

PEDIATRIC OBESITY AND INSULIN RESISTANCE: Chronic Disease Risk and Implications for Treatment and Prevention Beyond Body Weight Modification

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■ **Abstract** The study of childhood obesity has continued to grow exponentially in the past decade. This has been driven in part by the increasing prevalence of this problem and the widespread potential effects of increased obesity in childhood on lifelong chronic disease risk. The focus of this review is on recent findings regarding the link between obesity and disease risk during childhood and adolescence. We describe recent reports relating to type 2 diabetes in youth (2), prediabetes (69, 166), metabolic syndrome (33, 35), polycystic ovarian syndrome (77), and nonalcoholic fatty liver disease (58, 146), and the mediating role of insulin resistance in these conditions. In addition, we review the implications of this research for the design of more effective treatment and prevention strategies that focus more on the improvement of obesity-related metabolic abnormalities and chronic disease risk reduction than on the conventional energy balance approach that focuses on weight management.

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CONSEQUENCES OF OBESITY IN CHILDREN
AND ADOLESCENTS

Type 2 Diabetes and Prediabetes

The incidence of type 2 diabetes has increased among children worldwide (49, 132, 140, 154), and this is thought to be a consequence of the pediatric obesity epidemic (87, 135). Estimates suggest a 20-fold increase in the incidence of type 2 diabetes in children and adolescents in the past two decades. However, because these estimates are based almost entirely on clinical observations of the number of diagnosed cases of type 1 versus type 2 diabetes, they should be interpreted with caution. Several small studies have examined the prevalence of type 2 diabetes as well as prediabetes in high-risk populations, and these are summarized in Table 1. Among these studies, relatively small numbers of children have been diagnosed with type 2 diabetes (Table 1). In addition, the documentation of type 2 diabetes in pediatric obesity is not a new phenomenon. For example, one study from 1968 found 6% of obese multiethnic children had diabetes, presumably type 2 (139).

Unfortunately, the current overall prevalence of type 2 diabetes in childhood remains unknown. One study in U.S. adolescents aged 12–19 who participated in National Health and Nutrition Examination Survey (NHANES) III (1988–1994) reported a 0.41% prevalence for all forms of diabetes, approximately one third of which were considered to represent type 2 (49) (Table 1). However, the sample size in this study was too small to provide a stable estimate of diabetes prevalence. In addition, these data preceded more recent reports regarding the rise in obesity (135) in adolescents, and therefore may underestimate the true prevalence of type 2 diabetes in the general pediatric population.

Youth diagnosed with type 2 diabetes are almost always obese, have usually reached puberty, and have a family history of type 2 diabetes (2). In the United States, the increase in type 2 diabetes appears particularly noteworthy among minority populations such as African Americans, Latinos, and Native Americans (37, 50, 65), groups that also have the highest prevalence of obesity among North American youth (87, 135). Prevalence estimates of type 2 diabetes in higher risk Native American adolescent populations in Canada and the United States approach 3%–5% (37, 50, 65). Thus, obesity in childhood seems to be a primary risk factor for type 2 diabetes (2), as it is in adults (55, 129), particularly among high-risk

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TABLE 1 Prevalence of prediabetes (impaired fasting glucose and impaired glucose tolerance) and type 2 diabetes in pediatric populations*

Reference	Population	Age (years)	Test	Impaired fasting glucose	Impaired glucose tolerance	Type 2 diabetes
(139)	66 multiethnic obese children	4–16	OGTT	Not reported	17%	6%
(49)	U.S. general adolescent population, oversampling of African American and Mexican American; n = 2867	12–19	Fasting glucose (n = 1083), random glucose (n = 1784)	1.76% ^a	Not assessed	0.14%
(165)	U.S. obese children; BMI = 30–32; mixed ethnicity (62% non-Hispanic white); n = 55	4–10	OGTT	Not reported	25.4%	0%
	U.S. obese adolescents; BMI = 37–41; mixed ethnicity (56% non-Hispanic white) n = 112	11–18			20.5%	3.6%
(69)	Overweight, Latino children; BMI percentile = 94%–96%; positive family history type 2 diabetes; n = 150	8–13	OGTT	0% ^a 12.3% ^b	28%	0%

(Continued)

TABLE 1 (Continued)

Reference	Population	Age (years)	Test	Impaired fasting glucose	Impaired glucose tolerance	Type 2 diabetes
(189a)	Obese; BMI-SDS 2.6–3.0; European, mixed ethnicity (89% Caucasian); n = 102	7–18	OGTT	11.8% ^a	36.3%	5.9%
(182a)	Obese; BMI-SDS 1.9–4.7; European, Caucasian; n = 520	8.9–20.3	OGTT	3.7% ^c	2.1%	1.5% ^d
(188)	Moderate to severe obesity; BMI-SDS 2.3–2.8; U.S. mixed ethnicity (40% white; 30% black; 27% Hispanic); n = 439	10.9–13.1	OGTT	Not reported	14.4%–19.9%	0%

^aImpaired fasting glucose defined as fasting plasma glucose ≥ 110 and < 126 .

^bImpaired fasting glucose defined as fasting plasma glucose ≥ 100 and < 126 in extended study cohort (n = 211) (186).

^cImpaired fasting glucose defined as fasting plasma glucose 100–109.

^dDiabetes defined as fasting plasma glucose ≥ 110 (misclassified), or two-hour OGTT glucose ≥ 200 .

* Abbreviations: BMI, body mass index; OGTT, oral glucose tolerance test; SDS, standard deviation score.

ethnic groups. In adults, the progression from normal glucose tolerance to overt type 2 diabetes involves an intermediate stage of hyperglycemia, characterized by impaired fasting glucose and/or impaired glucose tolerance, now known as prediabetes (3). Recent reports have documented a high prevalence of prediabetes among obese children and adolescents (summarized in Table 1).

In a clinic-based population, Caprio and colleagues (166) detected impaired glucose tolerance in 25% of obese children (4–10 years of age) and in 21% of obese adolescents (11–18 years of age); type 2 diabetes was identified in 4% of the obese adolescents. Similarly, we found that 28% of obese Hispanic children with a positive family history for type 2 had impaired glucose tolerance, but found no cases of type 2 diabetes (69). An unexpected finding was that the prevalence of children with impaired glucose tolerance was unaffected by overweight severity (69). These studies have also revealed another interesting common feature in that prediabetes in children and youth is more frequently characterized by impaired glucose tolerance, whereas the prevalence of impaired fasting glucose (glucose ≥ 110 mg/dl < 125 mg/dl) is typically low (69, 166).

