

Metabolic Syndrome in Pediatrics: Old Concepts Revised, New Concepts Discussed

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KEYWORDS

- Obesity • Children • Metabolic syndrome
- Insulin resistance • Type 2 diabetes

The worldwide epidemic of childhood obesity in the last decades is responsible for the occurrence in pediatrics of disorders once mainly found in adults, such as the metabolic syndrome (MS). First described by Gerald Reaven, MS has been defined as “a link between insulin resistance, hypertension, dyslipidemia, impaired glucose tolerance and other metabolic abnormalities associated with an increased risk of atherosclerotic cardiovascular diseases in adults.”¹ A key factor in the pathogenesis of MS is insulin resistance, a phenomenon occurring mainly in obese subjects with a general resistance to the insulin effect only on carbohydrates and lipid metabolism.² The pathogenesis of insulin resistance has been studied for many years and it is now known that free fatty acid (FFA) accumulation in the liver, fat cells, pancreas and, particularly, skeletal muscle of obese patients, interfering with the normal insulin signaling cascade, appears as the primary determinant of insulin resistance.² Moreover, FFA accumulation in the liver makes it resistant to insulin in terms of the ability of the hormone to suppress glucose production. Under these conditions, hyperinsulinemia turns the liver into a “fat-producing factory” with all of its negative downstream effects, including the genesis of hypertriglyceridemia.² On the other hand, the fat cells’ resistance to insulin causes an increase in lipolysis, with a consequent increase in discharging lipids in the plasma.² As a consequence of insulin resistance, the pancreas

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needs to increase its insulin production to maintain normal value of glycemia, promoting, in this way, the FFA accumulation, further worsening insulin resistance and generating a vicious cycle.

In spite of the emerging difficulties in transposing the definition of MS from adults to children,³ MS in children is commonly defined as the co-occurrence of three or more of the following features: severe obesity (usually with a waist circumference higher than the nintieth sex- and age-specific percentile), dyslipidemia (increase of triglycerides and decrease of high-density lipoprotein or HDL), hypertension and alterations of glucose metabolism, such as impaired glucose tolerance (IGT) and type 2 diabetes (T2D).⁴⁻⁸

Recently, to overcome conflicts arising from different definitions, the International Diabetes Federation consensus group proposed an easy-to-apply definition to begin using in clinical setting (**Table 1**).³ In fact, the numerous definitions now used make it difficult to follow the epidemiology of MS in childhood. A study by Goodman and colleagues⁹ has clearly shown how changes in MS definitions dramatically influence prevalence differences, ranging from 15% to 50% according to which definition is used. Moreover, given that MS is driven by obesity, the prevalence of the latter will strongly influence the prevalence of MS. One should also take into account that, because the known differences of insulin resistance between different ethnic groups (with African American and Hispanic children more insulin-resistant than Caucasians) it may be important to consider ethnicity in the evaluation of MS.¹⁰⁻¹³ Difficulties in defining MS in children and adolescents also come by the lack—for some components of MS, such as HDL, triglycerides, waist circumference and blood pressure (BP)—of normative values that might find a worldwide application. This inevitably determines that the definition of MS in pediatrics is driven by that given for adults.

Age Group	Obesity (WC)	Triglycerides (mg/dl)	HDL (mg/dl)	Blood Pressure (mmHg)	Glucose (mg/dl)
6 < 10	≥90th percentile				
10 < 16	≥90th percentile or adult cut-off if lower	≥ 150	< 40	Systolic BP >130 or diastolic BP > 85	FPG >100 or T2D
>16 Adult criteria	WC ≥94 cm for males and ≥80 for females	≥ 150	<40 in males, <50 in females	Systolic BP >130 or diastolic BP >85	FPG >100 or T2D

According to these criteria, MS cannot be diagnosed under 6 years of age, but further measurement and a strict follow-up should be provided according to family history. Different thresholds for different ethnicity are also suggested.

Abbreviations: BP, blood pressure; FPG, fasting plasma glucose; T2D, type 2 diabetes; WC, waist circumference.

