

Insulin Resistance Markers in Children

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Key Words

Obesity · Overweight · Insulin resistance · Children · Adolescents

Abstract

The prevalence of obesity among children and adolescents is progressively increasing around the world. One of the important consequences of obesity is the development of insulin resistance (IR). This condition has a multifactorial pathogenesis and is associated with cardiovascular risk, diabetes, hypertension, polycystic-ovary syndrome and a shorter life-span. IR during childhood may be diagnosed by physical examination or there may be clues in the histories of the patient and his/her family. When IR is suspected, tests on a blood sample (which are more reliable) are recommended. Most of the biochemical markers have been well defined in adults, but appropriate reference data for children are still lacking. Here we discuss the usefulness of various currently known biochemical markers to evaluate insulin sensitivity (homeostatic model assessment, the quantitative insulin sensitivity check index, the oral glucose tolerance test, Matsuda method and the whole-body insulin resistance index), hormones (leptin, adiponectin, resistin, glucocorticoids, the insulin-like growth factor-1-binding protein/growth hormone axis, ghrelin, sex hormone-binding globulin and retinol-binding protein-4) and inflammatory markers (C-reactive protein, IL-6, intercellular adhesion molecule-1, vascular adhesion molecule-1 and E-selectin), which can be used in the diagnosis of IR in children.

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Introduction

Obesity among children and adolescents is a problem worldwide that has become an epidemic in the last centuries. In the USA between 1988 and 1994 (the years of the National Health and Nutrition Examination Survey, NHANES, III), 10.5% of 12- to 19-year-olds were classed as being overweight (BMI greater than the 95th percentile for age and sex). By 2002 this had increased to 15.5%. In the same period, the figure for 6- to 11-year-olds increased from 11.3 to 15.3%, and that for 2- to 5-year-olds rose from 7.2 to 10.4% [1]. In the NHANES survey performed in 2003–2004, the proportion of adolescents who were overweight (defined as at or above the 95th percentile of the sex-specific BMI for age growth charts) reached 17.1%. In adults, the prevalence of obesity (BMI ≥ 30) was 32.2%, and the prevalence of extreme obesity (BMI ≥ 40) was 6.9% in women and 2.8% in men [2]. Today, in the USA the populations with the highest frequency of children and adolescents who are overweight or obese are the Mexican-American and non-Hispanic black [3].

In Canada, the proportion of obese and overweight children and adolescents is lower than that in the USA, but it is increasing. This is also the case for the populations of Latin America, which share with their northern neighbors a sedentary lifestyle and unhealthy dietary habits. It is important, however, to point out that the definition of obesity used in the Canadian study was different from that used in the NHANES study. The Canadian group used the definition from the Childhood Obesity

Table 1. International Diabetes Federation (IDF) definition of at-risk groups (top) and of metabolic syndrome (bottom) in children and adolescents [9]

Age 6 to <10 years	Age 10 to <16 years	Age ≥16 years
Obesity ≥90th percentile, as assessed by waist circumference	Obesity ≥90th percentile (or adult cutoff if lower), as assessed by waist circumference	Use existing IDF criteria for adults
Metabolic syndrome cannot be diagnosed, but further measurements should be made if the patient has a family history of metabolic syndrome, T2DM, dyslipidemia, cardiovascular disease, hypertension or obesity	Triglycerides ≥1.7 mmol/l; HDL cholesterol <1.03 mmol/l; blood pressure ≥130 mm Hg systolic or ≥85 mm Hg diastolic; glucose ≥5.6 mmol/l (oral glucose tolerance test recommended) or known T2DM	

Working Group of the International Obesity Task Force. Youths with BMI values that corresponded to an adult BMI of ≤ 24.9 were classified as normal and those with values that corresponded to an adult BMI of 25.0–29.9 were classified as overweight (preobese) [4]. In 2005, Chilean statistics showed that 38% of children at 6 years of age were overweight, 17.3% were obese and 1.3% were morbidly obese [5]. In addition, a high percentage of obese children become obese adults. Sun et al. [6] conducted a study that followed a group from childhood to adulthood, with the aim of evaluating their risks of being obese adults and developing metabolic syndrome. They found that boys who had a BMI that exceeded the 75th percentile from 12 to 17 years of age and girls who exceeded the 60th percentile from 13 to 17 years of age at more than one examination in childhood had significantly higher ORs (1.6–29 for boys, 1.5–10.5 for girls) of developing a BMI ≥ 30 as adults, compared with boys and girls of similar age whose BMI exceeded the criterion values at only a single examination in childhood.

