

CARDIOVASCULAR ENDOCRINOLOGY 2

Obesity and Risk of Type 2 Diabetes and Cardiovascular Disease in Children and Adolescents

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Overweight/obesity continues to increase in children and adolescents, and annual obesity-related hospital costs in 6–17 yr olds have reached \$127 million per year. Overweight children and adolescents are now being diagnosed with impaired glucose tolerance and type 2 diabetes, and they show early signs of the insulin resistance syndrome and cardiovascular risk. Several risk factors have been identified as contributors to the development of type 2 diabetes and cardiovascular risk in youth. These factors include increased body fat and abdominal fat, insulin resistance, ethnicity (with greater risk in African-American, Hispanic, and Native American children),

and onset of puberty. There is no clear explanation of how these factors increase risk, but they appear to act in an additive fashion. We hypothesize that the constellation of these risk factors may be especially problematic during the critical period of adolescent development, especially in individuals who may have compromised β -cell function and an inability to compensate for severe insulin resistance. Therefore, the purpose of this paper is to review the pathophysiology of type 2 diabetes and cardiovascular risk in obese children and adolescents. (*J Clin Endocrinol Metab* 88: 1417–1427, 2003)

Scope of problem

Overweight in children is defined by a statistical approach used for the Centers of Disease Control (CDC) 2000 growth charts. The approach is based on standards from five national data sets of height and weight collected before 1980 (1). Overweight is defined as a body mass index (BMI) above the 95th percentile for age and gender, and at risk for overweight is defined as a BMI between the 85th and 95th percentiles for age and gender. In this review, we use a working definition of obesity as a BMI above the 85th percentile for age and gender using the CDC standard data. The most recent estimates of obesity prevalence are based on the National Health and Nutrition Examination Study (NHANES) 1999–2000 data (an ongoing cross-sectional random sample from the United States). These data suggest that 15.5% of 12–19 yr olds studied in 1999–2000 have a BMI above the 95th percentile (age and gender adjusted) for children studied in the 1960s (up from 11% during 1988–1994; Ref. 1). Similarly, 15.3% of 6–11 yr olds in 1999–2000 have a BMI above the 95th percentile (up from 11% during 1988–1994), and 10.4% of 2–5 yr olds in 1999–2000 have a BMI above the 95th percentile (1). Other studies show steady increases in overweight and obesity over the period 1986–1998, especially in Hispanic and African-American children (2). By 1998, the prevalence of a BMI above the 85th percentile for age and gender had risen to 35% in Hispanic and African-American children and just over 20% in Caucasian children (2). Although no national data are available, the prevalence of risk of overweight is also

widespread among Native American children and adolescents, with a population-based prevalence of approximately 20% in Native American schoolchildren aged 5–17 yr (3, 4). The economic burden of childhood obesity, in terms of annual obesity-related hospital costs, has increased 3-fold over the last 20 yr, reaching \$127 million per year (5).

Of even greater concern is the fact that type 2 diabetes has now emerged as a critical health issue in overweight children, especially within minority overweight African-American, Hispanic American, and Native American adolescents (6). Several clinical observations suggest a large increase in the incidence of type 2 diabetes in children and adolescents (6), with one study reporting a 10-fold increase between 1982 and 1994 (7). However, a potential caveat is that this phenomenon could be explained by increased surveillance and improved screening methods in clinical practice. Population-based studies however suggest low prevalence estimates ranging from 0.4% in NHANES III (includes type 1 and type 2 diabetes; Ref. 8) to 5.1% in 15- to 19-yr-old Pima Indians (6). However, there is no thorough population-based screening study based on clinical assessment with the oral glucose tolerance test. This may be important because most studies that have diagnosed type 2 diabetes or impaired glucose tolerance in children and adolescents have done so on the basis of circulating glucose levels after an oral glucose challenge.

More recently, impaired glucose tolerance has also emerged as a major concern in overweight/obese children and adolescents. In a clinic-based study published in 2002 (9), 25% of 55 obese children and 21% of 112 obese adolescents had impaired glucose tolerance (based on a 2-h glucose value > 140 mg/dl during an oral glucose tolerance test). In

Abbreviations: BMI, Body mass index; DEXA, dual energy x-ray absorptiometry; HDL, high-density lipoprotein(s); LDL, low-density lipoprotein(s).

addition, 4% of the sample had undiagnosed type 2 diabetes. Interestingly, an older study from 1968 (10) in a sample of 66 obese children showed that 17% had impaired glucose tolerance, based on the same American Diabetes Association standard definition, and 6% had undiagnosed diabetes. We have also found a high prevalence of impaired glucose tolerance in obese Hispanic adolescents (BMI above the 85th percentile for age and gender) with a family history of type 2 diabetes in Los Angeles County, California. To date, we have screened 110 adolescents aged 8–13 yr using an oral glucose tolerance test and found that 28% have impaired glucose tolerance (based on a 2-h glucose value > 140 mg/dl), yet none have impaired fasting glucose (our unpublished observations). Therefore, impaired glucose tolerance and type 2 diabetes may not necessarily be new phenomena in children, but they are becoming more apparent as we conduct more careful health screening measures. In addition, these risks may be affecting more absolute numbers of children because of the rising prevalence of obesity.

