intimal medial thickening, and the development of early aortic and coronary arterial fatty streaks and fibrous plaques (78). Whether childhood obesity, like adult obesity, increases the risks of myocardial infarction, stroke, and certain malignancies is currently unproved.

Hypertension. Hypertension occurs more commonly in obese persons at every age. Childhood obesity is the leading cause of pediatric hypertension. Genetic, metabolic, and hormonal factors such as insulin resistance, increased serum aldosterone levels, salt sensitivity, and possibly elevated leptin levels are linked to the hypertension of obesity. Systolic blood pressure correlates positively with BMI, skinfold thickness, and waist to hip ratio in children and adolescents (79).

Respiratory factors

Asthma and other respiratory problems. The association between asthma and overweight or obesity is debatable. One possible explanation for the apparent association between asthma and obesity is that both asthma and obesity share coincident increased prevalence. In obese people symptoms of breathlessness and wheezing may be due to the increased work of breathing. Alternatively, obesity may have a direct effect on the mechanical behavior of the respiratory system by altering compliance or elastic recoil, resulting in reduced effective lung volume, airway caliber, or respiratory muscle strength (80).

Sleep disorders. There is a strong association between obesity and obstructive sleep apnea (OSA) according to several cohort studies (81). Obese children are 4–6 times more likely to have OSA, compared with lean subjects (82). OSA is diagnosed by an overnight sleep study to measure the apnea-hypopnea index (AHI). An AHI of 5/h or more establishes the diagnosis of OSA. Weight reduction is the preferred modality to minimize AHI. OSA in adults has been related to the development of hypertension, cardiovascular diseases, behavioral disorders, and poor quality of life (83).

Visceral factors

Nonalcoholic fatty liver disease. Obesity is associated with a spectrum of liver abnormalities, referred to as nonalcoholic fatty liver disease. Characteristic biochemical findings include 4- to 5-fold elevations in hepatic transaminases, and 2- to 3-fold elevations in alkaline phosphatase and γ glutamyl transpeptidase. Bilirubin, albumin, and prothrombin may rise in later stages. The natural history varies according to histology: hepatic steatosis is frequently characterized by a benign clinical course without histological progression; however, nonalcoholic steatohepatitis may become associated with increasing fibrosis and eventual rare cirrhosis (84).

Most children and adults are relatively asymptomatic. Some individuals may have right upper quadrant pain, abdominal discomfort, weakness, fatigue, or malaise. Hepatomegaly and stigmata of liver disease, such as palmar erythema, vascular spiders, muscle wasting, jaundice, and hepatic encephalopathy, may sometimes be present.

Gallbladder disease. Obesity, MS, and hyperinsulinemia, or alternatively rapid and significant weight loss are important risk factors for gallstone development (85). The mechanisms involved are not entirely clear. Early recognition of the severity of gall bladder disease is necessary for successful management. Thus, gall bladder disease should be considered in the differential diagnosis of persistent abdominal pain in obese adolescents.

Orthopedic factors

Overweight children are susceptible to developing bony deformities that can predispose them to other orthopedic problems later in life. Excess weight may cause injury to the growth plate and result in slipped capital femoral epiphysis, genu valga, tibia vara (Blount's disease), flat kneecap pressure/pain, flat foot, spondylolisthesis (low back pain), scoliosis, and osteoarthritis (86).

Dermatologic factors

Acanthosis nigricans, frequently found in young obese individuals, is characterized by hyperpigmented, hyperkeratotic, velvety plaques on the dorsal surface of the neck, in the axillae, in body folds, and over joints. Severe skin changes correlate with elevated serum insulin levels and can be ameliorated by weight loss and consequent reduction in insulin resistance. Other skin problems commonly encountered include skin tags and keratosis pilaris (87).

Neurologic factors

Obesity is associated with idiopathic intracranial hypertension, or pseudotumor cerebri, manifested by headache, vision abnormalities, tinnitus, and sixth nerve paresis. Although the prevalence of intracranial hypertension increases up to 15-fold with increasing BMI, the risk of intracranial hypertension is increased even in persons who are only 10% above ideal body weight (88).

Prevention

Perinatal life: is there a need for preventive strategies in infancy or even prenatally?

Birth weight, postnatal weight gain, and subsequent obesity. Human and animal data link the intrauterine environment to postnatal health, with the underlying mechanisms still unknown. A U-shaped relationship exists between birth weight and obesity in young adult life. Low birth weight owing to maternal undernutrition, smoking, or placental insufficiency, or alternatively large size at birth attributable most often to GDM, may both be associated with obesity (89, 90). Furthermore, the timing of prenatal nutritional deprivation is apparently important in the future development of obesity, as discerned in the study of Dutch men exposed to wartime famine (91). Obesity and ensuing metabolic complications often persist into middle age. Restricted prenatal growth with rapid postnatal growth may be key to the early pathogenesis of adulthood disease. It is likely that genetic factors in combination with intrauterine programming influence outcomes (92). As discussed above, breast-feeding is not unconditionally protective for future obesity, although there are numerous other benefits.

