Metabolic Complications of Childhood Obesity

Identifying and mitigating the risk

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The growing number of obese children and adolescents across the world creates a diagnostic challenge to caregivers. The early clinical manifestations of abnormalities related to childhood obesity, attributed to obesity-driven insulin resistance, are impaired glucose metabolism and nonalcoholic fatty liver disease. Both have no symptoms and demand a high index of suspicion and the proper choice of tests for establishing the diagnosis. The clinician should gather information derived from thoroughly taken history and a focused physical examination to stratify patients by their risk. Focused lifestyle modification–aimed interventions are showing promising results in improving the metabolic profile of obese children. Early diagnosis may help allocate resources for intensive interventions that may benefit individuals at greatest risk for early obesity-related morbidity.

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The rise in the prevalence of obesity in children and adolescents is one of the most alarming public health issues facing the world today. Although in the U.S. the problem of childhood obesity affects all racial and ethnic groups, African-American and Hispanic youth have shown the greatest increases in the prevalence of obesity over the last decade (1). As the prevalence of childhood obesity increases, its health implications are becoming more evident (2). The earliest alterations are abnormalities of glucose metabolism that can lead to type 2 diabetes. Obesity is associated with significant health problems in children and is an early risk factor for much of adult morbidity and mortality (3). Importantly, childhood obesity tends to track to adulthood and thus represents an early beginning of a potentially lifetime pathological process (4). Many of the metabolic and cardiovascular complications of obesity have their origins during childhood and are closely related to the presence of insulin resistance/hyperinsulinemia, with the most common abnormality associated with obesity. The obesity-related morbidities that emerge early in childhood are an alteration in glucose metabolism and fatty infiltration of the liver (nonalcoholic fatty liver disease [NAFLD]). Although an accelerated atherogenic process is present, the clinical manifestations of cardiovascular disease do not appear in the pediatric age-group. The problematic aspect of diagnosis and risk assessment arises because both impaired glucose tolerance (pre-diabetes) and NAFLD are conditions with no clinical manifestations, and their diagnosis depends on the right choice of screening and diagnostic tests.

As overweight and obese children and adolescents are so commonly seen, the clinician is faced with the challenge of identifying individuals at greatest risk for morbidity. Interventions to halt weight gain and promote weight loss in children are of limited success and demand significant resources and continuous follow-up and monitoring (5). This puts the caregiver in the dilemma of where to allocate the limited available resources and who among the continuous flux of obese children will benefit most from a focused therapeutic and/or behavioral intervention.

IMPACT OF GENETIC, INTRAUTERINE, AND CHILDHOOD FACTORS

— The importance of obtaining a meticulous history of the obese child's prenatal period, early childhood, and family history cannot be overemphasized. It is well established that traits and components of the metabolic syndrome tend to cluster in families. In comparison to children whose parents do not meet the criteria for the metabolic syndrome, individuals with at least one parent who meets the criteria for the syndrome have a significantly increased odds ratio for having abdominal obesity, for having high triglycerides, and of meeting the pediatric criteria for the syndrome (6). Whereas the heritability of the syndrome itself has been reported to be in the range of ~25%, heritability of some of its individual components may be as high as 60% (7). Positive family history of type 2 diabetes has been associated with early alterations in glucose metabolism—mainly reduced insulin sensitivity and a low disposition index (8). Youth with type 2 diabetes have been reported to have a first- or second-degree relative with diabetes 75–100% of the time (9). In the National Heart, Lung and Blood Institute Family Heart Study of 445 families, genetic correlations between BMI, waist circumference, HDL cholesterol, triglycerides, insulin, and plasminogen activator-1 antigen were found (10). A positive family history of cardiovascular disease at an early age, type 2 diabetes, hypertension, or dyslipidemia, specifically in a parent that is not necessarily obese, may

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Abbreviations: ALT, alanine transaminase; IGT, impaired glucose tolerance; IMCL, intra-myocellular lipid; NAFLD, nonalcoholic fatty liver disease.

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suggest that the child already is at risk for the development of adverse outcomes and that the addition of obesity may add a major metabolic burden and thus promote and accelerate pathological processes even more.