The findings from these studies have important clinical implication for the screening of high-risk children for prediabetes based on a fasting blood sample, as is recommended by the American Diabetes Association (2). In other words, the use of a fasting blood sample, as opposed to an oral glucose tolerance test, may miss the diagnosis of a significant number of children who have prediabetes. The recent lowering of the cut point for diagnosis of impaired fasting glucose from 110 mg/dl to 100 mg/dl by the American Diabetes Association may increase the likelihood of detecting adverse changes in glucose homeostasis. We found that when a fasting glucose threshold of 100 mg/dl was used in a cohort of overweight Hispanic children in Los Angeles, 12% of children were identified as having impaired fasting glucose, compared with less than 1% when the 110 mg/dl cut point was used (186). However, the relative risk of developing type 2 diabetes if a child has impaired fasting glucose, impaired glucose tolerance, or both remains to be determined through ongoing longitudinal studies. Although studies in adults suggest that both states of glucose dysregulation increase the risk of progression to overt type 2 diabetes (3), this remains to be shown in children.

The Metabolic Syndrome

The metabolic syndrome was first described by Reaven in 1988 (148), but it wasn't until recently that both the World Health Organization (136) and the Adult Treatment Panel (ATP) III of the National Cholesterol Education Program proposed clinical definitions (48). The availability of a clinical definition prompted numerous reports on the prevalence of the metabolic syndrome and provided evidence that the metabolic syndrome is an entity that places individuals at risk of type 2 diabetes (86, 110) and cardiovascular disease that is associated with increased cardiovascular disease mortality (93, 112).

Although a clinical definition of the metabolic syndrome in children does not currently exist, several large population studies have attempted to establish the

prevalence of the metabolic syndrome during childhood. Despite differences in definitions and cut points (26, 27, 33, 109, 144), these studies suggest that the prevalence of the metabolic syndrome in children and adolescents is relatively low (3%–4%) when compared with rates in the adult population. For instance, the age-adjusted prevalence of the metabolic syndrome in U.S. adults, based on the ATP III definition, was 23.7%, whereas in adults aged 20–29 years it was 6.7% (59). The overall prevalence of the metabolic syndrome in U.S. adolescents was 4.2% (33). In this study, the authors chose to use a definition similar to that proposed in ATP III. Adolescents were classified as having the metabolic syndrome if they had three or more of the following: triglycerides ≥ 110 mg/dl, high-density lipoprotein-cholesterol (HDL-C) ≤ 40 mg/dl; waist circumference > 90 th percentile (for age and gender), fasting glucose > 110 mg/dl, and blood pressure ≥ 90 th percentile (for age, gender, and height) (33).

Although the above studies suggest that overall prevalence rates of the metabolic syndrome in youth are low, the perspective is very different in overweight adolescents (33, 188). In NHANES III, the prevalence of the metabolic syndrome was 28.7% in overweight adolescents (BMI ≥ 95 th percentile) compared with 6.1% in adolescents at risk for overweight (BMI ≥ 85 th but lower than 95th percentile), and 0.1% in those with a BMI below the 85th percentile (33). Eighty-nine percent of overweight adolescents had at least one abnormality of the metabolic syndrome and more than half (56%) had two abnormalities (33). The individual prevalence of abdominal obesity, high triglycerides, low HDL-C, and high blood pressure in overweight adolescents was 74.5%, 51.8%, 50%, and 11.2%, respectively. Impaired fasting glucose was only present in 2.6% of overweight adolescents. Similarly, several other studies have found a high prevalence of the metabolic syndrome among severely overweight children and adolescents. For example, Cruz et al. (35) described a prevalence of 30% in Hispanic children > 85 th percentile for BMI, and Weiss et al. (188) saw a prevalence of 39% and 49.7% in obese adolescents above the 97th and 99th percentile, respectively, for BMI. Thus, the prevalence of the metabolic syndrome is clearly related to increasing severity of obesity.

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) encompasses the entire spectrum of liver disease, which includes simple hepatic steatosis without inflammation (which may not lead to progressive liver injury), nonalcoholic steatohepatitis (NASH), and the resulting cirrhosis (which may be devoid of steatosis). NAFLD is thought to be the most common liver disease in the United States and obesity is probably the single most important risk factor (30). The disorder is increasingly recognized in the pediatric population (11, 146, 153, 175), especially in children who are obese or with type 2 diabetes (11, 159, 175). In one study, 83% of patients diagnosed with NASH were obese, 30% had elevated serum triglycerides, and 19% had elevated serum cholesterol (146). Collectively, these studies have brought to light the magnitude of the problem of NAFLD in overweight children as well as the potential for the future burden of liver disease in affected subjects (146, 153).

The early development of NASH in childhood may lead to chronic end-stage liver disease later in life, most significantly cirrhosis (20, 125). In fact, a recent case study report documented the development of cirrhosis from NASH in two overweight boys aged 10 and 14 (125).

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS) is a common comorbidity of obesity in adolescent girls (77). PCOS is defined as ovulatory dysfunction with evidence of hyperandrogenism not due to other causes (115). Most girls with PCOS demonstrate reduced sex hormone-binding globulin (163) and elevated free testosterone (7, 77, 116, 163); elevations in total testosterone, androstenedione, and DHEA-sulfate may also be seen (115, 163). Insulin resistance is generally present and may be higher than in BMI-matched controls (116). About half of adult women with PCOS are obese (18, 61, 66), and there is a predisposition to central obesity (88). Comparable percentages among adolescents are not known, but PCOS can be seen in both obese and nonobese adolescents (163). Women with PCOS have increased incidence of other comorbidities including prediabetes, type 2 diabetes, hypertension, and dyslipidemia (46, 190). With respect to comorbidities in adolescents, Palmert (138) showed that 33% of overweight predominantly Caucasian adolescents with PCOS had either impaired glucose tolerance or undiagnosed type 2 diabetes. The prevalence of impaired glucose tolerance in adolescents with PCOS may approach 50% in some populations (7).

WHY IS FAT BAD? RELATIONSHIP BETWEEN INCREASED ADIPOSITY AND HEALTH RISK IN CHILDREN

Location of Body Fat

For children as well as adults, there are several hypotheses that might explain the link between increased body fat and health risk (62). The following sections review these hypotheses and the evidence for them in pediatric studies.

One of the earlier theories, termed the “portal theory,” links visceral adipose tissue to insulin resistance and is based on the direct effects of free fatty acids on the liver (62). Numerous studies support a link between body fat, visceral fat, and metabolic risk factors in children (23, 63, 80, 114). Earlier studies showed the presence of visceral fat in children at an early age (72), although to a highly variable degree (73), and the gradual expansion of this fat compartment during growth and development (90). Due to the high colinearity between visceral fat, subcutaneous abdominal fat, and total body fat, it is challenging to obtain a representative indication of the unique contribution of each of these fat compartments to health risk.