Overweight and obesity in youth are also associated with various risk factors for cardiovascular disease (11, 12) and have been shown to be associated with the early development of atherosclerotic lesions (13). Recently, the Pathobiological Determinants of Atherosclerosis in Youth study, which was designed to examine the effects of risk factors for adult coronary heart disease on atherosclerosis in autopsied persons aged 15–34 yr, reported that obesity (measured via BMI) is associated with accelerated coronary atherosclerosis in adolescent boys and young men (14). These findings, coupled with the continued increase in childhood obesity, could lead to an increase in the incidence of cardiovascular disease in adulthood (15, 16). The Bogalusa Heart study, a community-based study of risk factors for cardiovascular disease in black and white youth, pooled data from 9167 subjects aged 5–17 yr. These investigators found that children with a BMI above the 85th percentile for age and gender were 2.4, 3.0, 3.4, 7.1, and 4.5 times more likely to have adverse levels of cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, and blood pressure, respectively, than normal weight subjects (12). Moreover, obese children have increased levels of hemostatic and inflammatory factors, including fibrinogen, plasminogen activator inhibitor 1, and C-reactive protein (17–19). These factors may contribute to endothelial dysfunction and early atherogenesis in obese youth. Thus, the well known clustering of obesity, hyperglycemia, hyperinsulinemia, dyslipidemia, and hypertension (Syndrome X or the Insulin Resistance Syndrome; Ref. 20) occurs in children (21–23).

Contributing role of body fat

The clearest factor contributing to increased risk of type 2 diabetes and cardiovascular disease in children and adolescents is increased body fat, and possibly specific depots of body fat. Some of the earliest evidence for this came from the Bogalusa Heart study that showed weak, but significant correlations ($r = 0.3$ – 0.4) in children between central body fat (measured by skinfolds) and fasting insulin (24). Later work (25) using more precise measures of body fat found higher

correlations in 10-yr-old children between percentage body fat and fasting insulin (Spearman rank $r = 0.78$). Additional studies using other measures, in addition to fasting insulin, showed that insulin and the insulin-to-glucose ratio were significantly higher in obese *vs.* control 8- to 11-yr-old boys during a 3-h oral glucose tolerance test (26). Other studies demonstrated that the higher fasting insulin and insulin response to a fixed meal in obese adolescent children were not necessarily due to differences in insulin sensitivity as determined from a hyperinsulinemic euglycemic clamp, and that impaired insulin sensitivity is more apparent as the duration of obesity increases (27).

Using euglycemic and hyperglycemic clamp techniques, Caprio *et al.* (28) showed that obese adolescent girls had impaired glucose disposal and failed to increase glucose oxidation and suppress lipid oxidation in response to insulin infusion. This finding has been verified using other measurement techniques and includes studies in African-American (29, 30) and Hispanic (31) children. For example, using the minimal model to assess insulin sensitivity and dual energy x-ray absorptiometry (DEXA) for body fat measures, our group has previously shown high inverse correlations between insulin sensitivity and body fat mass across the spectrum of lean and obese prepubertal boys and girls (32), suggesting that total fat mass is the major contributor to variance in insulin sensitivity in children.

More detailed studies have examined whether specific depots of fat, such as visceral fat, have unique effects on insulin resistance. In a previous study using a multiple regression approach, which incorporated all available measures of body fat into one model, we showed that visceral fat has unique metabolic effects on fasting insulin but not insulin sensitivity and that this effect was independent of other fat compartments (32). In another study, we attempted to examine whether total body fat in general or visceral fat in particular was associated with greater metabolic risk in Caucasian and African-American children (33). The influence of total body fat and visceral fat on insulin parameters was examined by comparing subgroups of children with high or low fat *vs.* high or low visceral fat. In this analysis, we showed that body fat in general is the predominant factor influencing insulin sensitivity, but visceral fat may have additional effects on fasting insulin. Similar effects were shown in a later longitudinal study (34). These data tend to support the hypothesis that in children, total body fat mass may influence insulin sensitivity, whereas visceral fat may influence fasting insulin. Initial evidence from a study in Hispanic children (31) suggests that both total fat and visceral fat contribute independently to lower insulin sensitivity. Thus, the contribution of total fat and visceral fat to insulin resistance may vary across different ethnic groups. In addition, we cannot discount the possibility that the impact of visceral fat may become more substantial later in life as this fat depot increases in greater absolute and relative amounts.

Abdominal obesity in childhood, more so than overall adiposity, is also associated with cardiovascular disease risk factors (35). Central adiposity, measured via skinfolds, waist circumference, and waist to hip ratio, is closely related to adverse lipids and lipoproteins (12, 36) and blood pressure (37). More recently, with the use of imaging techniques, it has

been shown that the relationship between central fat and cardiovascular disease risk factors is due to visceral fat (32, 38, 39). Similarly, in obese prepubertal black and white children, visceral fat but not sc abdominal fat, measured via magnetic resonance imaging, explained a significant proportion of the variance in several lipid/lipoprotein risk factors including LDL particle size (40). The role of visceral fat in determining cardiovascular disease risk factors is not limited to the obese. In a mixed cohort of white and black prepubertal children with a wide range of body fat, we found that visceral fat measured via computed tomography (but not total fat mass measured via DEXA) was positively related to triglycerides and HDL-cholesterol. However, after multiple adjustment for total body fat and insulin sensitivity, the relationship was only significant for triglycerides (32).