Data from Zimmet P, Alberti KG, Kaufman F, et-al. IDF Consensus Group. The metabolic syndrome in children and adolescents—an IDF consensus report. *Pediatr Diabetes* 2007;8:6.

Beyond any definition, the precocious identification of the components of MS is of primary importance to address the treatment and the behavior of those children who will develop cardiovascular and metabolic issues in adulthood. That is why several studies have been focused on clinical and biochemical markers predicting MS, demonstrating in some cases a strong link between changes of the risk variables of MS, such as body mass index (BMI), HDL, triglycerides, glucose, and insulin from childhood to early adulthood and cardiovascular risk later in the life.¹⁴

IDENTIFYING CHILDREN WITH MS

Although there is no complete agreement on the fine definition of MS in youth, given the limitations described above, the cornerstones of its definition still remain and need to be identified by pediatricians.

BMI is a predictor of coronary artery disease (CAD) risk factors among children and adolescents,^{15,16} and its utility has been endorsed by International Obesity Task Force and the Centers for Disease Control (CDC).¹⁷⁻¹⁹ The cut-off points of the CDC, based on a distribution approach, identify children with a BMI higher than the eighty-fifth percentile as "at-risk of overweight" and children with a BMI higher than the ninety-fifth percentile as "overweight." Data from multiracial cohorts of obese children, in which obesity was defined according to the CDC cut-off, showed that the severity of obesity and the prevalence of MS are strongly associated.⁵ However, obesity per se is not a marker sufficient for identifying children at-risk for MS and consequently for CAD. Fat distribution plays an important role in influencing the occurrence of metabolic complications consequent to obesity. Visceral fat accumulation, in fact, is strongly associated with MS in childhood²⁰ and CAD later in life,²¹ and waist circumference has been recognized as the best clinical predictor of visceral fat accumulation.²² Although reference values for waist circumference in children do exist for Canada,²³ Italy,²⁴ the United Kingdom,²⁵ and the United States,²⁰ and cut-off points beyond which there is an increase of the prevalence of CAD risk factors have been provided,²⁰ this measure is not commonly used in children, probably because no organization has endorsed a waist circumference cut-off for children.

The importance of measuring waist circumference is corroborated by multiracial cohort studies in children and adolescents showing that subjects with high waist-circumference values are more likely to have elevated CAD risk factors, compared with those with low waist circumference, within a given BMI category.²¹ This means that waist circumference may be, for such an extent, considered a more reliable measure for predicting MS than BMI alone. In fact, as in adults,²⁶⁻³⁰ in children an increased waist circumference has been correlated with abnormal systolic and diastolic blood pressure and elevated levels of serum cholesterol, low density lipoprotein (LDL), triglycerides, insulin, and lower HDL concentrations.³¹⁻³³ The association between the clustering of cardiovascular risk factors and waist circumference is not only a reflection of the obesity degree, but it has a psychopathologic background, given that visceral adiposity is one of the main risk factors for the development of insulin resistance, diabetes mellitus (DM), hypertension, and cardiovascular disease.^{34,35} The mechanisms involved in these common clinical associations are not completely known, but include the impaired suppression of hepatic glucose production,³⁶ the increased portal release of FFAs,³⁷ the increased visceral production of glycerol,³⁸ and the abnormal production of adipose tissue-derived hormones and cytokines, such as tumor necrosis factor (TNF)- α , leptin, and adiponectin.^{39,40} In fact, some studies have shown that the removal of visceral fat reverses insulin resistance in two models of obesity, and that the metabolic consequences of visceral fat

removal were associated with improved hepatic insulin action^{41,42} and with reduced adipose tissue expression of proinflammatory cytokines.⁴³

Although the anthropometric measurements obtained during the physical examination, such as BMI and waist circumference, can be very helpful and rich in meaning,⁴⁴ family history needs to be deeply investigated as well, given that heritability of the single components of MS has been well demonstrated.^{45,46} In fact, heritability for obesity ranges from 60% to 80% and heritability for blood pressure varies from 11% to 37%, while those for lipid levels varies from 43% to 54%.⁴⁵ Moreover, a recent study by Weiss and colleagues⁴⁷ shows that those children who do not show MS early in childhood are less prone to develop it later, further supporting, indirectly, a strong genetic component in the development of MS.