A history of being born small for gestational age has been shown to be an independent risk factor for the development of insulin resistance and the metabolic syndrome in adulthood (11). Insulin resistance seems to be the key element driving the development of the pathophysiological processes leading to the development of altered glucose metabolism, dyslipidemia, and hypertension. Newborns who are born small for gestational age suffered from a period of limited nutritional resources and/or of the effect of other stressogens during the intrauterine period. The period of exposure to limited energy resources is followed by a postnatal period of "catch-up growth" resulting from a practically limitless supply of calories. These intrauterine and postnatal growth patterns possibly cause a programming of specific genes in multiple tissues that promotes efficient energy storage, which in the context of energy surplus, may lead to early development of insulin resistance. Of note, not all individuals born small for gestational age will develop the metabolic syndrome in adulthood; thus, a complex interaction of early intrauterine exposures, specific genetic susceptibility, and several environmental factors may all have independent and cumulative contributions to the development of the metabolic syndrome in adulthood.

A history of maternal gestational diabetes also has significant implications for the offspring. Independently of the genetics that predispose individuals to develop type 2 diabetes, the intrauterine exposure to hyperglycemia and hyperinsulinemia probably has a genetic "programming effect" that affects later extra-uterine energy balance. Maternal gestational diabetes is associated with adiposity and higher glucose and insulin concentrations in offspring girls, as early as at the age of 5 years (12). There appears to be a U-shaped relationship of birth weight and type 2 diabetes, with children at either end of the spectrum at higher risk. In the Pima Indian population, it has been shown that offspring born after their mother developed diabetes were more obese as children and more likely to have diabetes in their 20s than their siblings who were born before their mothers developed diabetes (13). The absence of a similar phenomenon in offspring of diabetic fathers suggests a "programming effect" characteristic of the diabetic intrauterine milieu.

Another factor that has to be taken into consideration when assessing children and adolescents is their stage of pubertal development. Mid-puberty is characterized by a reduction of peripheral insulin sensitivity by ~30% (14), thus adding further demand on the β-cell.

IMPACT OF RACE AND ETHNICITY

— The rise in the prevalence of obesity in children and adolescents in the U.S. is significantly more pronounced in youth of ethnic minorities, specifically Hispanics and African Americans. In parallel to the rise of the prevalence of obesity, the emergence of type 2 diabetes in the pediatric age-group is more common in ethnic minorities (15). One of the putative explanations for the effect of ethnicity is that youth of ethnic minorities are more obese and more insulin resistant in comparison to their Caucasian peers (16). Obese African-American and Hispanic children and adolescents with normal glucose tolerance have been shown to have an increased acute insulin response and reduced insulin clearance per given degree of insulin sensitivity in comparison to Caucasians (17–19). This suggests that youth of ethnic minorities have greater β-cell demand to secrete adequate amounts of insulin as well as greater circulating insulin concentrations in the face of equal degrees of insulin sensitivity in comparison to Caucasians. While the former may facilitate increased stress and earlier β-cell failure, the latter may be the culprit of several of the components of the metabolic syndrome and enhance a vicious cycle that promotes further weight gain (20). Dyslipidemia related to insulin resistance is typically characterized by low HDL cholesterol and high triglyceride concentrations (21,22) and is known to increase cardiovascular disease risk (23). de Ferranti et al. (24) found that low HDL and hypertriglyceridemia are the most prevalent metabolic abnormalities present in adolescents from a population-based cohort. As in adults, hypertriglyceridemia and low HDL were most common among Caucasians and least common among African Americans (25). Components of the metabolic syndrome seem to differ between children and adults of different ethnic background, since African Americans have a greater prevalence of hypertension and a seemingly lower prevalence of dyslipidemia (26). These differences remain after adjustment for differences in dietary factors (27). The higher triglyceride levels observed in Caucasian youth seem to result from differences in VLDL subclasses, specifically greater large VLDL particles (28). African Americans have also been shown to have larger LDL particles in comparison to their Caucasian peers (29). Similarly, African Americans have a lower prevalence of NAFLD in comparison to Caucasians (30). In contrast to their seemingly favorable lipid profile, African-American children and adolescents have a greater systolic blood pressure per given degree of obesity and display differences in renal handling of potassium (31).