Insulin resistance (IR) is an important condition that is associated with being overweight and obese. In 1988, Reaven [7] described the association of central obesity, hypertriglyceridemia, hypertension, low levels of HDL cholesterol and hyperglycemia, which was called syndrome X. The presence of this cluster in adults denotes a higher risk of developing type 2 diabetes mellitus (T2DM), atherosclerosis, coronary heart disease, stroke and of having a shorter lifespan. This association in children is less clear, but we know that the persistence of obesity from childhood into adulthood may also favor an early onset of diabetes, as suggested by the recent trend of the early onset of type 2 diabetes in individuals who have suffered from obesity since childhood [8]. Importantly, recent criteria to define metabolic syndrome, where IR is a key element, do not include the direct measurement of insulin as an element to consider in children

(table 1) [9]. This fact is probably due to the lack of normative data for the distribution of insulin and many of the IR markers in childhood. As will be discussed in detail, no specific cut-off values are available to make a diagnosis of IR. Therefore, in this age group it is suggested that several indirect markers of IR should be used.

IR is defined as a condition in which plasma insulin at normal concentrations has an impaired ability to adequately promote peripheral glucose disposal, hepatic glucose suppression and inhibition of very low density lipoprotein output [10].

IR frequently has a multifactorial pathogenesis: a genetic predisposition that interacts with the environment. Obese and overweight patients represent heterogeneous subgroups with different metabolic and phenotypic expressions of IR. Subjects with the same BMI may show very different degrees of IR and metabolic consequences of their obesity. Conversely, in patients with a genetic predisposition to obesity, ingesting a diet with high levels of fats and carbohydrates enhances their ability to store excess calories in tissues as fat and to promote gluconeogenesis using proteins as substrates (thrifty phenotype) [9]. In children and adolescents, obesity usually precedes the development of hyperinsulinism, which serves to compensate for the IR and, thus, prevents the appearance of glucose intolerance or T2DM. Hyperinsulinism stimulates triglyceride accumulation in hepatic and muscle tissues, and consequently decreases glucose transporter-4 translocation and favors β cell apoptosis. These two paths lead to a loss of the capacity to correctly elevate insulin after meals, and such patients have an excessive and delayed rise in insulin secretion [11, 12].

The prevalence of glucose intolerance and T2DM is increasing in children and adolescents. In 2003, Sinha et al. [12] reported that the prevalence of impaired glucose tolerance was 25% in children of 4–10 years of age who had marked obesity (BMI 32 ± 1). Similarly, the preva-

Table 2. Genetic mechanisms of insulin resistance in children and adolescents [10]