There are several potential hypotheses that might explain the link between visceral fat, insulin resistance, type 2 diabetes, and cardiovascular risk (41, 42). One hypothesis relates to the possibility that visceral adipose tissue may secrete or express a factor that influences systemic metabolism, and there is some evidence to suggest that visceral adipose tissue may overexpress certain factors. This hypothesis is supported by the fact that leptin, for example, is more highly expressed in and secreted from sc compared with visceral adipose tissue (43). Furthermore, some cytokines produced by adipose tissue may influence insulin resistance, such as IL-6 and TNF- α (44), and there is evidence to suggest that IL-6 is more highly secreted from visceral compared with sc adipose tissue (45). Other recently discovered adipocyte cytokines, such as adiponectin and resistin, may be involved in the link between increased adiposity, insulin resistance, and increased disease risk (42, 46, 47). Another potential hypothesis linking visceral adipose tissue to risk for type 2 diabetes relates to the effects of free fatty acids released from visceral adipose tissue into the hepatic portal vein with direct exposure to the liver, termed the portal theory (41). This hypothesis is attractive because it has been shown that visceral adipose tissue is more lipolytic and more sensitive to lipolytic stimulation (48). Increased exposure of the liver to free fatty acids increases hepatic glucose production and output of very LDL (via increased triglyceride synthesis), which could in turn result in glucose intolerance and hypertriglyceridemia (49). In addition, free fatty acids may interfere with hepatic insulin extraction (50), which may contribute to increased circulating insulin levels.

There is also growing interest related to the possibility that build up of triglycerides in other organs may contribute to insulin resistance and disease risk, in what has been termed the ectopic fat storage syndrome (42). Lipid accumulation in skeletal muscle may be important in this regard because it is the primary site of insulin action. Studies in adult and animal models show that lipid accumulation in muscle is correlated with insulin resistance (51, 52). Traditionally, lipid accumulation in skeletal muscle has been measured by biopsy samples, but more recently nuclear magnetic resonance spectroscopy techniques have been developed, and these have been used in a few studies in children (53, 54). Ashley *et al.* (54) measured muscle lipid levels by spectroscopy in 41 prepubertal boys, showing correlations with waist circumference ($r = 0.42$), BMI ($r = 0.32$), and the fasting glucose/

insulin ratio ($r = -0.59$). More detailed measures (but in a smaller sample) were examined by Sinha *et al.* (53) who showed that both intramyocellular and extramyocellular lipid accumulation in soleus muscle was greater in 14 obese *vs.* 8 nonobese adolescents. In addition, there was a significant inverse correlation between intramyocellular lipid and insulin sensitivity that persisted after controlling for total body fat and abdominal sc fat ($r = -0.73$), but was only borderline significant after adjusting for visceral fat ($r = -0.54$; $P < 0.08$).

Contributing role of ethnicity

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 (24, 55). Subsequently, other studies, have demonstrated lower insulin sensitivity and a greater acute insulin response in African-American children (30, 32), and these differences were independent of body fat, visceral fat, dietary factors, and physical activity (56). Previous studies in African-American children compared with Caucasian children suggest that the lower insulin sensitivity is associated with a higher than expected acute insulin response to glucose (32), and the higher insulin levels in African-Americans are partly attributable to increased secretion and a lower hepatic extraction (57). These findings have been verified in other groups using the 2-h hyperglycemic clamp (58).

Studies of obesity, insulin resistance, insulin secretion, and the β -cell response in the Hispanic population are limited, even in adults. Compared with non-Hispanic whites, Hispanic adults are reported to have greater fasting and post-challenge insulin (59) and greater insulin resistance (60, 61). However, some previous studies show no difference in insulin action or secretion between Hispanic and non-Hispanic white adults, after adjusting for BMI and waist to hip ratio, suggesting that obesity accounted for this ethnic difference (59). Because only crude anthropometric indices were used in this adjustment, further studies using more detailed measures of body fat would be useful. One prior study in third-grade children in Corpus Christi, Texas (62), showed that Hispanic compared with non-Hispanic white children had significantly higher levels of fasting insulin. However, it was not clear whether this difference remained significant after accounting for differences in obesity, and the outcome measures were limited to fasting insulin and anthropometry.

In a recent study that compared Caucasian, African-American, and Hispanic children in Los Angeles, we showed that Hispanic children are also more insulin resistant than Caucasian children, to an equal degree than African-American children (63). Similarly, this difference in insulin resistance was independent of adiposity (63). 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, as previously observed (57). Hispanic children, on the other hand, compensated to the same degree of insulin resistance with greater insulin secretion (63). Thus, in African-American

cans, there may be a conservation of the need to increase insulin secretion in response to lower insulin sensitivity by the adaptive reduction in hepatic insulin extraction. This modification provides a means to increase peripheral insulin levels without the need to increase secretion. Therefore, in this situation, the acute insulin response may not be indicative of insulin secretion. Hispanic children on the other hand increase insulin secretion to maintain the low insulin sensitivity. In this situation, the requirement to increase insulin secretion to maintain the low level of insulin sensitivity may eventually be a contributing factor to β -cell exhaustion and eventual β -cell failure.