METABOLIC PHENOTYPE OF CHILDREN AND ADOLESCENTS WITH MS

Because insulin resistance represents one of the most important pathogenetic primers in the development of MS, all patients should be investigated for insulin resistance. Weiss and colleagues⁵ have demonstrated how the increase of insulin resistance parallels the increase of the risk of MS in obese children and adolescents. In this latter study, a strong loading of insulin resistance to obesity and glucose metabolism factor and moderate loading to the dyslipidemia factor has been shown.⁵ Some studies suggest a direct effect of hyperinsulinemia consequent to insulin resistance on the single components of the syndrome.⁴⁸

Although it is difficult to dissect the effect of insulin resistance and obesity on blood pressure, it has been demonstrated that insulin resistance per se may determine hypertension. Insulin levels in children between 6 and 9 years of age have been shown to predict blood pressure levels in adolescence;⁴⁹ moreover, the Bogalusa Heart Study showed a strong correlation between the persistently high fasting insulin levels and the development of CAD in children and young adults.⁵⁰ Some studies showed not only a strong correlation between hyperinsulinemia and blood pressure in children, but also that fasting insulin predicted the levels of blood pressure 6 years later.⁴⁹ As has been suggested, the adverse direct effect of hyperinsulinemia on blood pressure may be ascribed to the effect of insulin on (i) sympathetic nervous system activity,⁵¹ (ii) sodium retention by kidney,⁵² and (iii) vascular smooth-muscle growth stimulation.⁵³

A strong effect of hyperinsulinemia on lipid metabolism has also been demonstrated. In vivo studies showed that hyperinsulinemia stimulates the synthesis of triglycerides by increasing the transcription of genes for lipogenic enzymes in the liver.⁵⁴ Moreover, recent reports showed that the forkhead transcription factor FoxO1 acts in the liver to integrate hepatic insulin action to very low-density lipoprotein (VLDL) production. Augmented FoxO1 activity in insulin-resistant livers promotes hepatic VLDL overproduction and predisposes to the development of hypertriglyceridemia.⁵⁵

Although obesity is the most important cause of insulin resistance among obese and adolescents, one should not forget that a transient insulin-resistant state occurs in children during puberty, possibly because of the increase in growth hormone and insulin-like growth factor 1,⁵⁶ and that this state may worsen the insulin resistance present in obese children, accelerating the progression to MS and T2D.

Along with insulin resistance, MS in children is associated with a proinflammatory state,⁵ which in turn seems to be associated with a worsening in the risk of CAD. The relationship between inflammatory markers and individual components of MS is still unclear. In fact, it is not yet known if the proinflammatory state is a result of MS and insulin resistance or if, vice versa, the increase of inflammatory cytokines derived from adipocytes may be partly responsible for insulin resistance and MS.

It has been demonstrated that obese children show an elevation of C-reactive protein (CRP), which is a biomarker of the inflammation associated with adverse cardiovascular outcomes and altered glucose metabolism (**Fig. 1**).⁵ However, most studies in children do not conclusively confirm that CRP levels are associated with insulin resistance or MS,^{7,57-59} which is why some investigators suggest that an underlying inflammation may be an additional factor contributing to adverse long-term cardiovascular outcomes, independent of the insulin-resistance degree.⁵ Because CRP is just an indirect marker of inflammation, several studies have been focused on the contribution of proinflammatory adipocytokines, such as TNF- α and interleukin (IL)-6 molecules produced by adipose tissue (or adipose resident macrophages). In a multiethnic cohort of obese and lean children, IL-6 levels have been shown to increase with the degree of obesity (see **Fig. 1**); results concerning the association between TNF- α , childhood obesity, and its metabolic complications are less clear.⁶⁰ In particular, studies dealing with TNF- α in obese children show contrasting results, with some of them showing a positive association with body fat and other showing a decrease of TNF- α in obese prepubertal children;^{61,62} on the other hand,