More recently, the “ectopic fat” theory has been proposed (147). This approach suggests that fat deposition outside of adipose tissue (e.g., in muscle or liver)

contributes to insulin resistance. Intramyocellular lipid (IMCL), for example, has been shown to be a major determinant of insulin resistance in adults (101), as well as obese individuals (60) including adolescents (9, 165). In addition to IMCL, fat deposition in the liver has also been associated with insulin resistance and hyperinsulinemia in both nonobese normal subjects (122, 133, 161) and in obese subjects with type 2 diabetes (102, 122), and this association seems to be independent of total body adiposity. Liver fat may also be a significant factor in children, although there are no studies in this area. In support of both the portal theory and ectopic fat theory, a recent study in adults showed that removal of subcutaneous abdominal fat by liposuction had no metabolic benefits, a finding that suggests other fat depots may be more clinically relevant (104). Thus, the location of body fat deposition seems to be an important factor in explaining the link between adiposity and health risk, though more direct evidence of this concept is needed.

Fat as Endocrine Organ

Since the discovery of leptin in 1994 (191), it has become evident that adipose tissue is not an inert tissue but instead is a critical tissue involved with metabolic regulation (103). Adipocytes produce and secrete several important mediators related to insulin resistance, cardiovascular disease, and type 2 diabetes. These mediators, collectively termed "adipocytokines," exhibit diverse actions at various central (e.g., hypothalamus) and peripheral (e.g., skeletal muscle) sites and may provide insight into the underlying mechanisms linking adiposity with disease risk. Although the number of identified adipocytokines has grown exponentially in recent years, the current section focuses on leptin, tumor necrosis factor alpha (TNF-alpha), interleukin-6 (IL-6), and adiponectin and their respective relations to metabolic and cardiovascular health in children.

The majority of mechanistic evidence in relation to adipocytokine action is derived from animal models of obesity, whereas the data from pediatric populations has primarily looked at associations between adipocytokines and markers of health. In general, the findings from pediatric studies are similar to those from studies of adults, showing significant positive correlations between adipocytokines and measures of adiposity (130), with the exception of adiponectin, which appears to have insulin-sensitizing properties and is inversely related to measures of obesity (10). Although it remains unclear whether adipocytokines in children are simply markers of degree of adiposity, several recent reports have established significant relations between adipocytokines and insulin resistance that are independent of body composition (10, 172).

LEPTIN Leptin was the first characterized adipocytokine, and has its primary mechanism of action in the hypothalamus, where it is thought to regulate energy intake and expenditure by suppressing food intake and stimulating energy expenditure (191). Leptin is directly related to adiposity and insulin resistance in children (84, 128), which suggests that overweight children, like adults, exhibit resistance

to the antiobesity effects of leptin (111). Recent research further extends adipose-related leptin resistance in overweight children to include the associated metabolic complications. Chu and colleagues (29) observed significant positive associations between leptin levels and both insulin resistance as well as metabolic syndrome scores that were independent of body composition in children. Because leptin has been shown in animal models to stimulate both lipid and glucose metabolism, it is not altogether surprising that leptin resistance in youth extends beyond the dysregulation of body composition (98). For example, baseline leptin levels predict the development of diabetes in Japanese men (but not women), and this effect was independent of baseline body fat and insulin resistance (124). We are not aware of similar studies in children and adolescents.

TNF-ALPHA AND INTERLEUKIN-6 (IL-6) These two adipocytokines are proinflammatory mediators with detrimental effects on insulin sensitivity and atherosclerosis in adults (176). Similar to leptin, TNF-alpha and IL-6 are positively correlated with measures of adiposity in children (16, 130), but unlike leptin, TNF-alpha and IL-6 have been shown to impair glucose homeostasis in rodent models (160, 181). Plasma levels of TNF-alpha and IL-6 increase in response to acute and chronic inflammatory events in children (157). Obesity and the metabolic syndrome are considered disorders related to chronic inflammation (56), and TNF-alpha and IL-6 presumably act as inflammatory mediators of adiposity-associated metabolic disturbances in children. To date, very little work has established relations between metabolic dysregulation independent of body composition and TNF-alpha or IL-6.

ADIPONECTIN In contrast to other adipocytokines, adiponectin is inversely related to total adiposity in children (130). Weight loss in children is associated with an increase in adiponectin and an improvement in insulin resistance (149, 150). These observations have led to studies of the potential role of adiponectin as a protective adipocytokine against insulin resistance and early cardiovascular disease in youth. Weiss and colleagues (187) evaluated adiponectin, insulin sensitivity, abdominal fat distribution, and IMCL levels in 8 nonobese and 14 obese adolescents. Significantly lower adiponectin levels were observed in obese compared with nonobese children. Additionally, they found a strong inverse correlation between adiponectin and IMCL ($r = 0.73$, $P < 0.001$) that was independent of both total and abdominal fat. However, when groups were analyzed separately, the inverse association was only significant in the obese children, a finding that suggests a potential adiposity-related threshold effect between adiponectin and IMCL levels. Adiponectin was also found to correlate positively with insulin sensitivity ($r = 0.52$, $P < 0.02$) and negatively with plasma triglyceride ($r = -0.80$, $P < 0.001$), and these relations persisted after controlling for percent body fat.

Bacha et al. (10) observed similar differences in adiponectin levels between lean and obese youth. However, in contrast to Weiss et al. (187), Bacha and colleagues found a significant relationship between adiponectin and abdominal adiposity whereby obese adolescents with higher visceral fat had lower levels of

adiponectin compared with those with lower visceral fat. These relations were not reported in the lean children. Significant associations between adiponectin and several features of the metabolic syndrome were also established in that systolic and diastolic blood pressure and triglycerides were inversely associated with adiponectin, whereas HDL-C was directly associated. After controlling for adiposity, however, adiponectin levels were significantly correlated only with HDL-C. Collectively, these observations suggest that adiponectin is more than a biomarker of adiposity in youth and may prove to be an important mediator of adiposity-related metabolic dysregulation. Changes in adiponectin levels track closely with changes in body fat and precede changes in insulin sensitivity (169). Adiponectin levels predict the development of diabetes (low levels = increased risk) in Pima Indians (118), but not changes in body weight (182).