The well documented ethnic differences in insulin action and secretion could be explained by either genetic or environmental factors. In previous studies, we have been unable to explain the lower insulin sensitivity and higher acute insulin response in African-American children compared with Caucasian children by factors such as diet, physical activity, and socioeconomic status (64, 65). More recently, we have examined whether genetic admixture, determined from approximately 20 ancestry informative markers, explained these ethnic differences (66). The analysis indicated that greater African-American genetic admixture was independently related to lower insulin sensitivity ($P < 0.001$) and higher fasting insulin ($P < 0.01$) and provides initial evidence that these ethnic differences may have a genetic basis. In summary, the underlying pathophysiology leading to the development of type 2 diabetes is likely to be different in African-Americans *vs.* Hispanics, and more studies, especially on the potential roles of genetics, environment, and metabolism across different ethnic groups are needed.

Ethnic differences in lipids, lipoproteins, and blood pressure are well documented in adults and begin early in childhood. Most studies have compared cardiovascular disease risk factors in children from the three largest ethnic groups in the United States, namely Caucasians, Hispanics, and African-Americans. Results from several large population studies have found that African-American children and adolescents have higher total cholesterol, LDL cholesterol, and HDL cholesterol than either Caucasian or Hispanic youth, but lower triglycerides (67, 68). Ethnic differences in lipids remained after adjustment for BMI (67), suggesting an intrinsic difference among the races. Studies comparing differences in lipids and lipoproteins between Native American and Caucasian children are limited. One relatively small study that included 103 Native American children and adolescents aged 4–19 found higher total cholesterol and HDL-cholesterol levels in Native American youth in the age group 10–19 yr, compared with Caucasians. However, the data were not adjusted for differences in adiposity despite the fact that Native American youth were heavier (69). Although it is well known that African-American adults have a higher prevalence of hypertension than either Caucasians or Hispanics (70), the age at which this emerges is unclear. Several studies in school-aged children have shown higher blood pressure in African-American children compared with Caucasian and Hispanic children (71, 72), but others have not (73). The lack of consistency between studies could be due to confounding factors such as age and adiposity and requires further investigation.

Contributing role of puberty

Pubertal insulin resistance has been well documented in several cross-sectional studies (74–79). The original observation of pubertal insulin resistance was reported in 1987 when Amiel *et al.* (76) showed that insulin-stimulated glucose metabolism was about 30% lower in a sample of children at Tanner stages II to IV compared with children at Tanner I or adults. Previous cross-sectional reports consistently show that pubertal development is associated with an approximate 25–30% reduction in insulin sensitivity, with the peak reduction occurring at Tanner stage III, followed by a recovery by Tanner stage V (77). One previous longitudinal study looked at 60 children (33 males, 27 females; 32 Caucasians, 28 African-Americans) who were examined at Tanner I (age, 9.2 ± 1.4 yr) and then again after 2.0 ± 0.6 yr of follow-up, by which time 29 children remained at Tanner I, and 31 had progressed to Tanner III or IV (80). Pubertal transition from Tanner I to Tanner III was associated with a 32% reduction in insulin sensitivity and increases in fasting glucose, insulin, and the acute response to glucose. These changes were similar across gender and ethnicity, and the percentage drop in insulin sensitivity was similar in lean and obese children. The increase in the acute insulin response to glucose was not as large as that predicted by the fall in insulin sensitivity, suggesting a conservation in β -cell function or an inadequate β -cell response to the fall in insulin sensitivity. In addition, the magnitude of the reduction in insulin sensitivity was not associated with changes in body fat, visceral fat, IGF-I, androgens, or estradiol.

The regulatory purpose of these changes in insulin action and secretion is not clear; it is thought to be selective for glucose but not protein metabolism (81). These changes may also provide a mechanism for increasing the anabolic effects of insulin and GH during a period of rapid somatic growth (74, 82). It is generally thought that the transient fall in insulin sensitivity in puberty is not related to changes in body fat, because body fat increases continuously before and during puberty, whereas the fall in insulin sensitivity is transient, occurring in midpuberty and recovering to prepubertal levels by the end of puberty (77). However, some studies have hypothesized that the effect may be due to changes in body fat (78, 83) because of the more accelerated increase in body fat that occurs during (compared with before) puberty. Our longitudinal study reviewed above does not support the body fat theory because the percentage fall in insulin sensitivity was similar across lean and obese subgroups of children, and the magnitude of the fall in insulin sensitivity was not correlated with changes in body fat content (80).

Although changes in sex hormones may contribute to pubertal insulin resistance, this theory has not previously been examined in detail. In general, changes in sex steroids are not thought to drive changes in pubertal insulin resistance because sex steroids increase in early puberty and remain high, whereas insulin sensitivity returns to normal levels by the end of puberty. Travers *et al.* (78) compared insulin sensitivity in 50 Tanner stage II boys and girls with 47 Tanner stage III boys and girls. The effect of Tanner stage on insulin sensitivity was only significant in girls, and neither testosterone nor estradiol was correlated with insulin sensitivity.