Proposed suggestions for preventing childhood obesity beginning in prenatal life and throughout the life cycle at all levels of society are shown in Table 3.

School-age population

How can we promote a healthy eating environment for children? Public health strategies to prevent obesity should begin with schools and extend to the entire community (93). Schools must review their policies and procedures to promote healthy eating. This should include review of vending machine offerings, food available in school cafeterias, and types of food allowed for classroom events. A curriculum for nutrition education to promote healthy eating habits, healthy body image, and weight management is essential from preschool through high school. Healthy eating opportunities include affordable, palatable fresh fruits and vegetables and lower-fat food choices in school cafeterias and vending machines (94, 95). Regulatory agencies should ban advertising of fast foods directed at preschool children and restrict advertising to school-age children.

How can we encourage physical activity? Lack of physical activity is not limited to inner-city populations but cuts across socioeconomic, gender, and racial lines (96). A first step toward increasing activity is to restrict sedentary activities. Another crucial element for children is to make exercise readily accessible at all ages in schools and residential areas. Age-appropriate exercises should be fun, not punitive. Schools should mandate minimum standards for physical education, including 30–45 min of strenuous exercise two to three times weekly.

TABLE 3. Proposed suggestions for the prevention of obesity

A. Pregnancy
1. Normalize BMI prior to pregnancy.
2. Do not smoke.
3. Maintain moderate exercise as tolerated.
4. In gestational diabetics, meticulous glucose control.

B. Postpartum and infancy
1. Breast-feeding is preferred for a minimum of 3 months.
2. Postpone introduction of solid foods and sweet liquids.

C. Families
1. Eat meals as a family in a fixed place and time.
2. Do not skip meals, especially breakfast.
3. No TV during meals.
4. Use small plates and keep serving dishes away from the table.
5. Avoid unnecessary sweet or fatty foods and soft drinks.
6. Remove televisions from children's bedrooms; restrict times for TV viewing and video games.

D. Schools
1. Eliminate fundraisers with candy and cookie sales.
2. Review contents of vending machines for healthier choices.
3. Install water fountains.
4. Educate teachers, especially physical education and science faculty, about basic nutrition and benefits of physical activity.
5. Educate children from preschool through high school on appropriate diet and lifestyle.
6. Mandate minimum standards for physical education, including 30–45 min of strenuous exercise two to three times weekly.
7. Encourage "the walking schoolbus."

E. Communities
1. Increase family-friendly exercise/play facilities for all age children.
2. Discourage the use of elevators and moving walkways.
3. Provide information on how to shop and prepare healthier versions of cultural-specific foods.

F. Healthcare providers
1. Explain biological and genetic noncontrollable contributions to obesity.
2. Give age-appropriate expectations for body weight in children.
3. Work toward classifying obesity as a disease to promote recognition, reimbursement for care, and willingness and ability to provide treatment.

G. Industry
1. Mandate age-appropriate nutrition labeling for products aimed at children (*e.g.*, red-light/green-light foods, with portion sizes).
2. Encourage marketing of interactive video games in which children must exercise in order to play.
3. Use celebrity advertising directed at children for healthful foods to promote breakfast and regular meals.

H. Government and regulatory agencies
1. Classify obesity as a legitimate disease.
2. Find novel ways to fund healthy lifestyle programs, *i.e.* with revenues from food/drink taxes.
3. Subsidize government-sponsored programs to promote consumption of fresh fruits and vegetables.
4. Provide financial incentives to industry to develop more healthful products and to educate the consumer on product content.
5. Provide financial incentives to schools that initiate innovative physical activity and nutrition programs.
6. Allow tax deductions for the cost of weight loss and exercise programs.
7. Provide urban planners with funding to establish bicycle, jogging, and walking paths.
8. Ban advertising of fast foods directed at preschool children, and restrict advertising to school-age children.

Screening

Are screening programs indicated? The justification of any screening program is to improve important health outcomes with benefits that will outweigh inconvenience and cost and direct risks to the subjects. Screening programs for obesity and its complications would be justified if earlier intervention were shown to reduce morbidity and mortality. Several systematic reviews have examined the evidence regarding the benefits, limitations, and cost-effectiveness of a broad range of clinical preventive services for obesity (97). None of the published trials has evaluated mass screening, but surrogate measures, *i.e.* preventive strategies, have been examined. Firm evidence for the long-term effectiveness of any single preventive strategy in children is lacking (98). Nonetheless, in the opinion of this group, primary care physicians should screen all children for overweight and obesity. Ideally, where resources permit, children with BMI indicative of overweight status (*i.e.* >85th percentile by the U.S. CDC graphs or >~91% by the European-Cole graphs) should receive weight management counseling, and those with obesity, *i.e.* BMI at or above the 95th or 99% percentile in the respective population graphs, should be screened for comorbidities discussed above under *Causes and Risks* and referred to appropriate specialists if these problems are detected.