SUMMARY Undoubtedly, the number of cytokines produced and secreted by adipose tissue will expand, as will the diverse mechanisms by which these proteins regulate adiposity-related pathophysiology. Very little is known regarding how the pattern of secreted cytokines changes during growth and development or of the role these factors play in regulating the growth process. As a better understanding of these complex and interconnected relations is elucidated, researchers and clinicians may be better able to develop meaningful interventions to help delay or prevent the comorbidities associated with childhood obesity.

The Role of Insulin Resistance

Perhaps the most accepted hypothesis linking adiposity to increased chronic disease risk, and one supported by prospective studies, relates to insulin resistance (40, 148). The following sections review the pediatric evidence relating to the role of insulin resistance in various chronic diseases associated with obesity as depicted in Figure 1.

TYPE 2 DIABETES Insulin resistance is one of two primary features in the pathogenesis of type 2 diabetes; the other feature is impairment of insulin secretion. Prospective longitudinal studies demonstrate that both insulin resistance and diminished insulin secretion are independent predictors of the development of type 2 diabetes in obese adult Mexican American and Pima Indian populations (83, 189). Insulin resistance places increased secretory demand on the pancreatic B cell, resulting in increased compensatory insulin secretion and hyperinsulinemia (39). Although normoglycemia is maintained as long as compensatory insulin secretion is adequate, a relative failure to compensate for insulin resistance with adequate insulin secretion appears to develop in some individuals over time, leading to impairment in glucose homeostasis (19, 39). The cause of beta cell failure in the face of insulin resistance remains unknown, although it may relate to genetic factors or to physiologic events such as the accumulation of amyloid polypeptide in the pancreatic islets (91).

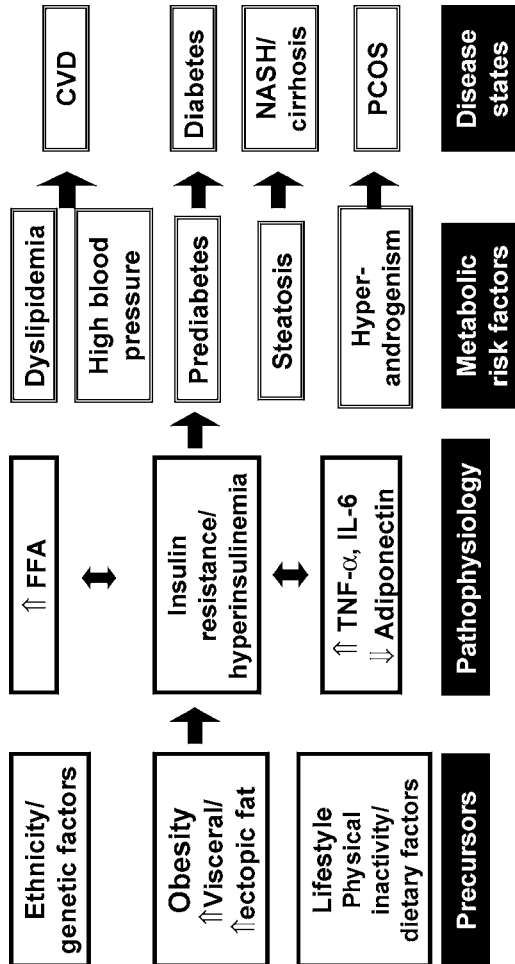


Figure 1 The central role of insulin resistance is highlighted in the proposed relationship between obesity and associated disease outcomes in children.

Early evidence indicates that the pathogenesis of type 2 diabetes in youth is likely to be quite similar to that in adults, albeit with an expression over a more accelerated time course. Studies in children have suggested that both insulin resistance and poor beta cell function may be responsible for dysregulation of glucose homeostasis (69, 166). In a multiethnic clinic-based study of obese children and adolescents, Caprio and colleagues found that insulin sensitivity measured indirectly via the homeostatic model was decreased in children with impaired fasting glucose compared with children with normal glucose tolerance (166). In contrast, among overweight Hispanic children, there were no differences in insulin sensitivity (measured via the frequently sampled intravenous glucose tolerance test and minimal modeling) between impaired glucose- and normal glucose-tolerant obese Hispanic children, but impaired glucose tolerance (69, 166) and impaired fasting glucose (186) were associated with deteriorating beta cell function. Ongoing longitudinal studies of such childhood cohorts should elucidate the relative risk of future development of type 2 diabetes in overweight children with prediabetes.

METABOLIC SYNDROME The role of obesity and insulin resistance in the etiology of the metabolic syndrome has been recently explored in children through cross-sectional and prospective studies (35, 145, 168). The Cardiovascular Risk in Young Finns Study was one of the analyses of the childhood predictors of the metabolic syndrome. To explore this, fasting insulin at baseline was related to the development of the metabolic syndrome [defined as having the three following conditions: high triglycerides and high blood pressure (>75 th percentile) and low HDL-C (<25 th percentile)] after six years of follow up in 1865 children and adolescents (aged 6–18 years) (145). The results from this study showed that baseline insulin concentration was higher in children who subsequently developed the metabolic syndrome, lending support to the view that insulin resistance precedes the development of the metabolic syndrome in childhood (144). Since obesity in childhood is closely associated with insulin resistance, it would have been important to establish if children and adolescents who developed the metabolic syndrome after a six-year follow-up period were also more overweight.

More recently, data from the Bogalusa Heart Study (a biracial community-based longitudinal cohort) was used to disentangle the relative contribution of childhood obesity (measured via BMI) versus insulin resistance (measured via fasting insulin) to the adulthood risk of developing the metabolic syndrome (168). In this study, 718 children aged 8–17 years at baseline were followed for an average of 11.6 years. The metabolic syndrome was defined as comprising the following four factors: BMI, fasting insulin, systolic (or mean arterial) blood pressure, and triglyceride/HDL ratio in the highest quartile for age, gender, ethnicity, and study year (168). Significant positive trends were seen between childhood BMI as well as insulin quartiles and the incidence of clustering in adulthood. Children in the top quartile of BMI and insulin versus those in the bottom quartile were 11.7 and 3.6 times more likely to develop clustering, respectively, as adults. A high childhood BMI was significantly associated with the incidence of clustering in

adulthood even after adjustment for childhood insulin levels. However, in this study, adjustment for childhood BMI eliminated the influence of insulin on the incidence of clustering in adulthood. Thus, in this biethnic, community-based study, childhood obesity (measured via BMI) was more closely associated with the presence of the metabolic syndrome in adulthood than was fasting insulin (168). These findings suggest that obesity in childhood precedes the development of the metabolic syndrome in adulthood.