Recent studies indicate that the rise in the prevalence of the metabolic syndrome alongside the rise in obesity is affecting the Asian pediatric population as well (32). As Asians differ in their body composition and lipid partitioning pattern, their risk for the development of adverse cardiovascular outcomes begins to rise at lower BMI thresholds (33). These observations imply that obese children and adolescents of different ethnic and racial background cannot be assessed for metabolic risk by using a single risk assessment tool. The clinician taking care of obese children and adolescents should thus take into account their specific vulnerabilities and typical clinical manifestations, based on their race and ethnicity. Whereas severe obesity may be a universal risk factor in all children, lower degrees of obesity may put specific children, such as those of Asian ancestry, at risk earlier than others and should thus be dealt with earlier. Dyslipidemia should similarly be seen in the context of ethnicity, and African-American thresholds that confer metabolic risk may be lower than those used for the other ethnicities. Further studies are needed to evaluate the utility of lipid particle subclasses in the assessment of obese children and adolescents.

IMPACT OF THE DEGREE OF OBESITY

— Classification of the degree of obesity in adults considers a BMI >30 and <35 kg/m^2 as class 1 obesity, BMI 35–39.9 kg/m^2 as class 2 obesity, and BMI ≥ 40 kg/m^2 as class 3 obesity (34). Numerous reports have shown that in adults, as the degree of obesity increases, so does the risk for the development of cardiovascular disease, type 2 diabetes, overall mortality, and even cognitive deterioration. At present, no classifications

for the degree of obesity exist for children and adolescents, except for the definition of individuals whose BMI is between the 85th and 95th percentile as "at risk for overweight" (equivalent to overweight in adults) and those at >95th percentile as "overweight" (equivalent to obese in adults). Similar to adults, several studies have recently shown that the degree of obesity has a similar adverse impact on the metabolic profile of obese youth, although no sub-categorization of the degrees of obesity within the upper five percentiles exists. Weiss et al. (35) divided obese children and adolescents to moderately (BMI *z* score of 2–2.5, corresponding to the 97th to the 99.5 percentile) and severely (BMI *z* score >2.5, corresponding to the 99.5 percentile) obese and compared them with overweight and nonobese youth. In that study, increasing obesity categories in children and adolescents were associated with worsening of all components of the metabolic syndrome. Specifically, an increase in fasting glucose, fasting insulin, triglycerides, systolic blood pressure, and the prevalence of impaired glucose tolerance and a decrease of HDL cholesterol were observed as the degree of obesity rose. The prevalence of the metabolic syndrome was ~30% in the moderately obese participants and nearly 50% in severely obese participants. When C-reactive protein and adiponectin, used as adverse and protective biomarkers, respectively, were tested, C-reactive protein was positively and adiponectin was negatively related with the degree of obesity. C-reactive protein serves as a surrogate of the subclinical inflammation typical of obesity. Low adiponectin is known to be associated with reduced insulin sensitivity and adverse cardiovascular outcomes. Thus, adverse biomarkers were already present in obese children and adolescents, and their degree worsened with increasing obesity. Freedman et al. (36) stratified the Bogalusa cohort participants according to discrete percentiles above the 90th for BMI. They found that individuals in the 99th percentile for age and sex had a much greater prevalence of biochemical abnormalities associated with the metabolic syndrome and had a very high predictive value for adult BMI of >35 kg/m^2. The only longitudinal study published thus far on the natural history of normal and impaired glucose tolerance (IGT) in children and adolescents showed that in children with IGT who had greater degrees of obesity at baseline and those who continued to gain weight rapidly developed type 2 diabetes (37). Moreover, baseline degree of obesity was a strong predictor of deteriorating glucose tolerance over time in both individuals with normal or impaired glucose tolerance. This longitudinal assessment was held in a standard care clinic setting in which patients were seen biannually and received dietary and physical activity guidance and recommendations. Thus, the implications of these studies is that, among obese children and adolescents, individuals at the 99th percentile in the "severely obese" category are an extremely high-risk group for the presence of components of the metabolic syndrome, adverse biochemical biomarkers, future class 2–3 obesity in adulthood, and progression to diabetes.

IMPACT OF LIPID PARTITIONING

— Although obesity is the most common cause of insulin resistance in children and adolescents, some obese youth may be very insulin sensitive and thus be at reduced risk for the development of the adverse cardiovascular and metabolic outcomes driven by insulin resistance. In a study aimed at discovering the underlying pathophysiology of altered glucose metabolism in obese children and adolescents, it was clearly demonstrated that individuals with IGT were significantly more insulin resistant than individuals with normal glucose tolerance, despite having an overall equal degree of adiposity (38). The difference in insulin sensitivity was attributed to different patterns of lipid partitioning. Individuals with severe insulin resistance were characterized by increased deposition of lipid in the visceral and intra-myocellular compartments.