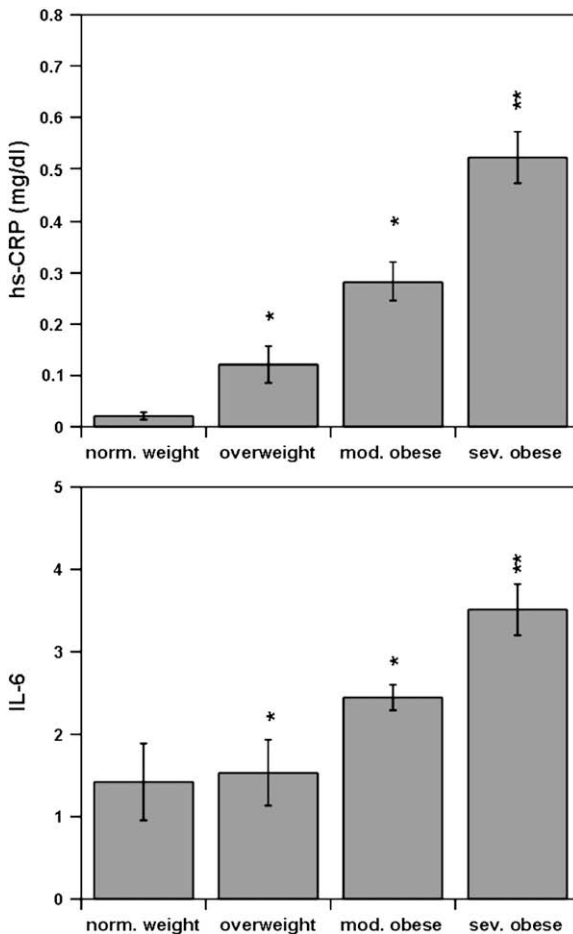


Fig. 1. Impact of severe obesity on biomarkers of inflammation in children and adolescents.

the effect of TNF- α on insulin resistance has been well demonstrated. In fact, this cytokine induces lipolysis in adipose tissue, inhibits insulin signaling, and affects the expression of some genes that are important for adipocyte function. TNF- α may also enhance the release of FFAs from adipose tissue, which affects whole-body energy homeostasis and overall insulin sensitivity.⁶³ Furthermore, a recent report demonstrated a positive correlation between IL-6, TNF- α , and adipocyte diameter studied by a needle biopsy of subcutaneous abdominal fat in obese children.⁶⁴

Along with the increase of cytokines affecting insulin sensitivity and CAD risk, adipose tissue of obese children reduces the production of the adiponectin, which is a cytokine exclusively expressed by adipocytes and that can be found in high concentration in the human blood.⁶⁰ It exerts several beneficial actions, such as anti-atherogenic, antidiabetogenic, and anti-inflammatory, hence protecting against the development of T2D and CAD.^{65,66} Interestingly, adiponectin is decreased in obesity and the decreased adiponectin levels are associated with parameters of MS in obese children.^{67,68} In summary, the co-occurrence of the insulin resistance and an adverse proinflammatory state drives the obese child to develop a worse metabolic asset, with a consequent occurrence of the most frightened complication of childhood obesity: type-2 diabetes.

IMPAIRED GLUCOSE TOLERANCE AND T2D IN YOUTH

The β -cell response to insulin resistance occurring in obese children and adolescents is by producing a vigorous state of hyperinsulinemia, which will maintain normal values of glucose levels. In the long run, however, β -cell function may deteriorate in some, and the insulin secretion will be not sufficient to maintain glucose levels within the normal range.

According to the American Diabetes Association criteria, T2D is defined as fasting plasma glucose levels higher than 126 mg/dL or plasma glucose levels higher than 200 mg/dL 2 hours after an oral glucose tolerance test (OGTT), while IGT is defined as having plasma glucose levels are higher than 140 mg/dL after OGTT.⁶⁹ Along with IGT, another prediabetic state has been individuated: impaired fasting glucose (IFG). IFG is defined as serum fasting glucose levels between 100 mg/dL and 125 mg/dL. Epidemiologic studies indicate that IFG and IGT are two distinct categories of individuals,⁷⁰ and only a small number of subjects meet both criteria, showing that these categories overlap only to a very limited extent in children, as already reported in adults.⁷⁰