Although obesity in childhood may be more closely associated than insulin resistance with the development of the metabolic syndrome, the question remains as to why some obese children develop the metabolic syndrome and others do not. The recent NHANES III data on the prevalence of the metabolic syndrome among U.S. adolescents found that approximately 30% of overweight children (BMI > 95th percentile) had the metabolic syndrome, whereas the remaining 70% did not (33). We recently addressed this issue in a cohort ($n = 126$) of overweight Hispanic adolescents (mean BMI percentile 97 ± 2.9 ; aged 8–13 years) with a family history for type 2 diabetes (35). We hypothesized that in overweight Hispanic children, insulin resistance would be more closely associated than overall adiposity with the metabolic syndrome. In this study, insulin sensitivity was measured via the frequently sampled intravenous glucose tolerance test and minimal modeling, and overall adiposity was measured via dual energy X-ray absorptiometry. We found that insulin sensitivity (after adjustment for differences in adiposity) was 62% lower in overweight youth with the metabolic syndrome (defined as having three or more of the following: hypertriglyceridemia, low HDL-C, high blood pressure, high waist circumference, or impaired glucose tolerance) compared with overweight youth without the metabolic syndrome. Furthermore, in multivariate regression analysis, insulin sensitivity, but not fat mass, was independently and negatively related to triglycerides and blood pressure and positively related to HDL-C. These results suggest that the effect of adiposity on lipids and blood pressure control is mediated via insulin resistance.

These findings in overweight Hispanic youth are in agreement with previous results in which directly measured insulin sensitivity has been shown to be independently associated with the separate components of the metabolic syndrome (34, 95, 164). Collectively, these findings in pediatric studies suggest that obesity coupled with insulin resistance may contribute to the development of the metabolic syndrome in childhood.

NONALCOHOLIC FATTY LIVER DISEASE In adults, insulin resistance is regarded as an essential factor for the development of NAFLD, and in turn, NAFLD is considered a feature of the metabolic syndrome (102, 122). Peripheral insulin resistance may lead to steatosis through increased adipose tissue lipolysis and delivery of fatty acids to the liver (156). In turn, excess delivery of free fatty acids to the liver may lead to hepatic insulin resistance, as has been observed in adults with NAFLD (102, 122). Supporting a central role of insulin resistance in NASH is a recent report that treatment with the insulin sensitizer pioglitazone was associated with

improvements in biochemical and histological features of NASH (143). In children, NAFLD has been shown to occur most commonly in conditions associated with insulin resistance, including obesity and type 2 diabetes (11, 146, 159, 175). A recent retrospective study found that children with biopsy-proven NAFLD were almost exclusively obese and had fasting hyperinsulinemia (159). These data suggest that NAFLD in childhood is also associated with an insulin-resistant state and may be a further metabolic abnormality associated with the metabolic syndrome.

POLYCYSTIC OVARIAN SYNDROME The majority of both obese and nonobese women with PCOS are insulin resistant, and the insulin resistance tends to be greater in obese women (41). Obese adolescents with PCOS show greater insulin resistance than those without PCOS matched for total body and abdominal adiposity (116). The relationship of obesity and insulin resistance to the pathogenesis of PCOS is still incompletely understood. The prevailing hypothesis is that insulin resistance resulting in increased compensatory insulin secretion and hyperinsulinemia leads to the hyperandrogenism seen in PCOS through multiple complex mechanisms. Insulin increases the pituitary gonadotrope sensitivity to gonadotropin-releasing hormone, which results in greater luteinizing hormone secretion (1); increases insulin-like growth factor-I binding to the ovary (142), which amplifies the effect of luteinizing hormone on androgen production in the ovary (25); directly stimulates ovarian androgen production via either the insulin receptor or the insulin-like growth factor-I receptor (13); activates ovarian enzymes involved in androgen synthesis (45); and decreases hepatic sex hormone-binding globulin production, resulting in higher free androgen levels (131).

INFLUENCE OF ETHNICITY ON INSULIN RESISTANCE Detailed studies comparing ethnic differences in metabolic risk factors have been helpful in understanding why certain subgroups of the population may be at increased disease risk. Studies in children are of increased significance because they allow examination of potentially underlying biological differences across subgroups of the population in the absence of potential confounding factors such as smoking, alcohol, aging, and menopausal status. Data from the Bogalusa Heart Study were the first to show evidence of increased insulin resistance in African American compared with Caucasian children based on measures of fasting insulin (63). Subsequently, other studies have demonstrated greater insulin resistance and a greater acute insulin response in African American than in Caucasian children (6, 76), and these differences were independent of body fat, visceral fat, dietary factors, and physical activity. Previous studies have shown that African American children have a higher than expected acute insulin response to glucose than do Caucasian children (68); the higher insulin levels in African Americans are partly attributable to increased secretion and a lower hepatic extraction (75, 180) and may have a genetic basis (74).

Studies of obesity, insulin resistance, insulin secretion, and the beta cell response in the Hispanic population are limited, even in adults. The limited studies show that Hispanic adults have greater fasting and postchallenge insulin (82), greater insulin

resistance (83, 85), and a higher second-phase insulin response (28) compared with Caucasians. We recently showed that Hispanic and African American children are equally more insulin resistant than are Caucasian children (70). Interestingly, the compensatory response to the same degree of insulin resistance was different in Hispanic compared with African American children. African American children compensated with a higher acute insulin response to glucose, and this effect was in part due to a reduction in hepatic insulin extraction. Hispanic children compensated to the same degree of insulin resistance with greater second-phase insulin secretion (70). This difference may be the basis that could explain ethnic differences in disease risk profile.

The well-documented ethnic differences in insulin action and secretion could be explained by either genetic or environmental factors. We have been unable to explain the lower insulin sensitivity and higher acute insulin response in African American compared with Caucasian children by factors such as diet, physical activity, and socioeconomic status (108, 117). We have shown that greater African American genetic admixture was independently related to lower insulin sensitivity ($P < 0.001$) and higher fasting insulin ($P < 0.01$) (74). This analysis provides initial evidence that these ethnic differences may have a genetic basis.

In summary, distinct biological differences exist between high-risk ethnic groups, and we have only begun to scratch the surface of this concept. One clear finding is that minority children are more insulin resistant, and this seems to be independent of adiposity and other biological and behavioral factors and could have a genetic basis. From the limited available evidence, it seems that the pathophysiology of obesity-related metabolic conditions, and in particular the compensatory responses to insulin resistance, may be different across the various ethnic groups. These differences are likely to have implications for the development of effective intervention strategies that may need to be focused on ethnic-specific and/or target-specific metabolic factors.