Increased intra-myocellular lipid (IMCL) deposition has been shown to occur early in childhood obesity and be directly associated with peripheral insulin sensitivity (39). Importantly, not all obese children have increased IMCL levels, and those who do not are much more insulin sensitive (40). Offspring of diabetic parents have been shown to have lower mitochondrial content in skeletal muscle and that is postulated to predispose them to increased lipid accumulation within the myocyte (41). Fatty acid derivates of the stored IMCL cause a disturbance of the insulin signal transduction pathway, eventually leading to reduced glucose uptake (42). Thus, a tendency for increased IMCL deposition, which is partially genetically determined, predisposes individuals to greater insulin resistance, while obesity with low IMCL deposition seems to be more "metabolically benign". A paradoxical observation in this context is that an increased amount of lipid droplets is present in the myocytes of trained athletes, who have very high peripheral insulin sensitivity (43). Possibly, the availability of lipotoxic fatty acid derivatives may be influenced by the size of the lipid droplets and their location within the cell in relation to other cytosolic structures, such as the mitochondria and nucleus (44).

Increased visceral adiposity has also been shown to be related to a greater atherogenic metabolic profile in childhood (45). Visceral fat has been shown to be related to greater insulin resistance and lower insulin secretory response in obese children and adolescents (46). Adiponectin levels are lower in obese children with increased visceral fat deposition (47), even when the comparison is made between individuals with similar overall adiposity.

The assessment of IMCL is not feasible on clinical grounds; however, an estimation of visceral fat can be performed using measurement of waist circumference. Although waist circumference pediatric reference charts are not readily available, use of National Health and Nutrition Examination Survey (NHANES) derived data has been shown to be clinically useful in identifying youth at risk for the metabolic syndrome (48). The assessment of waist circumference as well as BMI should both be performed in obese children and adolescents, since the cumulative data may provide a better tool for risk assessment.

ALTERED GLUCOSE METABOLISM IN OBESE CHILDREN

— The rise in the prevalence and severity of childhood obesity has been accompanied by the appearance of a new pediatric disease: type 2 diabetes (2). The prevalence of type 2 diabetes in children and adolescents is increasing in both developed and developing countries (49,50). Although the diagnosis of clinically overt diabetes is not complicated, the diagnosis of IGT depends on the performance of an oral glucose tolerance test in asymptomatic individuals. Although no studies were published regarding the effectiveness of interventions in children with IGT, with appropriate changes in lifestyle and/or pharmacologic interventions, progression from IGT to frank diabetes in adults can be delayed or

prevented (51,52). The prevalence of IGT in obese children and adolescents is reported to be between 10 and 30% in various studies performed in different countries (48,53–55).

It should be emphasized that the majority of children and adolescents with IGT and, even some with silent type 2 diabetes, have normal fasting glucose levels (56). This is probably because obese youth with IGT have marked peripheral insulin resistance, which is mainly at the level of the muscle. The sensitivity of the liver to insulin is relatively preserved at this stage. The American Diabetes Association published screening guidelines for type 2 diabetes in children and adolescents (57) that recommend performing a fasting glucose sample in individuals who meet criteria for obesity and two additional risk factors (positive family history, specific ethnic background, and presence of insulin resistance, as evidenced by acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome). In contrast, the World Health Organization recommends performing an oral glucose tolerance test in individuals at risk. Because the performance of an oral glucose tolerance test is costly and labor intensive, it should be performed on individuals at greatest risk to find IGT (pre-diabetes) and diabetes.

Pre-diabetes is a very dynamic condition. In a study to determine the outcome of IGT with a limited sample size (37), 45% of obese youth with IGT converted to normal glucose tolerance and ~25% progressed to type 2 diabetes over a follow-up period of <2 years. Individuals who converted to normal glucose tolerance were less obese at baseline and gained minimal weight, whereas individuals who progressed to overt type 2 diabetes were more obese at baseline and gained on average ~27 kg over the follow-up time period.