Treatment

General considerations

What is the rationale for early intervention? Obese children and adolescents, like obese adults, are prone to develop many of the comorbidities outlined above; they also suffer emotional distress. The vulnerability of the obese child to serious complications makes the case for prevention and treatment irrefutable. Still there are some obese children and adults who appear to suffer few or no metabolic complications (99); the factors that differentiate such subjects from other obese patients are currently unknown, and this is a fertile area for future research.

At what point does excess weight gain justify intervention? Recent studies of American children and adolescents demonstrate that fasting serum glucose, insulin, triglycerides, C-reactive protein, and IL-6 concentrations and the prevalence of impaired glucose tolerance and systolic hypertension increase significantly with increasing obesity (BMI z score ≥ 2), whereas HDL-cholesterol and adiponectin levels decline (71). Even overweight children (BMI 85–95th percentile) are at increased risk for dyslipidemia and insulin resistance. In contrast, rates of dyslipidemia, hypertension, and glucose intolerance are low among children with BMI less than the 85th percentile for age. Thus, modified diets with decreased sedentary activities can be justified for children with BMI between the 85th and 95th percentiles, and more aggressive treatment should be directed toward children and adolescents with BMI at or above the 95th percentile (or z score ≥ 2) or in less obese children who suffer metabolic, orthopedic, or cardiopulmonary complications and/or psychological distress.

At what age should treatment begin? Most of the metabolic complications of childhood obesity emerge in adolescence and young adulthood. However, five lines of evidence reviewed above suggest that intervention is warranted, even in obese children. First, severe obesity in toddlers and young children is frequently accompanied by sleep apnea (82) and orthopedic anomalies (Blount's disease) (86). Second, some obese children develop glucose intolerance, T2DM, dyslipidemia, and hypertension even before the onset of puberty (71). Third, excessive weight gain between the ages of 2 and 10 yr increases the risks of adult obesity and glucose intolerance, especially when the parents are obese and/or have diabetes (12). Fourth, early vascular lesions have been detected in obese children as young as 3–8 yr of age, suggesting strongly that obesity-related atherogenesis begins in childhood (78). Finally, intervention to prevent or reverse obesity in its early stages perhaps may be more successful and beneficial than treatment of established, severe obesity in adolescence or adulthood.

What are the goals of treatment? Goal setting and treatment of pediatric patients, many of whom are still growing, must be individualized. The first goal is to restore the balance between energy intake and energy expenditure; in cases in which intake is clearly excessive, it will be necessary to restrict calories while increasing energy expenditure.

Stabilization of weight in growing children decreases BMI z score slowly. Nevertheless, studies in adults suggest that a 5–10% reduction in body weight at a rate of 0.5 kg/wk and maintained over a period of 2–5 yr may increase insulin sensitivity and improve glucose tolerance (100) among other salutary changes. Thus, obese children (and their physicians) should be encouraged by any reduction in BMI z score. The long-term objectives of treatment of childhood obesity are to reduce BMI z score to less than 2 and reverse and prevent short- and long-term comorbidities.

Lifestyle

Which treatment approach should be used first?

General considerations. The benefits of lifestyle intervention are most likely to be achieved when diet and exercise programs are coordinated with individual and family counseling and behavior modification (101). Long-term success requires continuous implementation; experience in adults indicates that discontinuation of any therapeutic approach leads to rebound weight gain in the great majority of subjects. Eating disorders and other psychiatric disorders are common in obese subjects and must be addressed; otherwise, therapeutic failure is assured.

Parents provide a child's contextual environment and thus should be considered key players in interventions aimed at preventing or treating weight-related problems. Parenting style and feeding style are crucial factors in fostering healthy lifestyle and awareness of internal hunger and satiety cues and deemphasizing thinness (102). In most family-based behavioral weight-loss programs for children, the obese child is the main target of change with varying degrees of parental involvement (103). Interestingly, recent reports suggest greater weight loss in obese children when parents alone are targeted for intervention (104). These data suggest that the stigma of obesity treatment *per se* may be counterproductive in this age group.

Dietary approaches. Mild caloric restriction is safe and can be effective when obese children and their families are motivated and encouraged to change longstanding feeding behaviors. An example of such a program aimed at families with children is the traffic light diet (105). Significant reductions in weight are unusual and often transient unless caloric restriction is accompanied by increased energy expenditure. Diets severely restricted in calories, including high-protein, very low-calorie diets, can facilitate more dramatic short-term weight loss. However, such diets cannot be sustained under free-living conditions (106) and are potentially dangerous. Severe caloric restriction may cause deficiencies of vitamins, minerals, and critical micronutrients; limit bone accretion and mineralization; reduce rates of linear growth; and disrupt menstrual cycles (107).