According to a recent report by the SEARCH for Diabetes in Youth Study Group,⁷¹ incidence rates of T2D among children and adolescents are higher among racial and ethnic minorities than non-Hispanic whites.⁷¹ The prevalence of T2D in the United States in children is estimated to be around 5%, while the prevalence of IGT it has been estimated to be around 15%.⁷² These prevalence rates are 10 to 20 times higher than those observed in European children, independent of ethnicity and race.⁷³ In addition, the prevalence of IFG among children in the United States seems to be about 10 times higher than that observed in European obese children.⁷⁴ Not only the environment, but more the genetic background may account for these differences.

Surely, different genetic predisposition plays an important role in the development of T2D. This idea is supported both by genome-wide association studies⁷⁵ and by clinical studies, clearly showing that subjects who develop IGT or T2D have a compromising insulin secretion, even before developing IGT or T2D. When estimating insulin secretion in the context of the "resistant milieu" of IGT subjects, and thus using the disposition index (DI), it has been found that IGT subjects had a significantly lower

DI than the normal glucose tolerance group. The lower DI indicates that the secretion of insulin is not able to compensate for the increased resistance, resulting in a marked decrease in insulin-stimulated glucose metabolism in the IGT subjects.⁷⁶ More recently, Cali and colleagues⁷⁷ showed that obese adolescents with normal glucose tolerance who successively progress to IGT manifest a primary defect in β -cell function. These data are in agreement with those reported by Lyssenko and colleagues⁷⁵ on mineral protein preparation and Botnia studies on adults showing that impaired insulin secretion and action, particularly insulin secretion adjusted for insulin resistance (DI), are strong predictors of future diabetes. Moreover, the progression of obese children with insulin resistance to T2D seems to be faster than in adults.⁷⁸ An accurate case report by Gungor and colleagues⁷⁸ suggested that, despite relatively robust initial insulin secretion, the deterioration in β -cell function in youth with T2DM may be much more accelerated (approximately 15% per year) than that observed in adults.

However, because T2D in youth is a recent phenomenon, longitudinal long-term follow-up data are lacking. Findings from the SEARCH study showed that youth with T2D and relatively short diabetes duration (1.5 years in mean) have a higher prevalence of CAD risk factors compared with nondiabetic of similar age, sex, and race.⁷⁹ In the same study, it has been also suggested that adiposity and glycemic control account for much of the association between T2D and an unfavorable CAD risk-factor profile in youth.⁷⁹

ASSOCIATION BETWEEN FATTY LIVER AND MS

The intrahepatic fat accumulation induced by insulin resistance causes the development of nonalcoholic fatty liver disease (NAFLD), which is a clinic pathologic condition of emerging importance in obese children.⁸⁰ NAFLD encompasses the entire spectrum of liver conditions, ranging from asymptomatic steatosis with elevated or normal aminotransferases to steatohepatitis (nonalcoholic steatohepatitis or NASH) and advanced fibrosis with cirrhosis.^{81,82} Concurrent with the worldwide epidemic increase in childhood obesity,^{80,83} NAFLD is rapidly becoming one of the most important metabolic complications in the pediatric population. NAFLD affects 2.6% of normal children⁸⁴ and up to 77% in obese individuals.^{85,86} Studies from autopsies of 742 children (ages 2–19 years) reported fatty liver prevalence at 9.6%, and in obese children this rate increased to an alarming 38%.⁸⁶ Moreover, in the United States, 3% of adolescents present abnormal serum aminotransferases values.⁸⁷

The natural history of NAFLD is not entirely known; nevertheless, mortality among NASH patients is higher than in those with NAFLD without fibrosis or inflammation.⁸⁸ Alarming data have been shown in pediatric population. NASH is increasingly recognized in obese children^{89,90} and it has been demonstrated that it may progress to cirrhosis in this age group.⁸⁹

