13 Pathogenesis of Insulin Resistance and Glucose Intolerance in Childhood Obesity

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CONTENTS

Key Words: Insulin resistance, pre-diabetes, visceral fat, skeletal muscle, liver, type 2 diabetes, metabolic syndrome, brown adipose tissue (BAT)

Obesity in children and adults is associated with resistance to the metabolic effects of insulin. The term "insulin resistance" is commonly used to describe the resistance of skeletal muscle and liver to insulin-dependent glucose metabolism: insulin resistance reduces myocellular glucose uptake and utilization, increases hepatic glucose production, and facilitates adipose tissue lipolysis. Reductions in hepatic insulin clearance and a compensatory up-regulation of beta cell insulin secretion lead to hyperinsulinemia.

It is important to recognize that the process of insulin resistance is tissue and pathway selective. Thus certain actions of insulin in liver (e.g., lipoprotein synthesis and suppression of sex hormone binding globulin and IGF binding protein-1), skin, ovary, and kidney are preserved; this explains in part the clinical manifestations of insulin resistance, which include dyslipidemia, acanthosis nigricans, hyperandrogenism, and hypertension. Together with glucose intolerance, these disorders are postulated to drive the development of atherogenesis and to increase the risk of cardiovascular disease in susceptible individuals *(1)*.

Insulin resistance can be induced by changes in metabolic demand during the lifespan: examples include the transient insulin resistance of puberty *(2)*, pregnancy, and acute illness. Sensitivity to insulin declines progressively with age and may be influenced by the macronutrient composition of the diet *(3)*. The clinical manifestations of insulin resistance depend upon the duration of the underlying disorder and on the susceptibility of the individual; thus the acute and long-term effects of insulin resistance are modulated by familial, genetic, racial, and ethnic factors.

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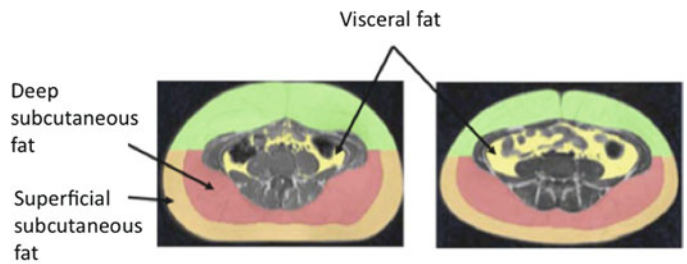
PATHOPHYSIOLOGY OF INSULIN RESISTANCE

The most common cause of insulin resistance in the pediatric age group is obesity. Most obese children and adults are insulin resistant; however even severely obese children can in some cases be highly insulin sensitive, normotensive, normolipidemic, and euglycemic *(4)*. The relationship between obesity and peripheral insulin resistance depends more on the distribution of lipid (or "lipid partitioning") in specific fat depots than on the absolute amount of fat per se. Different lipid depots have distinct metabolic characteristics reflected in their adipocytokine and cytokine secretion profiles *(5)*, sensitivity to hormones such as norepinephrine or insulin, and anatomical blood supply and drainage (portal vs. systemic) *(6)*. Increased visceral fat accumulation in obese children is associated with increased insulin resistance *(7)* and the clustering and heightened expression of cardiovascular risk factors *(8)* (Figs. 1 and 2). Some obese children manifest a unique lipid partitioning pattern characterized by a large visceral fat depot and a relatively smaller subcutaneous fat depot. Children with a predominance of visceral fat have adverse metabolic profiles in comparison with those with larger subcutaneous



Visceral	28 cm^2	58 cm^2
Subcutaneous	518 cm^2	338 cm^2
Visc / SQ	0.05	0.15
Deep / Superficial	1.15	1.39
Insulin sensitivity	1.90	0.27

Fig. 1. Representative MRI images of Caucasian female subjects with low and high levels of visceral fat. Note the inverse relationship between visceral fat and insulin sensitivity (Matsuda index). Adapted from Taksali et al. *(9)*.