The role of specific dietary macronutrients in the pathogenesis and treatment of obesity is highly controversial. A low-fat diet in combination with exercise and weight loss can reduce significantly the risks of T2DM and cardiovascular disease in adults with impaired glucose tolerance. Yet recent investigations showed that obese men and women lost more weight and had more significant reductions in plasma triglyceride concentrations on low-carbohydrate diets than on conventional low-fat diets (108). A 3-month study in overweight adolescents found similar effects (mean decrease in weight 9.9 kg in the low-carbohydrate group *vs.* 4.9 kg in the low-fat group); low-density lipoprotein (LDL) levels declined with the low-fat diet but not with the low-carbohydrate diet (109). A review of adult studies suggests that the efficacy of low-carbohydrate diets may be related to overall caloric restriction rather than reduction in carbohydrate intake *per se*. Moreover, the benefits of low-carbohydrate diets may diminish with time (110).

Limited evidence suggests that the nature or quality of ingested carbohydrate may modulate childhood weight gain. The insulin secretory response to foods containing rapidly absorbed, concentrated carbohydrates (high glycemic index) exceeds the response to foods containing high concentrations of protein, fat, and fiber. Studies of the effects of glycemic index on weight gain in children are inconclusive. Still, observations among adolescents have found that consumption of sugar-sweetened drinks is an independent variable associated with increasing BMI (53, 111). In a separate study, a modified low-glycemic diet (45–50% carbohydrate, 30–35% fat) reduced BMI (−1.3 *vs.* 0.7 with a low-fat diet) and fat mass in obese adolescents (112). Thus, it appears that elimination of carbonated drinks or other sugary drinks (juice and sports drinks) from the diet can significantly reduce caloric intake and obesity (113).

Other macronutrients, vitamins, and trace elements may modulate the risk of metabolic complications. For example, intake of fiber (particularly whole grains and cereal) correlates inversely with the risks of T2DM and cardiovascular disease (114). Insoluble and soluble fibers limit macronutrient absorption and thereby increase fat oxidation and improve glucose tolerance. The intake of magnesium (from whole grains, nuts, and green leafy vegetables) and dairy products containing vitamin D and calcium may also correlate inversely with the risks of obesity and T2DM in children and young adults (115).

Exercise. A sedentary lifestyle increases the risks of childhood obesity and predisposes to diabetes and cardiovascular disease, whereas exercise, in combination with caloric and fat restriction, reduces the rate of progression to diabetes in adults with impaired glucose tolerance and limits cardiovascular morbidity and mortality. The benefits of exercise are mediated, at least in part, by reductions in total and visceral fat stores and increases in lean body mass, which augment resting energy expenditure (116). Exercise enhances adipose tissue sensitivity to insulin; reduces fasting and postprandial free fatty acid, LDL, and triglyceride concentrations; and increases plasma HDL levels. The heightened sensitivity to insulin and induction of fatty acid oxidation enhance vascular endothelial function (117).

Available evidence, albeit limited, suggests that exercise can benefit obese children and reduce the risks of metabolic and cardiovascular complications. A randomized, modified cross-over study of 79 obese children (aged 7–11 yr) demonstrated that 4 months of exercise training (40 min of activity 5 d/wk) reduced percent body fat (5%) and decreased fasting insulin (10%) and triglyceride (17%) concentrations, even in the absence of dietary intervention (118). Additional uncontrolled trials suggest that aerobic exercise can also improve vascular endothelial function (119). The benefits of exercise are quenched or reversed rapidly if activity is not maintained.

The capacity for voluntary exercise declines as BMI rises. It is therefore critical to begin regular exercise before the child becomes morbidly obese and functionally immobile. A summary of proposed suggestions for basic lifestyle intervention in children is provided in Table 4. The Cochrane study concluded that "there are limited high-quality data on the effectiveness of obesity prevention programs, and no generalizable conclusions can be drawn. However, concentration on strategies that encourage reduction in sedentary behaviors and increase in physical activity may be fruitful" (98). Thus, lack of formal evidence does not preclude action.

Diet and exercise regimens may prove effective for short-term treatment of pediatric obesity. However, the long-term success of lifestyle intervention alone has been disappointing. For example, in an Italian multicenter study of nutritional intervention in 1383 obese pediatric patients, drop-out rates ranged from 30–34% after 3 months to 90–94% after 2 yr (120). Noncompliance was highest in the most obese children. A Cochrane review of randomized, controlled trials of duration 6 months or more (n = 18 studies, 975 participants) concluded that most studies are too small to detect effects of treatment, and few trials use the same comparisons and outcomes (103). Thus, the data are of limited quality.