Insulin receptor pathway defects	Fat cell or lipid homeostasis pathway defects	Hypothalamic level defects (Leptin-POMC-MCR4 pathway)	Others
Type A syndrome mutation in the insulin receptor	Congenital generalized lipodystrophy (mutations in 11q13, BSCL2, AGPAT2 gene on 9q34)	POMC, MC4R and MC3R mutations	Proteases – CALP10; impaired processing of prohormones; prohormone convertase deficiency (PC1); estrogen receptor mutations
Leprechaunism	Dunnigan's syndrome (lamin Mutation)	Leptin mutations	
Rabson-Mendenhall syndrome	Kobberling's syndrome (mutation in the PPAR γ gene)	Leptin receptor gene mutation; ghrelin polymorphisms; neuropeptide Y5 receptor polymorphisms; cocaine- and amphetamine-regulated transcript polymorphisms; cholecystokinin A receptor polymorphisms	
Polymorphism in plasma cell membrane glycoprotein-1 (PC-1)	Allelic variation in PPAR γ influence body fat mass by effects on adipocyte; polymorphisms of PPAR γ gene can lead to higher triglyceride and insulin levels; polymorphism of the lipoprotein lipase gene was both linked and associated with insulin resistance; polymorphism of UCP1, UCP2, UCP3 genes; polymorphism of β_2 - and β_3 -adrenergic receptors	Single-gene defects leading to disruption of hypothalamic pathways of energy regulation	Prader-Willi syndrome (15q11.2–q12, uniparental maternal disomy); Alström syndrome (ALMS1 gene mutants in the hypothalamus might lead to hyperphagia followed by obesity and IR); Bardet-Biedl syndrome; Cohen syndrome; Beckwith-Wiedemann syndrome; Biemond syndrome II; choroideremia with deafness

MC3R = Melanocortin 3 receptor; MC4R = melanocortin 4 receptor; POMC = pro-opiomelanocortin.

lence of impaired glucose tolerance was 21% in a group of 112 obese adolescents (11–18 years of age, BMI 41 ± 1) who had been referred to the Yale Pediatric Obesity Clinic. In this latter group, 4% exhibited silent type 2 diabetes [12]. In Chile, in a group of 71 obese (BMI z score 4.7 ± 1.6) and overweight subjects (8–17 years of age, BMI z score 1.7 ± 0.5) 11.5% showed glucose intolerance and 9 were diagnosed with T2DM [13]. The authors of another Chilean study [14], observed a 3.7% prevalence of impaired fasting glucose in a group of 489 children (BMI z score 2.6–4.0) who had been referred to an obesity clinic. According to these data, using the same criteria to define normal glucose metabolism, the prevalence of altered carbohydrate metabolism appears to vary depending on ethnic background and degree of obesity.

Hyperinsulinemia serves to compensate for IR and maintain glucose homeostasis. However, patients with hyperinsulinemia without carbohydrate abnormalities are still prone to other health problems, such as early atherosclerosis, hypertension, acanthosis nigricans, hypercoagulation, polycystic-ovary syndrome, dyslipidemia, fatty liver infiltration and some types of cancer [10, 11, 15, 16].

There are some patients who have rare genetic conditions associated with IR, which are important to recog-

nize. The first column of table 2 includes several conditions which may be secondary to defects in the insulin receptor, in the second column are other diseases related to fat cell defects and in the third are described conditions secondary to defects in hypothalamic pathways of energy control [10].

IR can be suggested by a patient's history, a physical examination and the presence of biochemical markers. The gold standard to establish the diagnosis is the hyperinsulinemic-euglycemic clamp, which requires insulin infusion and serial blood sampling. It is an invasive and costly determination, and so it is only justified in a research setting [10].

Markers of IR

Family and Personal History Associated with IR

A family history of obesity, T2DM or glucose intolerance, dyslipidemia and early atherosclerotic disease (onset at younger than 50 years of age) are risk factors for IR in children [17, 18]. Whitaker et al. [19] investigated the link between adult weight and childhood and parental obesity. They found that the chance of being obese in young adulthood ranged from 8% for children who were

Table 3. Familial, clinical and physical features as risks factors for IR in children and adolescents

Family history	Patient's history	Physical examination
Glucose intolerance or T2DM	Birth weight (small or large for gestational age)	Acanthosis nigricans
Overweight or obesity	Precocious pubarche	Striae
Hypertension	Evolution of obesity	Centripetal obesity
Metabolic syndrome	Dietary habits	Adipomastia
Hyperuricemia or gout	Physical activity	Hypertension
Coronary heart disease	Medication/drugs which affect appetite, glucose or lipid metabolism	Acne
Stroke		Hirsutism
Chronic pancreatitis		Tall stature
Gestational diabetes		Precocious puberty
Polycystic-ovary syndrome or hirsutism		Genu valgum
Nonalcoholic fatty liver disease		