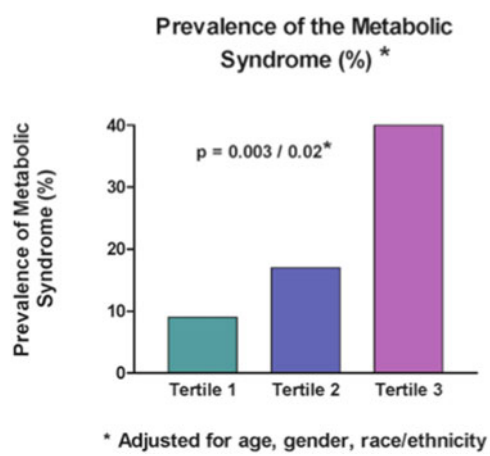


Fig. 2. Relation of tertiles of visceral fat and the prevalence of the metabolic syndrome. Adapted from Taksali et al. *(9)*.

fat depots, even when the latter have greater BMI and percent body fat *(9)*. Thus, the subcutaneous fat depot, localized more in the lower body region than in the upper body region *(10)*, serves as a "metabolic sink" that accumulates fat in states of excess energy intake/low energy output. Individuals with the ability to store excess fat in lower body subcutaneous depots appear to be able to gain excess weight without developing significant insulin resistance. In contrast, those with low capacity to store excess lipid in subcutaneous depots tend to accumulate fat in visceral depots and in insulin responsive tissues such as muscle and liver and develop insulin resistance.

The skeletal muscle is the primary site for post-prandial glucose uptake and utilization. Intramyocellular lipid deposition is higher in obese than in lean subjects (Fig. 3) and correlates inversely with peripheral insulin sensitivity *(11)* (Fig. 4) and is increased in offspring of patients with T2DM and in obese children with impaired glucose tolerance *(12)*. The effect of lipid within the myocyte on insulin signal transduction is indirect and probably mediated by several fatty acid derivatives such as ceramide, diacylglycerol, and fatty acyl CoA as well as reactive oxygen species that inhibit insulin signaling *(13)*. Similarly, hepatic fat accumulation is strongly associated with obesity and with hepatic resistance to the effects of insulin on glucose metabolism; it is also associated with an adverse cardiovascular risk profile in children (see Chapter 15 by Alisi et al., this volume).

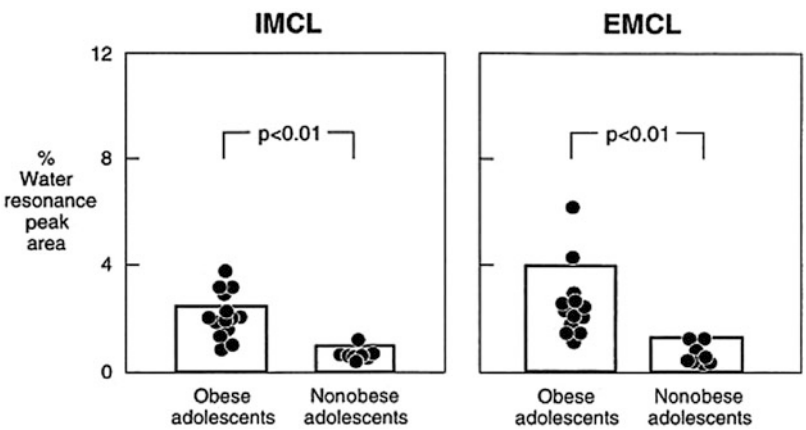


Fig. 3. Intramyocellular lipid (IMCL) and extramyocellular lipid (EMCL) content in lean and obese adolescents. From Sinha et al. *(11)* with permission.