TABLE 4. Basic treatment interventions: lifestyle changes

Dietary suggestions
1. Eliminate all sugary drinks (including juice), and replace with water, noncaloric beverages, and lowfat or skim milk.
2. Restrict calories enough to produce mild negative energy balance.
3. Reduce intake of saturated fats, salty snacks, and high glycemic foods including candy, white bread, white rice, pasta, and potatoes.
4. Create a balanced diet containing vegetables, fruits, whole grains, nuts, fiber, lean meat, fish and low-fat dairy products.
Exercise suggestions
1. Exercise should be fun, age-specific, and tailored to the child's fitness level and ability.
2. Involve large muscle groups to increase energy expenditure.
3. Increase frequency, intensity, and duration with time.
4. Restrict sedentary behaviors: television viewing, video games, and internet "surfing."

Pharmacotherapy

If supervised lifestyle intervention fails, the patient should be referred to a subspecialist for evaluation. The subspecialist should assess the extent and magnitude of comorbidities and may consider more intensive therapeutic approaches including pharmacotherapy. Current pharmacologic interventions are designed to increase energy expenditure (stimulants), suppress caloric intake (anorectic agents), limit nutrient absorption and/or modulate insulin production and/or action.

Stimulants. The use of metabolic stimulants for the treatment of obesity has a checkered history. Many antiobesity drugs once considered safe and effective, *i.e.* thyroid hormone, dinitrophenol, amphetamine, fenfluramine, dexfenfluramine, phenylpropanolamine, and ephedra, have been abandoned because they caused dangerous and in some cases life-threatening complications.

A single short-term trial compared caffeine plus ephedrine with placebo in adolescents taking a mildly hypocaloric diet. Although the drug-treated subjects lost more weight, adverse effects were more frequent (121). These agents cannot be recommended.

Anorectic agents. The only anorectic agent currently approved for use in obese adolescents (older than 16 yr) is sibutramine, a nonselective inhibitor of neuronal reuptake of serotonin, norepinephrine, and dopamine. In combination with caloric restriction and a comprehensive family-based behavioral program, sibutramine reduced BMI 8.5 $\pm$ 6.8% in 43 obese adolescents during an initial 6-month period; a 4.0 $\pm$ 5.4% reduction in BMI was achieved in 39 placebo-treated subjects (122). No additional weight loss occurred during a subsequent 6 months of therapy. Fasting insulin concentrations declined and HDL levels increased. However, 19 of 43 subjects treated with sibutramine developed mild hypertension and tachycardia, necessitating reduction in drug dose, and five had sustained elevations in blood pressure that required discontinuation of the drug. Other potentially serious complications include insomnia, anxiety, headache, and depression. There is a heightened risk of the serotonin syndrome if sibutramine is used in combination with monoamine oxidase inhibitors, buspirone, lithium, or meperidine, or selective serotonin reuptake inhibitors, such as fluoxetine, triptans, dextromethorphan, ergot alkaloids, or fentanyl.

Anorectic agents should complement, never replace, a diet and exercise program. The drugs have modest effects on total body weight (typically an additional 2–10 kg in obese adults), and responses vary considerably among individuals. Most of the weight loss from anorectic agents is achieved within the first 4–6 months of treatment due to the achievement of a negative plateau; regain of weight is the norm unless drug therapy is maintained. Administration of this drug is not recommended for more than 2 yr duration.

Leptin treatment has been given to children with genetic leptin deficiency resulting in dramatic weight reduction (26), but it is doubtful that individuals with nonleptin-deficient forms of obesity will benefit from similar treatment.

Drugs that limit nutrient absorption. The drug orlistat inhibits pancreatic lipase and thereby increases fecal losses of triglyceride. Orlistat decreases body weight and total and LDL cholesterol levels and reduces the risk of T2DM in adults with impaired glucose tolerance. In the United States, orlistat is currently approved by the Food and Drug Administration in children older than 12 yr. In obese adolescents, the combination of orlistat with lifestyle intervention reduced weight (-4.4 ± 4.6 kg), BMI (-1.9 ± 2.5 kg/m^2), total cholesterol (-21.3 ± 24.7 mg/dl or 0.55 ± 0.64 mmol/liter), LDL (-17.3 ± 15.8 mg/dl or 0.45 ± 0.41 mmol/liter), fasting insulin (-13.7 ± 19.0 μU/ml or 95.1 ± 132.0 pmol/liter), and fasting glucose (-15.4 ± 7.4 mg/dl or 0.85 ± 0.41 mmol/liter) concentrations and increased insulin sensitivity during a 3-month trial period (123). There was considerable variability in response to the drug. Variable reductions in body weight (-12.7 ± 2.5 kg) and fat mass were also noted in a study of 11 morbidly obese children aged 7–12 yr. Side effects are tolerable as long as subjects reduce fat intake, but vitamin A, D, and E levels may decline despite multivitamin supplementation. High study dropout rates (25% or more) suggest that long-term fat restriction is problematic in teenagers; dietary noncompliance results in flatulence and diarrhea that ultimately prove unacceptable.