However, no other hormones were examined. In addition, this study is limited because it only compared Tanner stage II to Tanner stage III, and significant changes may already have occurred by Tanner stage II. In another study, 4 months of testosterone administration to adolescents with delayed puberty led to an increase in fat-free mass (through reductions in protein breakdown and protein oxidation), an increase in circulating testosterone (23 ± 4 to 422 ± 45 ng/dl), IGF-I (210 ± 28 to 505 ± 40 ng/ml), and mean nocturnal GH (2.5 ± 0.5 to 6.0 ± 0.8 ng/ml), but had no effect on insulin sensitivity (84). The lack of effect of testosterone administration on insulin sensitivity in adolescents is consistent with other studies in adults (85).

Alternatively, it has been hypothesized that the fall in insulin sensitivity may be driven by transient changes in GH levels in puberty (84, 86). This hypothesis is attractive because of the increased pubertal secretion of GH (87, 88), leading to increased GH and IGF-I during midpuberty, mirroring the transient changes in insulin sensitivity. In addition, GH-deficient children have increased insulin sensitivity (89), and GH has strong effects on β -cells (90). Also, the increase in GH during puberty may contribute to insulin resistance via its effect on increasing lipolysis and free fatty acid concentration. However, not all studies have found supporting evidence for the GH theory. One study that performed detailed measures of GH (83) found no significant difference across pubertal groups in overnight GH secretion, peripheral GH responsiveness (as indicated by GH binding protein), or GH action (as indicated by circulating IGF-I). However, it may not be appropriate to base conclusions regarding the influence of GH on pubertal insulin sensitivity on these results, because no pubertal change in insulin sensitivity was observed in this study. In the longitudinal study reviewed above (80), there was a large increase in circulating IGF-I during puberty, but this was not correlated with the fall in insulin sensitivity. Further studies with more detailed measures of hormone function are needed to more thoroughly examine the relationship between changes in GH action and insulin action and secretion during puberty.

Given the increased risk of developing type 2 diabetes among different ethnic groups and the likely role of puberty, it is important to study whether the influence of puberty on insulin resistance varies across ethnic groups. In 20 prepubertal and 16 pubertal African-Americans, Saad *et al.* (91) measured insulin action and secretion with the hyperinsulinemic euglycemic clamp as well as body composition (DEXA) and body fat distribution (computed tomography scan). Similar to other cross-sectional studies, insulin sensitivity was 30% lower in pubertal children, but there was no difference in insulin secretion, suggesting a failure in the compensatory response to insulin resistance. In a longitudinal study that included both African-American and Caucasian children (80), there was a 30% drop in insulin sensitivity, but the compensatory increase in insulin secretion was less than expected, with similar changes in both blacks and whites. Further studies across different ethnic groups are needed to determine whether the fall in insulin sensitivity and ability to recover by the end of puberty, as well as β -cell compensation, are needed to examine whether these pubertal changes and ability to compensate/recover play a role in

the increased risk of developing diabetes in some ethnic groups.

Contributing role of low birth weight

Recent studies in Europe, Asia, and the United States have shown that low birth weight increases the risk of type 2 diabetes, dyslipidemia, and hypertension in adults (92–98). The association between low birth weight and increased risk of metabolic diseases later in life has been explained by the thrifty phenotype hypothesis, which proposes that infant malnutrition may contribute to insulin resistance (94), or as a selective survival of small babies genetically predisposed to diabetes and insulin resistance (99, 100). Several recent studies have reported inconsistent effects of low birth weight on insulin resistance among children in different age groups in Caucasians, Asians, Mexican-Americans, Pima Indians, and black South Africans. For example, Yajnik *et al.* (100) reported that low birth weight was associated with increased glucose and insulin concentration 30 min after an oral glucose load in 4-yr-old Indian children. A cross-sectional study in the United Kingdom reported that children who were thin at birth had higher plasma glucose concentration later in life (101). A U-shaped relation between postload glucose concentrations and birth weight was observed among Pima Indians aged 10–14 and 15–19 yr in the United States (102). In another study in 7-yr-old black South African children (103), Crowther *et al.* found that low birth weight and rapid childhood gains in weight predicted glucose tolerance.

We previously examined the effects of low birth weight on aspects of insulin resistance in 139 Caucasian and African-American children (104). Low birth weight was associated with higher fasting insulin and lower β -cell function, but did not significantly influence fasting glucose, insulin sensitivity (assessed by the minimal model), the acute insulin response to glucose, systolic blood pressure, HDL cholesterol, triglyceride, total fat mass, or visceral fat. In addition, there was a more pronounced influence of low birth weight on fasting insulin among African-Americans. The finding that the effect of low birth weight on fasting insulin was more detrimental in African-American children than in Caucasian children indicated that there might be a certain genetic predisposition that makes African-Americans more vulnerable to poor fetal growth, and hence, insulin resistance. Environmental conditions such as physical activity and energy balance or their interactions with genetic factors might also contribute to the higher vulnerability of insulin resistance among African-American children.