Although a multifactorial pathogenesis for the development of NAFLD has been demonstrated, a strong relationship between hepatic steatosis and insulin resistance has been clearly documented in large cohort-based studies of adults^{91,92} and in obese adolescent populations.^{80,93} To date, a widely accepted model for the pathogenesis of NAFLD is the “two-hit” hypothesis, where insulin resistance seems to be responsible for abnormalities in lipid storage and lipolysis in insulin-sensitive tissues, leading to an increased fatty acids flux from adipose tissue to the liver⁹⁴ and subsequent accumulation of triglycerides in the hepatocytes.⁹⁵

The “second hit” is oxidative stress, which activates inflammatory cytokines like TNF- α and generates reactive oxygen species, such as hydroxyl radicals and

superoxide anions, which can react with the excess lipid to form peroxides.^{96,97} Lipids per oxidation products may injure cells directly by interfering with membrane function or stimulate fibrosis by hepatic stellate cells.^{95,98}

It is becoming increasingly clear that NAFLD in obese youth is not only a marker of liver disease, but is also associated with important cardiovascular risk factors.⁹⁹ In fact, it has been suggested that, because of the high prevalence of fatty liver in association with obesity, insulin resistance, and alterations in glucose and lipid metabolism,^{80,99} NAFLD may be considered the hepatic manifestation of MS.

The association between NAFLD and MS has been clearly demonstrated by Burgert and colleagues.⁸⁰ In this latest study, as surrogate of liver injury, alanine aminotransferase (ALT) levels were measured in 392 obese adolescents. Elevated ALT (>35 U/L) levels were found in 14% of participants, with a predominance of White/Hispanic. After adjusting for potential confounders, rising ALT levels were associated with deterioration in insulin sensitivity and glucose tolerance, as well as increasing FFA and triglyceride levels. Furthermore, increased hepatic fat accumulation (assessed using fast MRI) was found in 32% of obese adolescents and was associated with decreased insulin sensitivity and adiponectin levels, and with increased triglycerides and visceral fat (**Fig. 2**).⁸⁰ These results demonstrate that in obese children and adolescents, hepatic fat accumulation is associated with the components of MS, such as insulin resistance, dyslipidemia, and altered glucose metabolism.

The relationship between fatty liver and glucose dysregulation has been recently demonstrated in a multiethnic group of 118 obese adolescents.¹⁰⁰ The cohort was stratified according to tertiles of hepatic fat content, measured by fat gradient MRI. All children underwent an oral glucose tolerance test and insulin sensitivity was estimated by the Matsuda Index and HOMA-IR. Independently of obesity, the severity of fatty liver was associated with the presence of prediabetes (IGT and IFG/IGT). In fact, paralleling the severity of hepatic steatosis, there was a significant decrease in insulin sensitivity and impairment in β -cell function, as indicated by the fall in the DI. Given the association with prediabetic phenotype and fatty liver, NAFLD may be considered a strong risk factor for T2DM in youth.^{80,100,101} Furthermore, paralleling the severity of fatty liver, there was a significant increase in the prevalence of MS, suggesting that hepatic steatosis may probably be a predictive factor of MS in children.¹⁰⁰

Recent studies have shown that patterns of fat partitioning are probably one major link between insulin resistance, NAFLD, and MS in obese children.¹⁰² In a multiethnic cohort study, 118 obese adolescents were stratified into tertiles based on the proportion of abdominal fat in the visceral depot. Abdominal fat and intramyocellular lipid were respectively measured by MRI and by proton magnetic resonance spectroscopy. A high proportion of visceral fat was associated with muscle and hepatic steatosis, insulin resistance, high triglycerides, and low HDL and adiponectin levels. As the proportion of visceral fat increased across tertiles, percentage subcutaneous fat decreased. Notably, the risk for MS was five times greater in the adolescents with this particular fat partitioning profile compared with those with lower visceral accumulation.¹⁰³ For this reason it has been suggested that obese adolescents with a high proportion of visceral fat and relatively low subcutaneous fat have a phenotype reminiscent of partial lipodystrophy. Those who fit this profile are not necessarily the most severe obese, yet they suffer from severe metabolic complications of obesity and are at high risk of having MS.^{102,103}