Insulin sensitizers and suppressors. The synthesis and storage of triglyceride in adipose tissue are stimulated by insulin. Thus, increases in nutrient-dependent insulin production and/or fasting hyperinsulinemia may contribute to fat storage and limit fat mobilization. By reducing fasting or postprandial insulin concentrations, certain pharmacologic agents may prove beneficial in the treatment of obese children and adults. In this drug class, only metformin treatment results in weight loss.

Metformin. Metformin is a bisubstituted, short-chain hydrophilic guanidine derivative that activates AMP protein kinase. Its major site of action is the liver: the drug increases hepatic glucose uptake, decreases gluconeogenesis, and reduces hepatic glucose production. Major advantages of the drug include decreased food intake, weight loss, decreased fat stores (sc more than visceral), improved lipid profiles, and a reduction in conversion to T2DM among adults with impaired glucose tolerance.

There have been two randomized, double-blind, placebo-controlled studies of metformin in obese adolescents with insulin resistance, normal glucose tolerance, and a positive family history of type 2 diabetes. In the first trial ($n = 29$), metformin reduced BMI z score (3.6% relative to placebo controls), plasma leptin, and fasting glucose (-9.8 mg/dl or 0.54 mmol/liter) and insulin (-12 μU/ml or 83.3 pmol/liter), even in the absence of dietary intervention (124). In the second trial ($n = 24$), in conjunction with a low-calorie diet, metformin reduced weight 2.7% relative to controls and decreased plasma leptin, insulin, glucose, cholesterol, and triglyceride concentrations (125).

Metformin is generally well tolerated, although many patients have transient abdominal discomfort, avoidable by taking the medication with food. Lactic acidosis is extraordinarily rare in pediatric patients, but metformin should not be administered to children with underlying cardiac, hepatic, renal, or gastrointestinal disease. Obese subjects with mild elevations in hepatic enzymes (less than 3-fold higher than established norms) may receive the drug; indeed, some studies suggest that metformin may be useful in treatment of hepatic steatosis. Concurrent use of a multivitamin is warranted because metformin increases urinary excretion of vitamins B_1 and B_6. Metformin is approved by the Food and Drug Administration for treatment of T2DM but not currently for treatment of childhood obesity or insulin resistance.

Octreotide. Octreotide binds to the somatostatin-5 receptor and thereby impairs closure of the β-cell calcium channel, reducing glucose-dependent insulin secretion. In a double-blind, placebo-controlled trial in children with hypothalamic obesity, octreotide reduced insulin secretory responses and rates of weight gain ($+1.6 \pm 0.6$ *vs.* $+9.2 \pm 1.5$ kg) and BMI (-0.2 ± 0.2 *vs.* $+2.3 \pm 0.5$ kg/m^2) (126). The cost of the medication, the need for parenteral administration, and the drug's side effects, which may include transient gastrointestinal distress, gallstones, suppression of GH and TSH secretion, and cardiac dysfunction, limit its current applicability to patients with intractable obesity from hypothalamic injury.

Bariatric surgery

The long-term success of lifestyle intervention and pharmacotherapy in subjects with severe obesity has in general been disappointing. Marked weight loss is highly unusual and rarely sustained, and metabolic and vascular complications are common, albeit not universal. More aggressive approaches such as bariatric surgery may be indicated in selected subjects with extreme obesity and serious comorbidities. The surgical approaches now used most commonly are the laparoscopic gastric banding procedure and the Roux-en-Y gastric bypass (RYGB).

Gastric banding may cause esophageal dilatation and achalasia and may exacerbate gastroesophageal reflux. Other potential complications include port site malposition or malfunction, balloon rupture, and infection. Complications of RYGB include iron-deficiency anemia (50%); folate, thiamine, or calcium deficiencies (at least 30%); cholecystitis (20%); wound infections and dehiscence (10%); small bowel or stomach obstruction (5–10%); atelectasis and pneumonia (12%); and incisional hernia (10%). Prophylactic tracheostomy may be required to maintain airway patency and correct preoperative hypercapnia. Other possible complications include leaks at the anastomotic junction, gastric dilatation, and dumping syndrome. Among the most serious complications are potentially fatal pulmonary emboli. Mortality rates for RYGB range from 1 to 5%. Complication rates may be reduced if bariatric procedures are performed through laparoscopy by an experienced surgeon. There have been relatively few published surgical trials pertaining to adolescents (127, 128); however, the outcomes seem to parallel bariatric surgery performed in adults (129) and warrant further investigation (130).

Care coordination

How should the clinician balance lifestyle intervention, pharmacotherapy, and surgery in the treatment of obesity? Lifestyle intervention is indicated for all overweight and obese children and should be maintained, even if more aggressive/intensive measures are adopted.

Pharmacotherapy may be considered for complicated obesity in peripubertal children or adolescents who fail to respond to at least a 6-month trial of supervised lifestyle intervention despite good faith effort. The term complicated obesity implies the presence of major comorbidities including glucose intolerance, hypertension, dyslipidemia, sleep apnea, or other comorbidities discussed above. Failure to respond means that the comorbidities persist or worsen despite lifestyle intervention. Good faith effort means the patient has attempted to follow dietary recommendations and has increased energy expenditure through regular exercise.