Contributing role of physical activity

It is well known, at least from studies in adults, that regular physical activity can reduce insulin resistance, improve glucose intolerance, reduce the risk of type 2 diabetes (105, 106), and reduce cardiovascular risk (107). This effect may act through selective reduction in visceral fat (108), improvements in peripheral insulin resistance (109), or improvement in cardiovascular fitness (110, 111). Several randomized control trials and other interventions in adults have shown that aerobic exercise improves insulin action, even in the face of stable body composition (112). Such changes are shown to

occur relatively quickly (within 1 wk of intervention) and without changes in body composition, suggesting that a training effect and changes in muscle morphology may not be necessary for these improvements to occur (113).

Physical activity and aerobic fitness (114, 115) are positively related to a healthier cardiovascular risk profile in youth, although the relationship may be due, in part, to a shared relationship with body fatness (116). Compared with adults, much less research has examined the influence of physical activity on obesity-related metabolic risk factors in children and adolescents, especially those related to risk for type 2 diabetes. However, the available data suggest that a physically active lifestyle exerts a positive influence. Over a 6-yr period, individuals (12, 15, and 18 yr old at baseline; 18, 21, and 24 yr old at follow-up) consistently categorized as physically active had lower fasting insulin compared with their consistently sedentary peers (117). Although this association was significant for males only, a similar trend was observed in females. In a biracial (Caucasian and African-American) sample of prepubertal 5–11 yr olds, Ku *et al.* (64) found that increased physical activity (hours per week of vigorous physical activity assessed by questionnaire) was related to greater insulin sensitivity, independent of body composition and race. Furthermore, in a large sample of Japanese 6- to 13-yr-old children ($n = 1330$), lower physical activity scores were related to increased fasting insulin levels (118), and although insulin sensitivity (determined by the homeostasis index) did not differ between Japanese male high school students categorized as exercisers ($n = 150$) *vs.* nonexercisers ($n = 114$), a subgroup of exercisers ($n = 62$) who performed highly dynamic exercise possessed greater insulin sensitivity than nonexercisers (119).

Generally, physical activity is positively related to a healthier metabolic profile, although studies using aerobic fitness as a primary outcome have been less conclusive. When the hyperglycemic clamp was used, maximal aerobic capacity did not explain group differences in insulin secretion and sensitivity between Caucasian and African-American children (84). Because group differences were not adjusted for other parameters known to influence insulin sensitivity, such as body fatness, it is unknown whether aerobic fitness differentially influenced insulin dynamics in this biracial sample of children. Gutin *et al.* (25) observed that aerobic fitness (peak VO_2/kg body weight) was inversely related to fasting insulin and positively related to fasting glucose in a sample of Caucasian and African-American 7- to 11-yr-old children. However, in multiple regression analyses, percentage body fat (measured by DEXA) proved to be the only independent predictor of insulin levels. As reported by others (120), this finding suggests that aerobic fitness may be influencing insulin levels indirectly through its impact on body fatness.

Few intervention studies have examined the role of exercise in improving risk factors for type 2 diabetes. However, the literature suggests that metabolic benefits can be gained by youth, especially by those at increased health risk. In a comparison of 10-wk programs for 7- to 11-yr-old obese African-American girls (121, 122), neither aerobic training ($n = 12$) nor lifestyle education ($n = 10$) led to improvements in fasting insulin levels. Both fasting glucose and glycosy-

lated hemoglobin decreased, although group averages were within the normal ranges both at preintervention and postintervention. The decreased glucose levels, considered in combination with similar insulin values (pre *vs.* post) suggest that insulin sensitivity may have improved over the course of treatment, but more specific measures of insulin sensitivity were not included. Subsequently, the same research group (123) examined the effects of an intensive aerobic training program (40-min training sessions; heart rate >150 beats per minute; 5 d/wk for 4 months) to obese boys and girls ($n = 79$) designed to improve risk factors for the insulin resistance syndrome. They also monitored participants for an additional 4 months once the program ended to evaluate the effects of detraining. Overall, the intervention led to statistically significant (yet small) decreases in fasting insulin and percentage body fat. Although visceral adiposity increased (0.5%) in the training group during the program, the gain was significantly lower than in the nonexercising control group (8.1%).

McMurray and Bauman (124) examined the role of exercise in improving fasting insulin and glucose concentrations in a sample ($n = 246$) of 10- to 14-yr-old boys and girls. Children participated in one of two exercise programs (3 d/wk for 8 wk) and were subsequently categorized as either improvers (aerobic fitness improved ≥ 3 ml/kg-min) or nonimprovers (aerobic fitness change < 3 ml/kg-min). Leisure time physical activity was not related to insulin or glucose levels, however, multiple regression analyses showed that an improvement in predicted maximal aerobic capacity was independently and significantly related to a decline in fasting insulin. However, this association accounted for a small amount (1.8%) of the total variance. Because body composition was estimated using BMI and a sum of two skinfolds (triceps and subscapular), it is not known whether more sophisticated measures of body fatness would have helped to explain insulin changes. Interestingly, improvers had lower fitness levels and higher insulin concentrations at baseline, implying that an exercise intervention may be most beneficial for those with a greater capacity to improve (and who may be at increased health risk).