Table 4. Medications associated with IR

Hormones	HIV therapy	Antipsychotic drugs	Immune suppressants	Others
Glucocorticoids	HIV nucleoside reverse-transcriptase inhibitors	Clozapine	Tacrolimus	Tiazides
Growth hormone	HIV protease inhibitors	Olanzapine	Cyclosporine A	Valproate
		Risperidone	Sirolimus	Glucosamine

obese at 1 or 2 years of age but whose parents were both not obese, to 79% for those obese between 10 and 14 years of age and who had at least one obese parent [19]. Maternal waist circumference, obesity and gestational diabetes have also been associated with the development of metabolic syndrome in children [20, 21] (table 3).

Birth weight is another important risk factor. Reduced fetal growth has been shown to be associated with an increased risk of IR, obesity, cardiovascular disease and T2DM, especially when accompanied by weight gain during early life [22–24]. The decrease in adiponectin plasma levels in small for gestational age infants between 1 and 2 years of age is inversely related to weight gain [25]. In young adults, decreased insulin sensitivity has recently been reported to be determined mainly by adult body fat mass [26], with no influence of birth length or weight, which highlights the contribution of postnatal trends in the development of IR.

Conversely, being born large for gestational age has been also associated with an increased risk of IR. In Pima Indian children, glucose concentrations after 2 h of an oral glucose tolerance test showed a U-shaped relationship with birth weight in subjects older than 10 years of age, and this relation was independent of current body size [27]. Similar results have been found in adolescents

from the USA, among whom fat mass and BMI were greatest in those who had a low or a high birth weight. The lean mass index was not different among these birth weight quartiles. Low birth weight was associated with higher insulin levels in adolescence, and the effect was independent of current adolescent weight [28].

Nevertheless, other studies have shown that at any given weight for children between 2 and 47 months of age, the proportion of body fat appears to be relatively high for children who were small for gestational age at birth and low in those who were large for gestational age at birth, with a greater lean mass in the group born large [29]. Probably the mechanisms underlying IR are different in those born large compared to those born small for gestational age.

The use of medications that impact on appetite, glucose and insulin or lipid metabolism may affect insulin sensitivity (table 4) [30].

Specific Diseases Related to IR

Patients with lipodystrophy, whether acquired or congenital, present with IR. Highly active antiretroviral treatments for HIV infection are currently the most frequent cause of acquired secondary lipodystrophic syndromes. The group of genetically determined lipodystro-

phies includes: congenital generalized lipodystrophy (Berardinelli-Seip Syndrome), acquired generalized lipodystrophy (Lawrence Syndrome) or acquired partial lipodystrophy (Barraquer-Simons syndrome). The Berardinelli-Seip syndrome is in most cases associated with recessive mutations in two genes: either BSCL2, which encodes seipin, or BSCL1, which encodes AGPAT2, an acyl-transferase involved in triglyceride synthesis. The etiology of other types of lipodystrophies is unknown. Recent studies demonstrate that leptin replacement is able to reverse metabolic complications in the majority of children with congenital generalized lipodystrophy [31].

Other conditions associated with IR which may not be evident at first glance, but which should be suspected, are conditions associated with an excess of counterregulatory hormones (growth hormone, parathyroid hormone, glucocorticoids, catecholamines, placental lactogen, pregnancy) and other conditions, such as ketoacidosis, starvation, aging, cirrhosis, infections and uremia [10].