Given its efficacy in treating obese, insulin-resistant adolescents, its track record of safety, and its ability to limit food intake and weight gain, the authors consider metformin the drug of choice for treating the obese adolescent with severe insulin resistance or glucose intolerance.

Anorectic agents such as sibutramine should not be administered to prepubertal children. Use of this drug in anyone under age 16 yr remains experimental and should be undertaken only in specialized pediatric treatment centers in the context of clinical trials approved by institutional review boards. Neuropsychologic testing before and during therapy may be warranted. Inhibitors of nutrient absorption such as orlistat are not tolerated by many obese children but might be applied successfully in selected, highly motivated patients. The use of octreotide for treatment of hypothalamic obesity, although promising, remains experimental. Other medications are in phase III studies in obese adults (reviewed in Ref. 131) but will not be available for children for several years.

Firm or uniform guidelines regarding duration of pharmacologic treatment are not feasible at this time. A trial off medication may be warranted if comorbidities are reversed, particularly if there has been a significant decline in BMI z score. In all cases, pharmacotherapy should be discontinued if the patient fails to respond to the drug.

Bariatric surgery should be reserved for treatment of adolescents with extreme obesity (usually defined as BMI $>$ 40 or $>$ 35 with established comorbidities) who have failed other treatment approaches. Surgery should be performed only under the rubric of clinical trials in medical centers that have expertise in bariatric surgical techniques and are supported by multidisciplinary teams with long-standing experience in the evaluation and management of obese children. Contraindications to bariatric surgery include substance abuse or psychiatric disabilities (including severe eating disorders) that prevent lifelong compliance with nutritional recommendations or medical surveillance (127, 128).

Who should receive intensive evaluation and treatment? In most cases, the primary care physician will be responsible for management of overweight infants and children. Clearly the burden is too large to be borne by specialty physicians. It is very important for primary care physicians to recognize individual overweight patients and intervene before they become obese (132). Basic dietary advice should be provided in the primary care setting. This should include elimination of all sweetened beverages, including juices, caloric carbonated drinks, iced tea, and lemonade; use of low-fat or fat-free milk in children over the age of 2 yr; portion control; increased fruit and vegetable intake; reduction in fast food consumption; and counseling about the need for daily vigorous exercise. Weekly office weigh-ins can monitor home progress, and if this is deemed insufficient, the child should be seen by a registered dietitian or enrolled in a formal weight-management program. Patients who have unusual distinguishing characteristics may require a specialist's consultation.

There are several examples of these characteristics. First, infants who have rapid weight gain and abnormally low linear growth are likely to have an underlying disease. In addition, infants with syndromic features, neurological deficits, or abnormal fat distribution associated with obesity require further expert evaluation.

In addition, children and adolescents who meet the criteria for obesity (BMI $>$ 95%) and those with eating disorders should be referred for expert evaluation and intervention. Children with an early age of adiposity rebound (the period when the BMI begins to increase after reaching a nadir in early childhood) are at highest risk for overweight, later glucose intolerance, and diabetes (133). These children also need a thorough clinical evaluation.

As genotype-phenotype knowledge increases, lifestyle, pharmacologic, and surgical therapies may be applied more rationally to specific individuals.

Where should delivery of advanced care be centered? Obese patients with comorbidities such as sleep apnea, glucose intolerance, hypertension, nonalcoholic steatohepatitis, polycystic ovarian syndrome, and dyslipidemia will require the expertise of subspecialists in pediatric endocrinology, gastroenterology, nutrition, cardiology, exercise and sports medicine, pulmonary medicine, orthopedics, and behavioral medicine; their efforts must be coordinated within the setting of specialized obesity clinics. Until a safe and effective treatment can be recommended for severely obese children, intensive inpatient treatment approaches should remain an option in specialized centers for limited durations in the context of a comprehensive, long-term management program. The intensive therapies that have been used to treat pediatric and adolescent obesity include very low-calorie diets, pharmacotherapy, and bariatric surgery. Psychosomatic units specializing in the treatment of eating disorders are the logical choice by providing a milieu for the obese children and adolescents with life-threatening medical complications. Such programs adhere to recommendations of the Expert Committee on Obesity Evaluation and Treatment for an effective behavioral and nutritional approach for child obesity (134). These include a group format with individualized behavioral counseling, intensive family involvement and training, behavior modification targeted at changing home and family