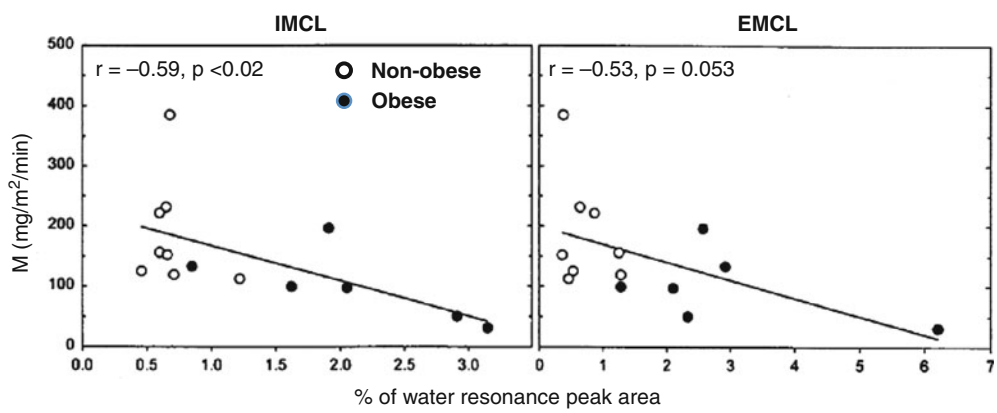


Fig. 4. Relation of intramyocellular lipid (IMCL) and extramyocellular lipid (EMCL) content to whole-body insulin sensitivity in lean and obese adolescents. Redrawn from Sinha et al. *(11)* with permission.

As the liver governs glucose metabolism in the fasting state and the muscle affects glucose metabolism mainly in the post-absorptive state, significant hepatic insulin resistance may have a stronger impact on fasting glucose levels and on the early post-absorptive suppression of hepatic gluconeogenesis following a meal. In contrast, muscle lipid deposition has a greater impact on post-prandial glucose levels. Combined resistance in skeletal muscle and liver induces a rise in blood glucose, which is noted first in the post-prandial state. This triggers an adaptive increase in beta cell insulin secretion and a reduction in hepatic insulin clearance. The net result is an increase in circulating insulin levels (hyperinsulinemia). In early stages, hyperinsulinemia maintains euglycemia; however, persistent insulin resistance imposes a continuous burden on beta cell insulin secretion. In the long run, this may contribute to beta cell failure *(14,15)*. The induction of adipose tissue lipolysis in insulin resistance raises circulating free fatty acids, which stimulate insulin secretion initially but ultimately reduce beta cell function in the presence of hyperglycemia. The high levels of insulin increase renal sodium retention, reduce uric acid clearance *(16)*, and promote ovarian androgen production *(17)*. Hyperinsulinemia may also activate the sympathetic nervous system *(18)* and impact the metabolism and secretion of pro-inflammatory cytokines as well as coagulation mediators *(19)*.

Some suggest that hepatic deposition of lipid is not a primary process but a "normal" response to elevated circulating insulin levels induced by muscle insulin resistance; they argue that hepatic steatosis is a consequence, not a culprit, of the adverse metabolic phenotype characteristic of insulin-resistant individuals. Exposure of the liver to hyperinsulinemia, along with increased free fatty acid flux, likely contributes to the dyslipidemia observed in individuals with insulin resistance. This dyslipidemia consists of elevated triglycerides, reduced HDL-cholesterol, and an increased concentration of small LDL particles, which are integral to the pathogenesis of atherosclerotic heart disease *(20,21)* (see also Chapter 14 by McCrindle, this volume).

In summary, peripheral tissue resistance to the action of insulin, specifically in metabolic pathways related to glucose metabolism in the muscle and liver, results in a compensatory hyperinsulinemia. Selective preservation of insulin signaling pathways yields a clinical picture characterized by dyslipidemia (specifically elevated triglycerides, low HDL-cholesterol, and the presence of small LDL particles), hypertension, and ovarian hyperandrogenism. Altered glucose metabolism, manifested as impaired fasting glucose, impaired glucose tolerance, or overt diabetes, reflects the inability of beta cells to secrete insulin in amounts sufficient to overcome insulin resistance. Insulin resistance and hyperinsulinemia enhance the expression of pro-inflammatory cytokines and factors related to hyper-coagulability. The clustering of these factors accelerates the process of atherogenesis and cardiovascular disease.