To improve outcomes related to body composition and risk factors for type 2 diabetes, most interventions have used some type or combination of aerobic exercise(s). However, emerging evidence from adults suggests that strength training (resistance training) also elicits meaningful physiological improvements (108, 112). To date, resistance training studies in younger populations have generally focused on issues related to safety, strength improvements, and muscle changes (125, 126) as primary outcomes. In one of the few studies to assess metabolic risk, Treuth *et al.* (127) conducted a resistance training trial with overweight Caucasian girls ($n = 12$). They demonstrated that resistance training (20-min sessions, 3 d/wk for 5 months) led to increased strength and attenuated visceral body fat accumulation (determined using computed tomography). That is, although the group increased in overall total body fatness, this gain was not accompanied by an increase in visceral fat. 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 this small group.

Role of dietary factors

Very few studies have been conducted in children relating diet to insulin resistance. In one detailed study, we previously examined whether dietary factors explained ethnic differences in insulin profile among children, independent of body composition and social class background, in a sample of 95 African-American and Caucasian children (65). Macronutrient and food group intake were derived from three 24-h recalls. Intake of fruits and vegetables was significantly higher, and dairy intake lower, among African-American children compared with Caucasians, after adjusting for social class and total energy intake. Several direct relationships were observed between diet and insulin action: carbohydrate and fruit intake were positively associated with insulin sensitivity ($P = 0.02$), and vegetable intake was negatively associated with acute insulin response ($P = 0.01$). However, neither macronutrient nor food group intake accounted for the ethnic differences in insulin factors.

Hu *et al.* (128) conducted a comprehensive review of the literature focusing on animal and adult studies. In adults, the main findings included that dietary intervention studies have shown no deleterious effects of a high-fat diet on insulin sensitivity, although some epidemiological studies have indicated positive correlations between saturated fat intake and high insulin/insulin resistance, independent of body fat (128). However, the larger Insulin Resistance Atherosclerosis Study (1173 men and women) using the frequently sampled iv glucose tolerance test found no relation between dietary fat intake and insulin sensitivity (129). Other studies show that the type of fat may be important. For example, in the Nurses Health Study, high vegetable fat was related to lower risk of developing type 2 diabetes over 6 yr (130). Other studies on the effects of fish oil (potentially beneficial) and trans-fatty acids (potentially harmful) provide some supportive evidence, but studies are not conclusive, as previously reviewed by Hu *et al.* (128). Regarding carbohydrate intake, there is no evidence that overall percentage carbohydrate intake changes risk, but several studies have shown that a diet with a low glycemic index may have beneficial effects (131).

Perspective and conclusions

Obesity-associated diseases, especially type 2 diabetes and cardiovascular risk, are emerging problems in the pediatric population. The fact that these obesity-related conditions are observed early in life suggests that the associated disease pathology is not necessarily a function of aging or deteriorating biological phenomenon, but is perhaps an intrinsic process. Despite numerous clinical reports and emerging research, very little is known about the etiology of impaired glucose tolerance, type 2 diabetes, and cardiovascular risk in obese children. Despite the well known link between increased body fat and disease risk, the reason why increased body fat causes or contributes to insulin resistance and risk for diabetes and cardiovascular disease is not clearly delineated. Two possible theories being increasingly studied are that either: 1) fat accumulation only becomes metabolically harmful when accumulated in specific depots; or 2) fat *per se*

is not harmful, but fat-derived metabolic products may contribute to insulin resistance (42).

More detailed screening studies are essential to reveal the full extent of this problem at the population level. Early screening and identification of obesity-related health issues are also important because of the frequent asymptomatic nature of these conditions, which may go unnoticed for years, perhaps decades, until irreversible damage occurs. The need for early screening raises the issue of whether this should occur at the population level or in high-risk subgroups of the population. Given the intensity of the needed screening measures, it seems more likely that this level of screening would occur in high-risk subgroups of the population (*e.g.* obese, positive family history, certain ethnic groups). For screening to be effective, further studies are needed to identify risk factors and biomarkers for disease progression that are specific to the pediatric population and perhaps specific to high-risk groups. In addition, normative data for children for risk factors such as fasting glucose would be very useful and would avoid the reliance on interpreting results on the basis of adult reference data. Although screening seems warranted, there is a current limitation of effective treatment and prevention programs that have been specifically designed for the pediatric population and high-risk subgroups. Programs and treatments that have been tried and tested in adults cannot be assumed to be safe or effective in the pediatric population because of the likelihood of differences in disease pathology and physiological differences due to maturation.

Studies in children and youth are important to establish whether the pathophysiology and natural history for the development of type 2 diabetes and premature cardiovascular disease are the same as in adults and whether specific treatment and/or prevention efforts are warranted. Although the risk factors may be similar (*e.g.* increased body fat, decreased physical activity, insulin resistance), the time course could be accelerated. For adults, it may take decades for full blown type 2 diabetes to develop, although there is typically evidence of underlying microvascular and macrovascular complications that may have been undiagnosed. In children and adolescents, full blown type 2 diabetes is likely to develop over a more rapid time frame. Type 2 diabetes in adolescence is also confounded by transient insulin resistance associated with puberty. Figure 1 provides a schema of the proposed pathophysiology for the development of type 2 diabetes and how this may differ in children/adolescents *vs.* adults.