TABLE 5. Summary of proposals

Definitions	Clinical overweight: BMI at or above 85th centile Clinical obesity: BMI > 95th centile on national charts (99th centile on UK charts) Epidemiological or international studies: IOTF cutoffs
Preventive strategies	Action is required antenatally, in schools, community facilities, marketing, government and regulatory agencies.
Screening	Population screening is required to identify overweight children with BMI > 85th centile
Assessment	Laboratory assessment of children above 95th centile should include: a) Thyroid and liver function tests, fasting glucose, insulin and lipid profile. b) Children at increased risk for the metabolic syndrome require periodic oral glucose tolerance tests from age 10. c) Screening for other comorbidities: *e.g.*, hypertension, sleep apnea, orthopedic problems, *etc*.
Treatment	Children with BMI at or above 85th centile should receive regular lifestyle counseling. Children with BMI > 95th centile require specialist pediatric care.
Service development	Children with comorbidity or severe obesity should receive their care in a multidisciplinary specialist service.

lifestyle, moderated caloric restriction targeted at inducing modest (5–10%) weight reduction associated with improvement of medical complications, a physical activity program emphasizing choice and reinforcing reduced sedentary behaviors, skills for managing high-risk situations, and skills for maintenance and relapse prevention.

Conclusions

In the foregoing pages, we have described the problems associated with childhood obesity, providing strong evidence that adult morbidities may begin in early life. Perhaps because of the rapid evolution of these problems, public policy makers have not yet taken action to address existing and future repercussions. Obesity is now a major contributing factor to increasing rates of disability among adults (135). Health care costs of patients with a BMI greater than 35 are approximately 44% more than those of nonobese patients. Furthermore, it is well established that the health care costs of treating patients with T2DM, a common sequel of obesity, are substantially higher than treatment for patients without diabetes. This should provide incentive for the private and public sectors to: 1) mobilize all available resources to stem the tide of increasing body mass in children and adults, 2) classify obesity as a disease, paving the way for public funding and ensurers' reimbursement for obesity treatment programs, and 3) spur further research to more effectively prevent and treat obesity. Precedents for successful public health campaigns include those designed to stem tobacco use, prevent the spread of HIV, and promote the use seat belts in motor vehicles and bicycle helmets in children. Professional societies (especially those dedicated to primary care and endocrinology), health care providers, and educators should assume leadership roles in achieving these goals (23). The WHO has formulated a plan to tackle obesity, and the IOTF has created a credentialing system for obesity specialists and treatment centers. In the United States, the Department of Health and Human Services recently convened an Obesity Summit to discuss the best means of addressing this critical public health problem. These are laudable milestones, which we hope will make inroads into ameliorating the crisis.

Measures to prevent childhood obesity are listed in Table 3, and basic lifestyle interventions are summarized in Table 4. An overall summary of this consensus development conference is presented in Table 5. These aspects must be emphasized as the safest means for primary care physicians to manage patients. The decision of when to intervene with pharmacotherapy or bariatric surgery must be made for children and adolescents on a case-by-case basis, according to the guidelines presented above. To date, although somewhat encouraging, only limited and short-term evidence is available to support the use of selected drugs or surgical procedures to alleviate morbid obesity in this population. Longer-term clinical trials with larger numbers of children and adolescents will be required before drug treatment or surgical intervention can be routinely employed.

Acknowledgments

The following participants convened in Ein Bokek, Dead Sea, Israel, March 24–27, 2004, and contributed to this manuscript: R. Bahar-Einav, D. Bass-Rotenstein (Pittsburgh, PA); Z. Bistrizer (Zerifin, Israel); G. Brill, E. Leiberman, Y. Limoni (Beersheva, Israel); S. Chalew (New Orleans, LA); J. Dahlgren (Gotheburg, Sweden); M. Golan, A. Hanukoglu, A. Zung (Rehovot, Israel); A. Golander, E. Gur, A. Kochli, Z. Laron, D. Levin, Y. Meirovitch, D. Modan-Mozes, N. Leventhal, Zohar Landau, E. Zubery (Tel Aviv, Israel); H. Guttman, I. Koren, Y. Levy, D. Tiosano (Haifa, Israel); H. Hirsch, H. Landau, D. Zangen (Jerusalem, Israel); L. Karaviti (Houston, TX); A. Kurtev (Sofia, Bulgaria); M. Lampit (Zefat, Israel); I. Poraz (Petah Tikva, Israel); Y. Rakover (Afula, Israel); T. J. Rozenberg (Jerusalem, Israel); J. Popovic (Kansas City, MO); C. Silverstein, S. Ten (Brooklyn, NY); R. Weiss (New Haven, CT); and O. Yogev (Jerusalem, Israel).

The working group also acknowledges the contributions of: N. Dixit (Tucson, AZ); L. Edmunds (Bristol, UK); C. Maffeis and L. Tatò (Verona, Italy); and A. Vargas (New Orleans, LA).

Received July 15, 2004. Accepted December 1, 2004.

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The work for the Consensus Conference was supported by Aventis, Ben Gurion University, Ferring Pharmaceuticals, Israel Society for Pediatric Endocrinology, Eli Lilly Co., Novo Nordisk, Pfizer, Roche, and Teva Pharmaceuticals.

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