EPIDEMIOLOGY OF ALTERED GLUCOSE METABOLISM IN CHILDHOOD

The epidemic of childhood obesity has been accompanied by a sharp increase in the incidence of type 2 diabetes (T2DM) in the pediatric age group. T2DM represents the end of a spectrum of altered glucose metabolism that includes at least two pre-diabetic conditions: impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). As not all those with a pre-diabetic condition progress to develop T2DM, the prevalence of these pre-diabetic conditions is much greater than that of overt diabetes. Recent data from the SEARCH for Diabetes study in the United States showed that the prevalence of T2DM in Caucasians (at ages 10–19 years) was 0.18/1,000, with higher rates in female than in male subjects (0.22 vs. 0.15 per 1,000, $p = 0.01$). The incidence of type 2 diabetes was 3.7/100,000, with similar rates for female and male subjects (3.9 vs. 3.4 per 1,000, respectively, $p = 0.3$) *(22)*. Among African-American youth aged 10–19 years, the prevalence (per 1,000) of T2DM was 1.06 (0.93–1.22) and the annual incidence (per 100,000) was 19.0 (16.9–21.3). For T2DM, the rates were $6.9/10^5$ (5.7–8.4) and $4.8/10^5$ (3.8–6.0) for female and male subjects, respectively *(23)*. It should be

noted that the SEARCH study excluded all subjects in seropositivity to islet antigens, even if they had a phenotype and family history characteristics of patients with type 2 diabetes. Nevertheless, among Hispanic female subjects aged 15–19 years, the incidence of type 2 diabetes exceeded that of type 1 diabetes ($p < 0.05$). The incidence of type 1 and type 2 diabetes for Hispanic male subjects aged 15–19 years was not significantly different *(24)*. In the most conservative estimate, more than 20,000 obese children in the European Union have T2DM, while more than 400,000 have impaired glucose tolerance *(25)*. Among US adolescents, the unadjusted prevalences of IFG, IGT, or either one were 13.1, 3.4, and 16.1%, respectively, with overweight adolescents having a 2.6-fold higher rate than those with normal weight (1.3–5.1) *(26)*. These data indicate that alterations in glucose metabolism, specifically of pre-diabetic conditions, are common among obese children and adolescents. Moreover, T2DM, previously considered rare in childhood, must now figure prominently in the differential diagnosis of any overweight or obese adolescent with hyperglycemia.

PATHOPHYSIOLOGY OF ALTERED GLUCOSE METABOLISM IN CHILDHOOD

The development of T2DM involves at least two mechanisms relevant to glucose metabolism pathways: increased peripheral insulin resistance and a failure of beta cell function to compensate adequately for such resistance. The most common cause of insulin resistance in childhood is obesity, which reduces insulin action in otherwise healthy individuals and exacerbates pre-existing insulin resistance in those with a predisposing condition. Predisposing factors include ethnic background (African-American, Hispanic, Native American, Asian, and Pacific Islander), a family history of T2DM in first-degree relatives, prematurity and intrauterine growth retardation, a history of exposure to gestational diabetes, sedentary behavior, and, possibly, specific macro and micronutrients in the diet *(27)*.