Nonalcoholic fatty liver disease is a severe complication of obesity described in adults and it is also of emerging importance in children and adolescents. This condition begins with an excessive accumulation of fat in the liver. Levels of aminotransferases are well recognized as IR markers, particularly alanine aminotransferase (ALT) which may predict the later development of type 2 diabetes [32, 33]. Burgert et al. [33] evaluated 392 obese adolescents and found a 14% prevalence of elevated ALT, especially in males and Hispanics. This feature was associated with lower insulin sensitivity and glucose tolerance and higher levels of triglycerides and fatty acids. Elevation of ALT may be associated with higher levels of γ -glutamyl-transferase and alkaline phosphatase. Usually the ratio of aspartate aminotransferase-to-ALT is <1 and increases as liver fibrosis advances [10]. Belfort et al. [34] reported a study of adults (with glucose intolerance or T2DM) who were treated with diet plus pioglitazone or diet plus placebo. Patients with pioglitazone plus diet showed improved glycemic control and glucose tolerance, normalized liver aminotransferase levels, decreased hepatic fat content (by 54 vs. 0%) and increased hepatic insulin sensitivity. Administration of pioglitazone was associated with an improvement in histological findings with regard to steatosis, ballooning necrosis, and inflammation. The pioglitazone-treated subjects exhibited a greater reduction in necroinflammation, but the reduction in fibrosis did not differ significantly from that in the placebo group [34]. There is no report of specific treatment of nonalcoholic fatty liver disease during childhood aside from dieting and exercise.

Physical Markers

During physical examination the degree of overweight or obesity should be assessed and BMI calculated, plotting the data on charts appropriate for age, gender and race.

In addition signs of IR evident upon physical examination are: acanthosis nigricans, centripetal obesity, hypertension, adipomastia in males, striae, acne and hirsutism (table 3). Puberty is also a physiological state of IR [35]. This phenomenon is present in white and black children, who show transient IR and diminished acute insulin response to glucose during puberty [36]. Therefore, it is important to take into consideration the pubertal stage for the interpretation of biochemical measures with adequate control data in the same stage.

Another important measurement during physical examination is waist circumference. Higher levels of abdominal fat deposits are associated with lower insulin sensitivity. In 1956, Vague [37] described the first observations of this fact. The appearance of abdominal obesity was labeled as central or visceral obesity (apple-shaped fat distribution) and if the subjects had predominance of adiposity on the thighs and buttocks, they were labeled as having a peripheral or gluteofemoral (pear-shaped) fat distribution. It is an easy task, but needs to be standardized [38]. Importantly, different reference values according to each population are available [39–41]. Lee et al. [42] demonstrated that both BMI percentile and waist circumference were significantly associated with insulin sensitivity. Waist circumference also remained significantly correlated with total and abdominal fat and insulin sensitivity after controlling for BMI percentile. Some studies indicate that waist circumference and BMI together are better predictors of metabolic risk than is either measure alone [43, 44]. Black and white obese adolescents show an association between visceral adiposity and lower insulin sensitivity measured by hyperinsulinemic-euglycemic clamp, but this was compensated for by higher insulin secretion only in whites [45]. A Chilean study in 47 obese female adolescents showed that no external body measurement of adiposity (skinfold thickness, waist circumference, waist-to-hip ratio) was associated with increased serum cholesterol or triglycerides, but they were associated with visceral fat and with a serum insulin $>17 \mu\text{U/ml}$ in teenagers with breast development at Tanner stage I or II [46].