In conclusion, it is unclear whether hepatic steatosis is a consequence or a cause of the metabolic derangements in insulin sensitivity (MS). However, it is clear that liver steatosis represents a major metabolic concern in obese children, which is why it

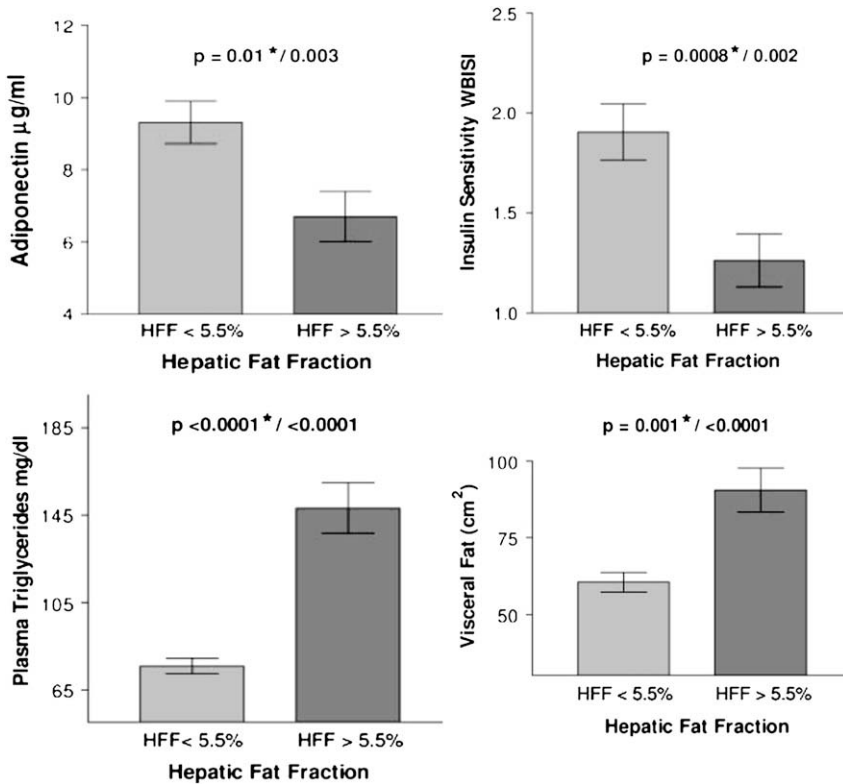


Fig. 2. Adiponectin levels, insulin sensitivity (WBISI), plasma triglycerides levels, and visceral fat in subjects with low- versus high-hepatic fat fraction (HFF). HFF was considered low when it was lower than 5.5% and high when it was higher than 5.5%. (From Burgert TS, Taksali SE, Dziura J, et al. Alanine aminotransferase levels fatty liver in childhood obesity: Associations with insulin resistance, adiponectin, and visceral fat. *J Clin Endocrinol Metab* 2006;91:6; with permission. Copyright © 2006, The Endocrine Society.)

would need to be deeply and precociously investigated and identified to prevent further metabolic complications.

CONCLUSIONS AND FUTURE PERSPECTIVES

Given the relatively recent occurrence of MS in childhood, long-term follow-up studies are not available yet. However, it is reasonable to think that the metabolic derangement observed in obese children will have dramatic repercussions on their health earlier than that observed in adults, with a consequent worsening of the prognosis in terms of morbidity and mortality when they are still youth. To date, we know that the physician has few arrows in his or her quiver to fight this disease. The majority of medicines needed to treat insulin resistance, hypercholesterolemia, hypertension, or even T2D are now off-label, although more and more studies dealing with pharmacologic treatment of obesity and its complications in pediatrics are occurring. The weight loss achieved by diet and physical exercise is still the most powerful and useful weapon against obesity and its metabolic complications.

Several genetic studies and programs dealing with childhood obesity, insulin resistance, and T2D are now ongoing all over the world. These studies have been designed

to find genes associated with these conditions and to discover how their alterations determine the occurrence of the disease. Hopefully, they will help us to achieve new objectives crossing the border that now does not allow us to give a strong and definitive answer to these diseases.

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