Conventional wisdom might suggest that the increased risk of obesity-related diseases in different ethnic groups might be explained by differences in body fat. However, recent studies have suggested that the greater insulin resistance across ethnic groups is both independent of adiposity and evident early in life. These factors suggest that at least a portion of the increased risk of type 2 diabetes may be intrinsic and explained by other factors not related to or explained by adiposity or aging, and that the effects of obesity and ethnicity are additive. In children, several likely mechanisms could explain the higher risk across ethnic groups. First, evidence suggests that children from certain ethnic groups are more insulin resistant, independent of

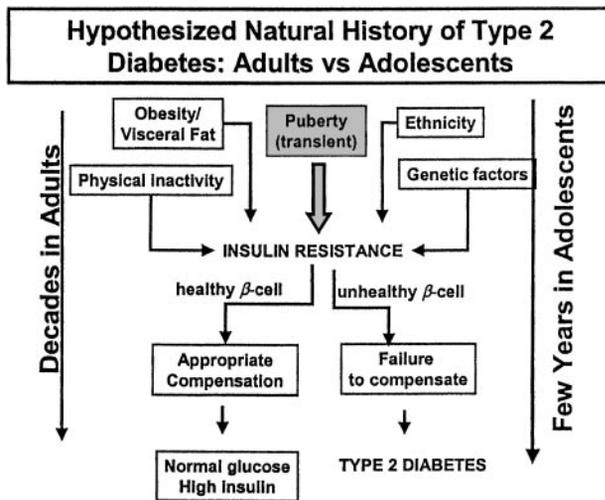


FIG. 1. Schema of proposed pathophysiology for development of type 2 diabetes.

body fat. So if one considers an obese child who is from a high-risk ethnic group, there are already several independent factors contributing to a state of greater insulin resistance. The fall in insulin sensitivity at the onset of puberty and the requisite insulin secretion that is needed to sustain a high degree of insulin resistance may become critical and insufficient. This may be especially detrimental in children who have an inability to adequately compensate through increased β -cell secretion. It is also likely that the mechanism may be different across different ethnic groups. This seems plausible given that the compensatory responses to insulin resistance have been shown to be very different in African-American (reduction in hepatic extraction of insulin) vs. Hispanic (increased second phase secretion of insulin) children. This finding suggests that the typical treatment/prevention programs may have different effects in different groups, and/or the metabolic targets for treatment/prevention may be different across high-risk subgroups.

One additional contributing factor that is specific to children is transient pubertal insulin resistance. Because this seems to be a natural phenomenon necessary for growth and maturation, it may not be prudent to use interventions that directly affect insulin resistance during this time period, and it will be important to identify optimal levels of insulin resistance that can be tolerated during this critical period. It may be more prudent to ensure adequate insulin secretion during this critical developmental stage. Further studies are needed to identify the factors that trigger the transient onset and later recovery of insulin resistance during puberty. When a more detailed mechanism of pubertal insulin resistance is identified, it may be important to identify interventions that ensure that insulin sensitivity recovers during later puberty and that β -cell function remains adequate to support this period of insulin resistance. More importantly, dietary and physical activity interventions should be explored for determining more traditional outcomes (*i.e.* decreasing body fat) as well as more specific risk indicators (*i.e.* increasing insulin sensitivity and sustaining β -cell function before and during pubertal development), especially in those subjects with very low levels of insulin sensitivity to begin with.

With regard to physical activity, relatively few studies have examined the interrelationships between physical activity, cardiovascular fitness, and risk factors for type 2 diabetes and cardiovascular disease in youth. The small amount of data that are available suggests that exercise-based interventions (aerobic and resistance training) can have beneficial effects on disease risk. Assuming that exercise programs are thoughtfully designed and implemented within a supportive, encouraging, and empowering environment, interventions that promote increased physical activity (as well as decreased physical inactivity) are inherently appealing because they have the capacity to influence several important physiological outcomes (*i.e.* body fat, insulin sensitivity, blood lipids) simultaneously. However, to date, methodological differences between studies (both observational and treatment) regarding how physical activity, aerobic fitness, body composition, and insulin dynamics have been measured preclude us from establishing definitive conclusions. An optimistic view of the literature suggests that physical activity and aerobic fitness, in and of themselves, are related to decreased risk of type 2 diabetes. However, it is unclear whether physical activity and fitness influence risk of type 2 diabetes in youth independently or through their effects on body fatness. As future interventions are being considered for the management of risk factors (*i.e.* overweight and hyperinsulinemia) for type 2 diabetes in youth, special attention should be given to designing randomized clinical trials that use rigorous and objective methodologies to evaluate metabolic risk factors. Because physical activity has the potential to have profound effects on reducing risk for obesity, type 2 diabetes, and cardiovascular disease and offers a natural and drug-free intervention approach, greater emphasis and research are needed to identify optimal approaches.

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