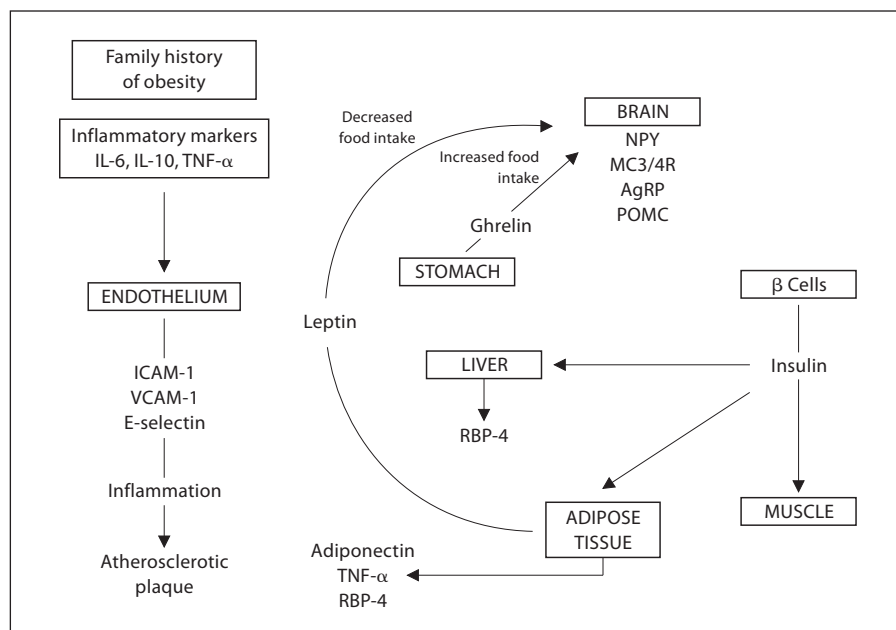


Fig. 1. Multiple mechanisms are involved in the development of IR. AgRP = Agouti-related protein; ICAM-1 = intercellular adhesion molecule-1; IL = interleukin; MC3/4R = melanocortin 3 and 4 receptors; NPY = neuropeptide Y; POMC = pro-opiomelanocortin; RBP-4 = retinol-binding protein-4; TNF- α = tumor necrosis factor- α ; VCAM-1 = vascular adhesion molecule-1.

Biochemical Definition and Methods of Measurement of IR

In children and adolescents it is difficult to have only one biochemical definition for IR, as in adults, because there does not exist a numerical definition for IR that is accepted worldwide. We can define a spectrum of insulin sensitivity and, thus, we can suspect IR. We do not know yet which thresholds to use for risk prediction in youths. As mentioned above, the gold standard to determine insulin sensitivity is the hyperinsulinemic-euglycemic clamp [47]. Nevertheless, since it is not applicable for routine evaluation, several methods have been developed in order to avoid it. Minimal model analysis of a frequently sampled intravenous glucose tolerance test (FSIVGTT) is today an alternative to the clamp technique. Although it has excellent correlation, it is also invasive and justified only in research settings [48]. The disposition index characterizes the relationship of insulin secretion to the degree of IR, calculated by acute insulin response \times insulin sensitivity obtained after the FSIVGTT. Importantly, normal values for Caucasian, African-American and Hispanic children at Tanner stages I–III are available [49]. Gungor et al. [50] evaluated 156 African-American and white children (8–19 years old) and demonstrated that insulin sensitivity measured by hyperinsulinemic-euglycemic clamp correlated strongly with the fasting glucose-to-insulin ratio, homeostatic model assessment (HOMA) and

the quantitative insulin sensitivity check index (QUICKI). They also found that the first and second phase insulin secretion correlated with fasting insulin levels, the fasting glucose-to-insulin ratio and HOMA. These results suggest that fasting glucose and insulin levels may be useful tools to evaluate insulin sensitivity and secretion in non-diabetic children and adolescents [50, 51].

In adults using an oral glucose tolerance test, fasting insulin levels of $\geq 15 \mu\text{U/ml}$ or an insulin peak of $\geq 150 \mu\text{U/ml}$ and/or $\geq 75 \mu\text{U/ml}$ 120 min after glucose charge suggest IR [52]. This approach is simple, albeit with lower sensitivity, but it correlates with indexes of insulin sensitivity obtained from glucose clamp studies and minimal model analysis [53]. Currently there are several methods used as proxies to measure IR from the oral glucose tolerance test, including HOMA, QUICKI and those of Cederholm, Matsuda, Gutt, Stumvoll, Belfiore, Soonthornpun and McAuley. All of these, with the exception of HOMA, QUICKI and the Matsuda method, have been well defined only in adults [10]. Recently, the model described by Matsuda has been validated for children with a high correlation with the hyperinsulinemic-euglycemic clamp. This model uses parameters derived from the oral glucose tolerance test to calculate the whole body insulin sensitivity index (whole body insulin sensitivity index = $10,000/\sqrt{[\text{fasting glucose} \times \text{fasting insulin}] \times [\text{mean glucose} \times \text{mean insulin during oral glucose tolerance test}]}$) [54].