THE INFLUENCE OF PUBERTY ON INSULIN RESISTANCE Puberty is associated with rapid and dynamic changes in various metabolic systems, including hormonal regulation, changes in body fat and fat distribution, as well as transient changes in insulin resistance. Several studies have demonstrated that insulin sensitivity decreases at the onset of puberty and recovers by the end of the maturation process (4, 32, 71, 126). In Caucasian children, decreased insulin sensitivity during puberty is accompanied by increased insulin secretion that normalizes as insulin resistance improves near the end of puberty (24). In a large cross-sectional study (164), insulin sensitivity (measured using the euglycemic-hyperinsulinemic clamp) was highest in Tanner stage I and lowest in Tanner stage III (~20% lower than stage I) and near prepubertal levels in Tanner stage V. Using a longitudinal design, we have previously observed (71) that the pubertal transition from Tanner stage I to III was associated with a 32% reduction in insulin sensitivity (measured by the intravenous glucose tolerance test) in Caucasian and African Americans, and this change was consistent across a range of body fatness.

PUTTING IT ALL TOGETHER: THE ADDITIVE EFFECTS In the prior sections, we have reviewed the multiple factors that influence insulin resistance (including ethnicity, puberty, and greater body fat, especially muscle, liver, and visceral fat). These factors seem to have additive and independent effects on insulin resistance. To understand the physiological impact of insulin resistance, Kahn et al. proposed the disposition index that characterizes the hyperbolic relationship between insulin resistance and insulin secretion (Figure 2). Thus, as insulin sensitivity of tissues decreases (i.e., greater insulin resistance), beta cells in the pancreas have to work harder to secrete more insulin. This relationship is characterized by a hyperbola. Figure 2 demonstrates hypothetical examples in the pediatric population at various degrees of insulin resistance. At the tail end of the hyperbola, very large decreases in insulin sensitivity are associated with very small requisite increases in insulin secretion. At the other end of the extreme, the same relative reduction in insulin sensitivity requires a huge increase in insulin secretion. Thus, overweight minority children are operating in the zone of the hyperbola where periods of exposure to insulin resistance (e.g., due to more weight gain or due to puberty) will have a significant impact on insulin secretion. These requisite increases in insulin secretion are hypothesized to lead to beta cell exhaustion over time in predisposed individuals.

Figure 2 also demonstrates that a key feature of effective interventions to improve metabolic health is based on a focus to decrease insulin resistance to move individuals into the “safe zone” of the hyperbola. In the sections that follow, we review various strategies to accomplish this aim that move beyond traditional energy balance/weight loss strategies.

PREVENTION AND TREATMENT OF THE METABOLIC CONSEQUENCES OF OBESITY IN CHILDREN AND ADOLESCENTS

The increased prevalence and incidence of pediatric overweight over the past 15 to 20 years has prompted health organizations and scientific associations to advocate for increased attention, resources, and research to address this emerging health crisis through prevention and treatment initiatives. Numerous reviews have been published, highlighting promising research and underscoring the need for additional study of pediatric overweight prevention and treatment strategies. However, there are very few examples of intervention studies designed specifically to address the underlying metabolic abnormalities. Most typical “weight management” programs for youth have been based on the traditional “energy balance” model and used restrictive diets, behavior modification techniques, physical activity, and/or drugs, but these approaches have generally not been successful and don’t necessarily address insulin resistance and the underlying risks beyond weight loss. In addition, a recent study shows that dieting approaches are generally ineffective in children and adolescents and may actually promote weight gain (57). Thus, as was

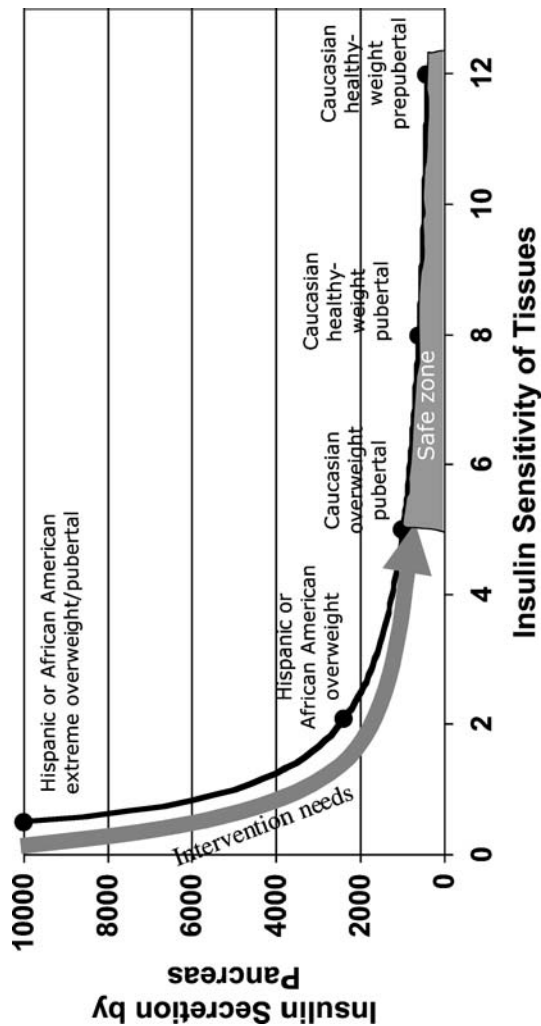


Figure 2 Hyperbolic relationship between insulin sensitivity and insulin secretion. This figure demonstrates examples at various degrees of insulin resistance and the focus of interventions to improve insulin resistance and secretion.

concluded in a recent *Cochran* review, conventional approaches targeting weight management in children have not been effective (173). The purpose of the discussion that follows is to review intervention studies that have addressed metabolic abnormalities related to obesity and aimed to reduce chronic disease risk beyond weight reduction.

Studies Using Physical Activity

In adults, regular physical activity and high levels of physical fitness are associated with reduced chronic disease risk (67, 92, 100, 105, 106), but much less research has examined this issue in children and adolescents; a summary of findings is presented below with a focus on effects on reducing chronic disease risk.

Cross-sectional studies in pediatrics have shown a positive influence of activity/fitness on disease risk (107, 158), whereas others show no effect (12, 81). Unfortunately, few intervention studies have been conducted in youth to examine the effects of physical activity/exercise on chronic disease risk reduction. Ferguson et al. (54) reported that four months of intensive aerobic-type exercise training without dietary intervention (five days/week for four months; 40-minute training sessions at a heart rate >150 beats per minute) in obese boys and girls ($n = 79$) resulted in significant decreases in percentage body fat as well as fasting insulin and triglyceride levels in comparison with control children. Although the authors were unable to determine whether reductions in insulin and triglyceride levels were a result of parallel decreases in body fat, these findings support the notion that increases in physical activity can lead to improvements of metabolic risk profile in overweight children. However, in another study from the same group, a comparison of 10-week programs for 7- to 11-year-old obese African American girls (79), neither aerobic training ($n = 12$) nor lifestyle education ($n = 10$) led to improvements in fasting insulin levels. Although some other investigations (99, 185) in youth provide evidence that increased physical activity can lead to improvements in the metabolic and cardiovascular risk of overweight children, the mechanisms of these improvements remain largely unclear. Furthermore, it has yet to be determined whether improvements in risk profile lead to decreases in future diabetes and/or cardiovascular disease outcomes.