Obese children and adolescents with pre-diabetic conditions have marked peripheral insulin resistance in comparison to normal glucose tolerant peers *(28)*. While glucose tolerant subjects have varying degrees of insulin sensitivity *(29)*, pre-diabetic subjects uniformly have very low insulin sensitivity. Development of insulin resistance triggers a compensatory increase in circulating insulin levels that is achieved by two independent mechanisms: increased secretion of insulin from pancreatic beta cells and reduced clearance of insulin by the liver *(30)*. The relation of insulin secretion to insulin resistance is hyperbolic (best described as sensitivity$\times$secretion = constant) and is called the disposition index (DI) *(31)*. As an individual's DI is largely genetically determined, one can have various degrees of insulin sensitivity for a given DI during the lifespan; yet as the degree of insulin sensitivity declines in a given individual, the demand for beta cell insulin secretion must increase *(32)* (Fig. 5). Failure to maintain adequate insulin secretion will translate to a new and lower DI that manifests as a relative hyperglycemia in comparison to the previous steady state.

Early defects in beta cell function have been demonstrated in obese children and adolescents with IGT and with T2DM. In the face of comparable degrees of insulin resistance, individuals with IGT display a pattern of first-phase insulin secretion that is reduced in comparison to those with normal glucose tolerance yet greater than those with T2DM. Second-phase insulin secretion is initially preserved in those with IGT but is reduced in those with early T2DM *(33)*. Thus, T2DM in obese adolescents manifests a dual defect in both phases of insulin secretion following glucose challenge and thus represents overt beta cell failure.

Mathematical modeling of beta cell function indices derived from oral glucose tolerance tests (OGTTs) demonstrates subtle yet significant defects in beta cell function in the various pre-diabetic conditions in obese youth. First-phase insulin secretion is progressively lower in IFG, IGT, and IFG/IGT, respectively, compared with NGT. Second-phase insulin secretion is significantly reduced only in the IFG/IGT group. Thus, IFG in obese adolescents is linked primarily to alterations in glucose

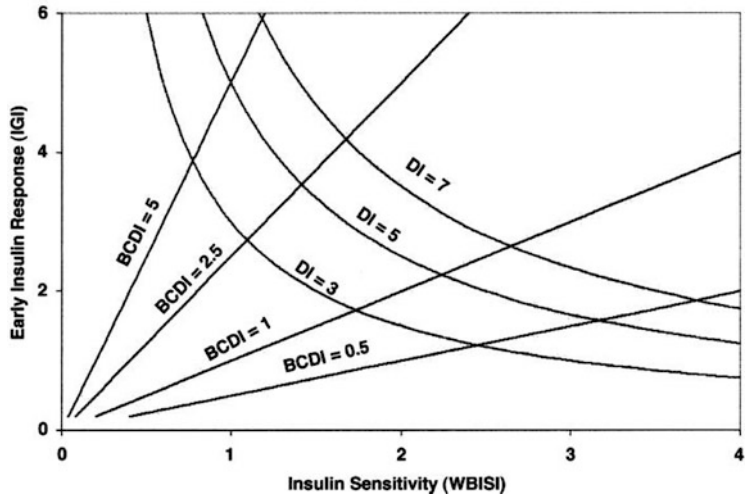


Fig. 5. Relation of OGTT-derived indexes of insulin secretion and sensitivity and their interactions. As shown, for a given DI, as insulin sensitivity is lower, early insulin response is higher. This translates to a greater BCDI (beta cell demand index), reflecting the metabolic burden placed on the β-cell in order to maintain a constant DI and normal glucose homeostasis. From Weiss et al. *(15)* with permission.

sensitivity of first-phase insulin secretion and liver insulin sensitivity. The IGT group has a more severe degree of peripheral insulin resistance and reduction in first-phase secretion. IFG/IGT is hallmarked by profound insulin resistance and by a new additional defect in second-phase insulin secretion. Thus, although we tend to categorize degrees of glucose intolerance based on thresholds for clinical purposes, the deterioration from normal glucose tolerance to T2DM represents a continuum that culminates as a significant defect of beta cell function. Milder defects in beta cell function can be detected even in subjects with glucose levels in the "high normal" range. However, beta cell function deteriorates further as glucose tolerance worsens *(34)*: isolated IGT, manifested as elevated 2-h glucose levels during an OGTT, represents an early first-phase beta cell defect, while the combination of impaired fasting glucose and IGT is associated with more profound beta cell dysfunction.