In addition, a very important point in the clinical setting to interpret the insulin plasma levels is the method employed to measure insulin [55]. There are several available techniques, which differ in sensitivity and cross-reactivity with similar peptides. It is important to take into account these data when interpreting the insulin levels obtained in a given patient and when comparing cut off values obtained with other assays. Other more stable peptides have been suggested as good markers of IR.

Rutter et al. [56] published this year a study that included a group of 2,720 adults from the Framingham Offspring Study in order to use alternative thresholds defining IR to predict the incidence of T2DM and cardiovascular disease. They concluded that different percentile thresholds might be selected to optimize sensitivity versus specificity for T2DM versus cardiovascular disease prediction if surrogate IR measures are used for risk prediction [56]. These conclusions are applicable only in adults, because currently we have little evidence in youths regarding the performance of markers of insulin resistance in the prediction of major cardiovascular disease endpoints later in life.

Hormones and Binding Proteins

Leptin is a hormone secreted by adipose tissue. It crosses the blood-brain barrier and acts on pro-opiomelanocortin expression and α -melanocyte-stimulating hormone release, which interacts with melanocortin 3 and 4 receptors to reduce food intake and increase energy expenditure by activating the sympathetic nervous system [10, 57]. In normal conditions of weight maintenance, leptin concentration is positively correlated with total body fat mass [57, 58]. Leptin levels show a greater correlation with subcutaneous adiposity than with visceral adiposity [59] (fig. 1).

Adiponectin is an adipocytokine that is inversely and strongly correlated with IR, especially in obesity, lipodystrophy and inflammatory states [57]. It improves insulin sensitivity, induces fatty acid oxidation, decreases lipid synthesis and the uptake of free fatty acid. In liver adiponectin suppresses gluconeogenesis, and in muscle it favors glucose and free fatty acid oxidation [57]. Adiponectin levels decrease with increasing obesity in children and adolescents, and are especially associated with metabolic syndrome [60–62]. In the blood vessel wall, adiponectin decreases the expression of inflammatory molecules, inhibits chemotaxis of macrophages and their conversion to foam cells and it also suppresses the proliferation of smooth-muscle cells and inflammatory events in atherogenesis [57]. Recently, Winer et al. [63] demonstrated that

low levels of adiponectin are associated not only with higher levels of C-reactive protein (CRP), but also with components of the metabolic syndrome, such as low HDL cholesterol and a high triglyceride-to-HDL ratio.

Resistin was associated with IR in obese mice, but it shows only 64% homology with human resistin. Currently it has not been associated with IR or obesity in humans. Therefore, the determination of resistin is not recommended [57, 64, 65].

Glucocorticoids are insulin antagonists and in visceral fat there exist more glucocorticoid receptors than in subcutaneous fat tissue [10, 57]. In obese subjects, growth hormone levels are decreased, which leads to higher 11 β HSD1 activity, leading to elevated levels of local cortisol converted from cortisone [66]. Omental adipose tissue contains high levels of 11 β HSD1, favoring this conversion [58] and subjects with IR have increased levels of free urinary cortisol secondary to diminished levels of corticosteroid-binding globulin [10, 67]. Routine measurement of cortisol is only recommended when Cushing syndrome is suspected.

The Insulin-like growth factor (IGF-1)-binding protein/growth hormone axis may be affected by obesity and IR. Children and adolescents with IR usually exhibit decreased levels of IGF-1-binding protein, although the total level of IGF-I is normal. Nevertheless, this imbalance may increase tissue bioavailability of IGF-I and enhance the hypoglycemic effect of insulin. These patients may also show an acceleration of linear growth, skeletal maturation and pseudoacromegaly when IR is severe [10]. During puberty there is a normal elevation of growth hormone/IGF-1 and sex steroids that contribute to the development of a physiological IR state. Increased aromatization of androgens to estrogens secondary to obesity may contribute to growth acceleration and bone maturation, as well as the propensity to lipomastia and gynecomastia in adolescent boys [68].