Although most studies in pediatrics have implemented aerobic training as a modality of exercise, evidence from adults (21, 22, 155, 178) suggests that incorporation of strength training (resistance training) may be important for improving insulin sensitivity, body composition (increased muscle mass and decreased fat mass), and fat redistribution (reduced visceral fat and IMCL). Resistance training has also been shown to improve insulin sensitivity and glucose regulation in adults with impaired glucose tolerance or type 2 diabetes (36, 42, 167). However, further studies are needed to identify whether these effects are mediated through changes in body composition or through other mechanisms. One previous study (141), for example, showed that improvement in insulin sensitivity after resistance training disappeared once the data were normalized for fat-free mass, a finding that

suggests the increased glucose disposal rate was due to a mass effect rather than an alteration in the intrinsic properties of the skeletal muscle.

Resistance training therefore may be an important exercise modality for overweight youth. Several organizations, including the American Academy of Pediatrics, have recently endorsed resistance training (with appropriate supervision and instruction) as a safe activity for children and adolescents as a means of improving strength and decreasing risk of sports-related injuries (51). However, to date, most studies of resistance training in younger populations have focused on issues related to safety, strength improvements, and musculature changes (53, 52). One prior study examined a six-week program that combined a dietary intervention (low energy, 20%–25% calories from fat, high in complex carbohydrate) with strength training in obese children (174). This study focused on lipid profile, which improved after the intervention (6% reduction in total cholesterol). We previously conducted a resistance training trial with 12 overweight Caucasian girls (178, 179). This study showed that resistance training (20-minute sessions, three days/week for five months) led to increased strength and improvement in visceral fat. Small improvements in glucose tolerance and insulin levels (determined using an oral glucose tolerance test) were noted, but these changes did not achieve statistical significance. In one other study recently completed (162), 16 weeks of twice-per-week progressive resistance training in Hispanic males (15.2 ± 1.7 years, Tanner stage 3–5, BMI percentile = 97.7 ± 2.8) led to a significant increase in insulin sensitivity in the training group by $45.1 \pm 24.2\%$ versus no change in the control group ($-0.8 \pm 40.7\%$). The between-group difference in change score was highly significant ($p < 0.001$).

Given the increasing prevalence rates of pediatric obesity and diabetes in this population and the potential for resistance training to improve parameters related to glucose homeostasis, further studies using this approach seem warranted. Moreover, resistance training may be a practical form of exercise, especially for very overweight children who may be extremely challenged by the difficulty in performing typical aerobic exercise interventions. In contrast, it seems very likely that overweight children who participate in resistance training will experience success and quick results that will encourage them to continue in an intervention.

In summary, current research suggests that physical activity interventions in overweight youth are efficacious for improving overall body composition (113), and perhaps more importantly, may improve the disease risk profile of overweight children (54, 78, 99, 177, 184). Further research is warranted to address the many questions that remain regarding the optimal frequency, intensity, duration, and mode of activity necessary to invoke risk profile improvement.

Dietary Approaches

The most successful long-term studies of obesity reduction in children have been reported by Epstein et al. (47). The dietary components of these family-based behavioral interventions have used what is called the “Traffic Light Diet, Food Guide Pyramid,” which differentiates food choices primarily based on fat content.

Other expert dietary recommendations for children have been nonspecific and have promoted well-balanced, healthy meals based on the food pyramid (15), nutritionally balanced meals to support growth (31), and a general emphasis on reduction in dietary fat intake rather than on types of fat or carbohydrate in the diet. Current clinical treatment guidelines therefore are generally based on empirical evidence and expert opinion (14).

Remarkably few studies have examined nutritional approaches for reducing obesity and chronic disease risk factors in children. Most studies have focused on diet and weight loss and have been conducted in Caucasian children. In terms of risk reduction, most previous studies have examined dietary intervention for lipid improvement in children. The Dietary Intervention Study in Children (DISC) examined the effects of nutrition education on lipid profiles in 663 children, mostly Caucasian, over three years (134). There was a small but significant 8% reduction in LDL-cholesterol, which was sustained two years after the intervention ended. However, a general trend of increasing triglyceride levels was identified in both the control and intervention groups, which indicates that other dietary combinations may be needed to obtain beneficial effects on multiple risk factors. Another large trial (Child and Adolescent Trial for Cardiovascular Health, or CATCH) sought to improve diet and physical activity in a national study involving 5000 children from approximately 100 schools. Despite improvements in diet and physical activity in schools, CATCH had very limited effects on overall dietary intake and physical activity and no significant changes were achieved in obesity measures, blood pressure, or cholesterol (121).

Based on our review of the literature we conclude that more specific, targeted, and individualized dietary approaches are needed for risk reduction in overweight children. Specifically, good evidence suggests that modification of the types and quality of carbohydrates in the diet may be effective for improving insulin sensitivity and reducing insulin secretion and may contribute to weight loss. This dietary strategy may be more effective than previous interventions to reduce calories and/or proportion of calories from carbohydrate in the diet (89). In particular, diets enriched with whole-grain carbohydrates, foods that elicit a lower glucose response, and foods higher in fiber have been shown to have beneficial effects. In a cross-sectional study in adolescents, whole-grain intake was associated with a lower body mass index as well as improved insulin sensitivity (170). In addition, epidemiological studies show that intake of whole grains is associated with protection from type 2 diabetes (127) as well as coronary artery disease (171). Dietary fiber, especially soluble fiber (e.g., psyllium), has beneficial effects on blood glucose control and blood lipids (38, 94, 119). Fiber intake also has beneficial effects on regulating food intake (by inducing satiation and satiety) and can improve glycemic control and reduce lipids (120).