NAFLD IN OBESE CHILDREN

— NAFLD represents fatty infiltration of the liver without excessive alcohol consumption (58). The spectrum of NAFLD ranges from isolated fatty infiltration (steatosis) to inflammation (steatohepatitis, also known as NASH) to fibrosis and even cirrhosis (59). NAFLD is by no means confined to adults, but is now the most common liver disease among obese adolescents in North America (60,61), with similar reports coming from other countries (62,63). NAFLD was found in the Third National Health and Nutrition Examination Survey to be most prevalent in obese African-American and Hispanic males, with type 2 diabetes, hypertension, and hyperlipidemia (64). These associations have led to the hypothesis that NAFLD may precede the onset of type 2 diabetes in some individuals. Although the natural history of NAFLD in children is unknown, it may progress to cirrhosis and related complications (65).

NAFLD is associated with increased visceral fat deposition in adults and children (66). The association between abdominal obesity and fatty liver may be partially explained by sustained exposure of the liver to an increased flux of free fatty acids from the visceral depot (67). NAFLD may represent an early manifestation of ectopic lipid deposition in the liver. It presents a challenge to the clinician because it is asymptomatic for the most part but associated with potential serious long-term outcomes. As the imaging modalities of the liver are improving, future noninvasive quantification of liver lipid deposition may enable detection of early fatty infiltration of the liver.

Screening the obese child for fatty liver infiltration may be accomplished by measuring alanine transaminase (ALT) and γ-glutamyl transferase. However, the sensitivity and specificity of these liver-derived enzymes is limited. To establish the diagnosis, the "gold standard" diagnosis of NAFLD is based on performance of a liver biopsy, an invasive and not routinely used procedure. Thus, the majority of epidemiological studies on NAFLD in children are based on surrogate measures such as ALT levels, alongside ruling out other potential diagnoses. The Third National Health and Nutrition Examination Survey data have shown that 6% of overweight and 10% of obese adolescents have elevated ALT levels (68), whereas a population-based study of autopsies revealed a prevalence rate of 38% in obese children. In an obesity clinic–based cohort, 14% of participants had ALT levels > 35 U/l, but when liver fat content was assessed using magnetic resonance imaging, 32% of participants had elevated liver fat, of whom only ~50% had elevated ALT (66). NAFLD should be suspected in obese children who present in early adolescence with elevated ALT levels and no specific complaints. Physical findings may include hepatomegaly, yet the presence of acanthosis nigricans (69) (in up to 50% of cases) and a positive family history of fatty liver should raise the index of suspicion (70). Because NAFLD can be present without elevated ALT levels (71), the clinician should seek other clues to suspect this diagnosis.

LIFESTYLE INTERVENTIONS FOR OBESE CHILDREN

— Obesity is perhaps the most critical, and potentially modifiable, factor in the development of insulin resistance and type 2 diabetes, and adiposity accounts for ~50% of the variance seen in insulin sensitivity. Adiposity may best be assessed with BMI or measurement of waist circumference. Visceral adiposity appears to be more correlated with basal and stimulated insulin levels and inversely with insulin sensitivity (72). Physical inactivity promotes obesity, insulin resistance, and diabetes, whereas physical activity and exercise reduce these risks. Studies performed in the school setting have shown the beneficial effects of exercise in children and youth. It has been shown that weight loss in obese adolescents improves insulin sensitivity and lowers glucose values (73) and that increased aerobic activity lowers insulin levels regardless of weight loss (74). Because the beneficial effects of both aerobic exercise and resistance training can be short lived, exercise and physical activity must be sustained to optimize health and maintain weight loss.

These data support that lifestyle interventions should be targeted to racial/ethnic minorities, already burdened with diabetes and obesity. Girls, pubertal or prepubertal children, and individuals who are overweight or at risk for being overweight, unfit, and sedentary are the likely targets for such programs and the individuals most likely to benefit if long-lasting behavior change occurs.

THE GOALS OF BEHAVIOR CHANGE PROGRAMS

— The goals of treating overweight or at-risk for overweight children are to decrease body weight, optimize body composition, improve well-being and lifestyle, and prevent or reverse insulin resistance, metabolic syndrome, and diabetes and other related comorbidities. These programs must be comprehensive, focusing on optimizing nutrition and weight loss, increasing physical activity, and inducing behavior change for the child and family. It has been shown that participants in a child and parent weight management program have significantly greater decreases in percent overweight 5 and 10 years postintervention (−11.2 and −7.5%, respectively) than a child-only

group, or a group with variable family participation (75).