Reductions in peripheral insulin resistance, whether achieved by diet-induced weight loss, exercise, or pharmacologic interventions, allow the affected individual to shift along the DI curve to a new steady state in which beta cell capacity is sufficient to maintain euglycemia. It is currently unclear if increases in insulin sensitivity can fully restore beta cell function once an individual has developed overt glucose intolerance.

DYNAMICS OF PRE-DIABETIC CONDITIONS

Not all obese children and adolescents with a pre-diabetic status progress to develop overt diabetes. For example, some adolescents with pre-diabetes at mid-puberty revert to normal glucose tolerance upon completion of pubertal development. The progression from IGT to T2DM is associated with a continuous reduction in insulin sensitivity, tightly linked to significant weight gain *(35)*. Indeed, changes in insulin sensitivity, mostly associated with weight dynamics, are the main predictors of changes in the 2-h glucose level during an OGTT. However, the progression from normal glucose metabolism to IGT or T2DM also reflects a defect in beta cell function manifest as impaired responsiveness to a rapid dynamic change in glucose *(36)*. The defect in beta cell function can be demonstrated using the DI, which deteriorates progressively from normal to impaired glucose

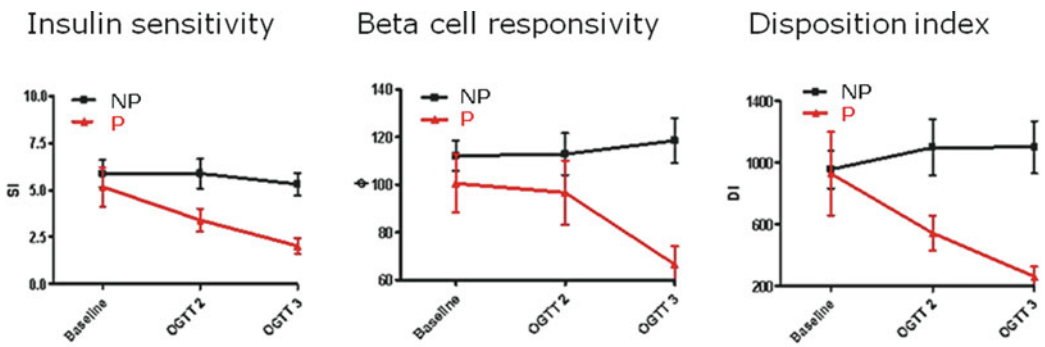


Fig. 6. Progression of glucose intolerance in insulin-resistant adolescents. NP, non-progressors, i.e., insulin-resistant patients who did not develop impaired glucose tolerance (IGT); P, progressors, i.e., those who progressed to IGT. Adapted from Cali et al. *(36)*.

metabolism to overt diabetes *(37)*. In combination with an increase in insulin resistance over time, a fall in beta cell insulin secretion leads to deteriorating glucose tolerance and eventually to impaired glucose tolerance (Fig. 6).

Persistent or progressive insulin resistance imposes a beta cell burden that is likely to translate to beta cell failure in predisposed individuals. Long-term exposure to inflammatory factors and free fatty acidemia play important contributory roles. On the other hand, those with good beta cell function may compensate adequately for marked insulin resistance for prolonged periods of time. Importantly, fasting levels of insulin or C-peptide are poor predictors of future deterioration in glucose tolerance; it takes a glucose challenge (oral or intravenous) to uncover subtle defects in beta cell function that reveal an individual's vulnerability.

An OGTT is a useful tool for assessing glucose tolerance in obese youth. Adults with IGT have residual beta cell function less than 50% of baseline; this may also be true in children. The reproducibility of the OGTT has been questioned; however, documentation of IGT on even a single study demonstrates the vulnerability of the patient to beta cell dysfunction in the advent of further weight gain, pregnancy, or treatment with glucocorticoids. IGT is a dynamic condition and represents a narrow window of opportunity; children and adolescents with IGT should therefore be a primary focus of preventive and therapeutic efforts.