These carbohydrate effects may work through improvement in the glycemic load (a measure of how much glucose is released into the blood after ingestion of a particular food). Foods with a low glycemic value have been hypothesized to be beneficial for reducing risk for type 2 diabetes because they reduce

the demand for high levels of insulin secretion (89). In both short-term (44) and long-term (43) studies in obese children, a low glycemic index has been shown to reduce plasma glucose and improve insulin resistance. An additional benefit is that voluntary food intake tends to be lower after consumption of foods with a low glycemic index (152). A recent 12-month intervention in obese children showed that promotion of a diet with a low glycemic index led to greater weight loss and improvement in insulin resistance than promotion of a typical low-fat diet (43). Another study in children has shown that a low-glycemic-index breakfast meal led to a reduced calorie intake in lunch (183). Previous studies that have modified the glycemic index of foods while retaining a Hispanic-style diet have been successful in improving glucose control and lipids in Hispanic patients with type 2 diabetes (96, 97). The low-glycemic-index approach also tackles the issue of soda and juice intake. Replacement of sugary drinks with water or lower-sugar versions may also result in improved glucose control. In fact, a recent school-based intervention that promoted water intake and reduced consumption of sugared beverages led to significant improvements in fasting glucose and insulin response (151).

Pharmacological Approaches

Although no medications are currently approved for the management of pediatric overweight (because of safety concerns), pharmacotherapy may be appropriate in overweight youth with comorbidities (e.g., prediabetes, sleep apnea) that increase health risk.

As with dietary and physical activity interventions in overweight youth, most interventions using pharmacotherapy have targeted weight loss. In a randomized and controlled study (137), Orlistat (a gastrointestinal lipase inhibitor) decreased BMI in obese adolescents to a greater degree in the experimental group than in the control group ($-4.09 \pm 2.9 \text{ kg/m}^2$ versus $+0.11 \pm 2.49 \text{ kg/m}^2$, respectively; $p < 0.001$). In another trial (123) of 20 adolescents (mean age 14.6 years, mean BMI 44), orlistat (120 mg) was administered three times daily with a multivitamin and a behavioral program (this was not a randomized study). Gastrointestinal side effects similar to those in adults were observed, and these decreased with time. The main outcomes were also similar to those of adults (4% weight loss and 21 mg/dl reduction in cholesterol, 17 mg/dl reduction in LDL-C, 14 uU/ml reduction in fasting insulin, and 15 mg/dl reduction in fasting glucose). In the concluding words of the authors, "Short-term treatment with orlistat, in the context of a behavioral program, is well-tolerated and has a side-effect profile similar to that observed in adults, but its true benefit versus conventional therapy remains to be determined in placebo-controlled trials."

The other FDA-approved drug for obesity, sibutramine, has also been tested in adolescents in a randomized double-blind study ($N = 82$; 13–17 years of age). This study compared a 6-month behavior intervention with placebo versus behavior intervention with sibutramine (17). There was significantly greater weight loss with the drug (8% versus 4%), but medication had to be reduced or discontinued

in 33 patients to manage increases in blood pressure or other symptoms. The authors concluded, "Until more extensive safety and efficacy data are available, medications for weight loss should be used only on an experimental basis in adolescents and children." Thus, the studies show that the general responses to these drugs in terms of safety and efficacy are similar in children and adults, and more additional longer-term safety/efficacy data are needed.

Few pharmacological studies have targeted the underlying insulin resistance associated with obesity. In one study, metformin, an insulin-sensitizing drug used for the treatment of type 2 diabetes in both adults and children, was used to treat overweight youth with a family history of type 2 diabetes and hyperinsulinemia. In a double-blind controlled trial in 29 obese adolescents (64), metformin (500 mg twice/day, administered for six months) resulted in significant improvements in body mass index and fasting insulin but not in insulin sensitivity. In another study, metformin was shown to improve insulin sensitivity and lower plasma total and free testosterone in obese adolescent girls with PCOS (8). Other agents that may prove beneficial in the treatment of insulin resistance in high-risk youth are the thiazolidinediones, which are much more potent insulin sensitizers than metformin. Thiazolidinediones have been shown to improve insulin sensitivity, glucose tolerance, and cardiovascular risk factors in nondiabetic obese subjects with impaired glucose tolerance (5).

In summary, pharmacotherapy may be indicated in children with comorbidities and in cases in which attempts to improve risk through lifestyle interventions have failed. Well-designed randomized controlled studies of the safety and efficacy of pharmacological agents in pediatrics are needed.

SUMMARY AND IMPLICATIONS: CONCEPT OF MULTIPLE TARGETS FOR TREATMENT AND PREVENTION

Most prior interventions for treating and preventing obesity in children have traditionally targeted body weight/body mass index through conventional approaches based on the energy balance model. Several arguments against this approach can be made. For example, it may take generations to reverse the population BMI trend, short-term weight loss may be effective but is not usually sustainable, and weight loss per se does not necessarily address health and metabolic risk factors. Finally, evidence suggests that a focus on body weight in children and adolescents is not effective. In a large cohort study, children who reported more dieting attempts were more likely to gain weight over a three-year period (57). Thus, the risks of a focus on weight loss in children and adolescents include greater weight gain, lower self-esteem (due to repeated failures), and body image and eating disorders.

Interventions designed to target specific metabolic factors/health outcomes may be more effective, especially in high-risk groups with elevated metabolic risk factors. One approach based on the centrally mediating role of insulin resistance, for

example, is to identify interventions for improving insulin sensitivity and reducing insulin secretion. Improvement in insulin resistance may be an efficient intervention strategy because this addresses multiple risk factors, targeted through one common mechanism. It remains to be tested, for example, whether improvement of insulin resistance can lead to reduced risk of type 2 diabetes and cardiovascular disease over and above any effects on risk reduction through weight loss.

Alternative diet and exercise strategies can be designed around this concept. For example, traditional dietary approaches (e.g., reduced calorie, low fat, and low carbohydrate) generally have been designed to lead to weight loss and have failed to recognize the data suggesting that the quality and type of fats and carbohydrates are more important than the amount in affecting metabolic outcomes and thereby potentially improving risk factors associated with obesity. For fat, replacing foods high in saturated fat and trans fats with foods rich in plant-based fat sources (MUFAs and PUFAs; nuts, fish, soy) may be effective. For carbohydrate, data are beginning to show that replacing sugary foods based on simple/processed carbohydrates with foods high in whole grain/unprocessed carbohydrates, fiber, and low glycemic index value may be effective not only for weight loss but also for disease risk reduction.

The purpose of this review was to summarize the negative health outcomes associated with obesity during childhood and to review the case for insulin resistance as a potentially mediating factor in this relationship. We presented existing data showing the efficacy of intervention strategies that also address risk factor reduction, beyond weight loss. Our general premise does not exclude any focus on body weight, but suggests a focus on multiple targets. Indeed, the emphasis on risk reduction (rather than weight reduction) may be more effective in the long run because it may take the patient's focus off body weight, a focus for which self-efficacy and outcome expectancy may not be optimal.

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