Encouraging examples of successful lifestyle modification interventions targeted at obese children and adolescents have recently been described in the literature. In an attempt to treat children at risk for overweight (BMI >85th percentile for age) and who are overweight (BMI >95th percentile for age), the Center at Children's Hospital Los Angeles established a family-centered weight management program called KidsNFitness in 1998. The program involves nutritional education, family therapy, and exercise activities. A recent evaluation of the program (76) demonstrated that at baseline, 49.5% of subjects had multiple risk factors associated with the metabolic syndrome that highly correlated with their degree of insulin resistance and 10% had impaired fasting glucose and/or impaired glucose tolerance. Upon completion of the intervention, 43 subject evaluations showed a statistically significant improvement in BMI (pre: 33.65 ± 1.15 vs. post: 33.19 ± 1.12 kg/m^2, $P < 0.005$), systolic blood pressure (pre: 118.3 ± 2.8 vs. post: 113.3 ± 2.8 mmHg, $P < 0.05$), lipids (total cholesterol pre: 183.0 ± 5.9 vs. post: 171.8 ± 5.3 mg/dl, $P < 0.005$, LDL cholesterol pre: 109.9 ± 4.7 vs. post: 103.3 ± 4.9 mg/dl, $P < 0.05$, and triglycerides pre: 148.1 ± 11.5 vs. post: 120.8 ± 8.7 mg/dl, $P < 0.05$), 2-h postglucose load (1.75 g/kg, max dose 75 g) glucose (pre: 111.5 ± 4.2 vs. post: 102.5 ± 2.5 mg/dl, $P < 0.05$), and leptin levels (pre: 32.0 ± 3.8 vs. post: 26.2 ± 3.0, $P < 0.05$) (18). Similarly, the Yale "Bright Bodies" program is comprised of an intensive family-based program including exercise, nutrition, and behavior modification, bi-weekly for 6 months and bi-monthly thereafter. When comparing >100 obese children and adolescents who completed the program to a group who received standard clinical care, 6-month improvements were sustained at 12 months, including changes in weight (+0.3 [95% CI −1.4 to 2.0] vs. +7.7 kg [5.3 to 10.0]), BMI (−1.7 [−2.3 to −1.1] vs. +1.6 kg/m^2 [0.8 to 2.3]), body fat (−3.7 [−5.4 to −2.1] vs. +5.5 kg [3.2 to 7.8]), and HOMA-IR (−1.52 [−1.93 to −1.01] vs. +0.90 [−0.07 to 2.05]). Thus, a focused intensive lifestyle intervention program for obese children has beneficial effects on body composition and insulin resistance in overweight children that are sustained up to 12 months (77).

While lifestyle interventions are safe and effective, pharmacotherapy must be viewed as an adjunct to lifestyle modification therapy. The use of medication to treat obesity, insulin resistance, and the metabolic syndrome must be done with caution for the following reasons: few drugs are currently approved by the Food and Drug Administration for children, there is no long-term data, lifestyle has been proven more efficacious for diabetes prevention (in adults), and there are few well-controlled scientific studies of safety and efficacy of pharmacological interventions in children. The relative risk for severe adverse events must be weighed against the long-term potential for reduction in obesity-related morbidity and mortality. One must keep in mind that many drugs previously used for the treatment of adult obesity have resulted in side effects and complications.

SUMMARY — The clinician who sees growing numbers of obese children and adolescents should attempt to identify those at greatest risk for the development of early morbidity. The multiple factors that affect "baseline vulnerability" and additional factors determined by history and physical examination should guide the clinician in the risk assessment process. A thoroughly taken pregnancy, postnatal, and family history provides clues to identify individuals predisposed to insulin resistance. Clinical judgment should be used to assess the degree of obesity and to identify greater visceral adiposity, both of which are strongly associated with increased metabolic risk. Importantly, anthropometric data should be interpreted in the context of the appropriate racial or ethnic references, since, for instance, similar degrees of obesity may confer different metabolic risks in children of different races. Screening for clinically silent conditions such as impaired glucose tolerance and NAFLD should be based on a high index of suspicion, using information gathered from history taking and anthropometric parameters. It is imperative that lifestyle interventions focus primarily on individuals at greatest risk. From a public health perspective, these programs need to be part of the school curriculum and available in communities as well as in the clinical setting. The challenging task of risk determination should be a critical focus of primary care and the pediatric endocrinologist.

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