INSULIN RESISTANCE ("METABOLIC") SYNDROME IN CHILDHOOD

The metabolic syndrome, also known as "the insulin resistance" syndrome, describes a cluster of cardiovascular risk factors that have been shown to predict the development of cardiovascular disease (CVD) *(38,39)* and type 2 diabetes (T2DM) *(40)*. The syndrome is characterized by abdominal adiposity, dyslipidemia, hypertension, and glucose intolerance *(41)*. Some have questioned the clinical utility of the term in adults *(42)* and in children *(43)* and advocate addressing individual risk factors in their clinical context. This debate has important clinical implications with regard to treatment decisions; yet it must be understood that the pathophysiological changes that lead to the metabolic syndrome have common features in people of all ages and are postulated to drive the development of atherogenesis and cardiovascular disease.

One must also appreciate that cardiovascular risk factors such as elevated fasting glucose or the degree of obesity represent continuous variables. For example, increasing BMI during childhood represents a continuous risk factor for the development of coronary heart disease in adulthood *(44)*;

nevertheless, severely obese children have a significantly worse metabolic phenotype in comparison with moderately obese children and are at higher risk for cardiovascular disease *(45)*. Likewise, a seemingly "upper normal" fasting glucose level in the context of obesity during late adolescence may signify future risk of type 2 diabetes *(46)*, and a rise in triglyceride levels within the "normal range" in late adolescence can predict the development of diabetes *(47)* and of coronary heart disease *(48)*.

Another issue that adds complexity to any definition of the metabolic syndrome is its generalizability for populations of different ethnic backgrounds. IGT and type 2 diabetes are more common in ethnic minorities in the United States *(49)* and in some European countries *(50)*. A potential explanation is that ethnic minority youth are more obese and more insulin resistant than their Caucasian peers *(51)* and have different lipid partitioning profiles when matched for BMI. Moreover, non-obese Hispanic and African-American children have increased insulin secretion and reduced hepatic insulin clearance relative to Caucasian children matched for degree of insulin sensitivity *(52)*. Thus, assessments of insulin sensitivity based on fasting or post-prandial insulin levels may in the future have to be ethnicity-specific. Moreover, anthropometric measures such as visceral and subcutaneous fat content should be ethnicity-sensitive and derived from outcome data of the relevant populations *(53)*.

SUMMARY

Insulin resistance, which is common among obese children and adolescents, manifests as a cluster of cardiovascular risk factors that include dyslipidemia, hypertension, and altered glucose metabolism. While cardiovascular disease is rarely observed in childhood, altered glucose metabolism manifests early and is commonly seen in obese youth. Obese individuals who exhibit an increase in the ratio of intra-abdominal to subcutaneous fat and deposition of lipid in insulin responsive tissues are mostly insulin resistant. Glucose intolerance reflects the confluence of severe insulin resistance and beta cell dysfunction, emerging most commonly in those with a family history of T2DM, intrauterine exposure to diabetes, or intrauterine growth retardation.

Editor's Questions and Authors' Response

- **Visceral adipose tissue is said to be more "metabolically active" than subcutaneous tissue with higher rates of lipolysis; this is said to explain the increases in free fatty acids and heightened liver fat deposition in people with visceral adiposity. Given the overall mass of the visceral fat depot, however, some investigators argue that circulating FFA are derived primarily from non-visceral stores. In your opinion, why does visceral fat play such an important role in the pathogenesis of insulin resistance?**
- As previously shown by Jensen et al, visceral fat contributes free fatty acids to the circulation in proportion to its overall size in comparison to total fat. The difference is that these free fatty acids reach the liver via the portal and not via the systemic circulation. It is postulated that free fatty acids reach the liver in high concentrations and have a local effect in various signal transduction pathways. Moreover, visceral fat seems to have a different secretion profile of adipocytokines and of inflammatory cytokines in comparison to subcutaneous fat. The pro-inflammatory molecules secreted from visceral fat act locally in the liver and likely affect muscle glucose uptake and the secretion of insulin from pancreatic beta cells.

- **The relative amount of visceral fat in obese African-American teenagers is significantly less than that in BMI-matched Caucasians. Yet the rates of type 2 diabetes in African-American adolescents are at least twofold to fourfold higher than those in Caucasians. How do you explain this apparent paradox?**
- Indeed, African-American children tend to have less visceral fat in comparison to their Caucasian peers, yet have a greater prevalence of diabetes. This paradox can be explained by the fact that the relation of insulin secretion and insulin sensitivity (i.e., the disposition index) is different between these groups. This translates to a greater insulin response in the face of the same degree of insulin sensitivity in African-American lean and obese children in comparison to Caucasians. That means in the face of marked insulin resistance characteristic of severe obesity, African-Americans must produce more insulin to maintain glucose tolerance. This greater beta cell demand predisposes them to earlier beta cell failure. In addition, higher rates of type 2 diabetes in African-Americans might be explained in part by dietary factors.

Editor's Comments

- The discussion in this chapter focuses largely on the distribution and metabolic activity of white adipose tissue, which is designed for energy storage. But newborn infants also contain large masses of *brown adipose tissue (BAT)*, which is essential for thermogenesis. The major depot of BAT (interscapular) regresses after birth. Until recently, it was thought that stores of BAT in older children and adults were too limited to exert a significant impact on energy balance. However, recent investigations show that BAT can be detected in the supraclavicular and paraspinal regions in a significant percentage of women and men (Saito et al., 2009; Au-Yong et al., 2009; van Marken Lichtenbelt et al., 2009; Cypess et al., 2009). The BAT is a mixture of brown and white adipocytes and stains positively for uncoupling protein-1 (UCP-1). The mass of BAT appears to correlate inversely with age, ambient temperature, light exposure, BMI, and visceral fat mass. The role of BAT in energy homeostasis in children and adolescents is currently unknown; but since BAT appears to protect against obesity and diabetes in mice (Almind et al., 2007), it is possible that the ratio of BAT/visceral fat may prove to be a determinant of childhood weight gain and metabolic function.
- The authors demonstrate convincingly that type 2 diabetes is the end result of a process of metabolic decompensation in which beta cell dysfunction is superimposed upon pre-existing insulin resistance. Formal glucose tolerance testing is useful for assessing states of pre-diabetes [impaired fasting glucose (100–125 mg%) and/or impaired glucose tolerance (2 h glucose 140–199 mg%)] and for identification of overt type 2 diabetes. However, the validity and clinical utility of the OGTT have been questioned: it may be difficult to bring certain adolescents to the clinic in early morning for a 2–4 h test and the results may vary over time. An American Diabetes Association expert panel (Nathan et al., 2009) recently suggested that measurement of HbA1c provides a clinically useful assessment of glucose intolerance in adults; values equal to or exceeding 6.5% were considered diagnostic of diabetes. Others have argued that a combination of fasting blood glucose and HbA1c may reduce the need for a formal GTT to diagnose impaired glucose tolerance (Manley et al., 2009). HbA1c can be measured under random conditions and provides an assessment of glucose exposure for the past 3 months. Values can be misleading in patients with hemoglobinopathies or in other states of increased red blood cell turnover. Nevertheless, the test can provide valuable information in children as well as adults; in our experience, HbA1c values equal to or exceeding 6.5% are

commonly associated with impaired glucose tolerance or overt type 2 diabetes, and impaired fasting glucose is common in patients with A1c values ranging from 6 to 6.4%. Still, the precise relationship between HbA1c and the OGTT should be assessed in pediatric patients.

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