Ghrelin is a hormone secreted by the gastric fundus which increases the sense of hunger and stimulates gastric emptying [57]. It stimulates secretion of neuropeptide Y to antagonize α -melanocyte-stimulating hormone, leading to an increase in feeding and stimulation of lipolysis [10]. Galli-Tsinopoulou et al. [69] demonstrated that in prepubertal, IR obese children, ghrelin is significantly suppressed shortly after glucose intake in an oral glucose tolerance test, and the fall in circulating ghrelin was negatively correlated with IR. A similar observation was reported in small-for-gestational age children who do not perform weight catch up growth [70]. Thus, ghrelin may be used in a research setting as a marker of IR.

Sex hormone-binding globulin levels are usually diminished in IR patients and correlate negatively with BMI. This condition increases the levels of free testosterone, leading to hyperandrogenism, expressed as hirsutism, acne and menstrual irregularities in women [10]. In males, increased aromatization of androstenedione in adipose tissue increases plasma estrone concentrations, causing gynecomastia in adolescent boys, but there is no information about a specific role of sex hormone-binding globulin in male gynecomastia. Plasma sex hormone-binding globulin levels are a good clinical marker of IR.

Retinol-binding protein-4 is a newly identified adipokine that is secreted by liver and adipocytes. A recent study in Chinese adults showed an important positive association with metabolic syndrome [71]. Serum retinol-binding protein 4 concentrations and its ratio to serum retinol are correlated with obesity, central obesity and components of metabolic syndrome in prepubertal and early pubertal children [72]. The determination of this factor is still limited only to research settings and thus it cannot yet be suggested as a routine clinical parameter. Since its levels are stable in plasma it may become useful when normal ranges are established in children of different ages.

Inflammatory Markers

Excess body weight may be associated with a state of chronic low-grade inflammation in children [73]. CRP levels become elevated with increasing obesity in children and adolescents, and this may allow the identification of a higher proportion of subjects with metabolic syndrome [62, 74]. Ford et al. [75] showed that, in a large representative sample of US children, CRP concentration was significantly elevated among those with a BMI \geq the 85th percentile, thus confirming previous findings of this association in children and adults. There are reports that have used a CRP cutoff point (measured by nephelometry) of <3 mg/l as normal, and another study found a cutoff value for CRP of 1.04 mg/l provided 58% sensitivity and 92% specificity to identify children at risk for coronary artery disease [74, 76]. However, no specific values for different age groups have been defined.

IL-6 is associated with IR as it can interfere with insulin signaling by inhibiting adipogenesis and the secretion of adiponectin [57, 64]. Levels of IL-6 are increased in black and white obese children and adolescents [61, 77]. IL-10 has been demonstrated to exert a protective effect against the development of atherosclerotic lesions in experimental animals [78], and it has been related to obesity, showing lower levels in adult women with obesity

and metabolic syndrome [79]. TNF- α is another cytokine that is related to IR. 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 inhibit synthesis of adiponectin and enhance the release of free fatty acids from adipose tissue, which affects whole-body energy homeostasis and overall insulin sensitivity [80]. Maffei et al. [73] demonstrated a positive correlation between IL-6, TNF- α and adipocyte diameter studied by a needle biopsy of subcutaneous abdominal fat in obese children.

Intercellular adhesion molecule-1, vascular adhesion molecule-1 and E-selectin are biomarkers of endothelial dysfunction. They are increased in response to inflammatory cytokines and play an important role in the formation of the atherosclerotic plaque [81]. Obese children and adolescents with IR may show increased levels of these markers, but with differences according to the individual's ethnicity. Caucasian children showed lower levels of intercellular adhesion molecule-1 and E-selectin with higher quartiles of insulin sensitivity, suggesting that excess adiposity and IR may contribute to increased circulating levels of adhesion molecules [77]. Thus, the interpretation of these markers has to be specific for ethnicity and age.

Conclusion

In summary the presence of IR may be suggested by history, physical examination and some biochemical markers. No normative data exist for the distribution of many of these biochemical markers in childhood, and no specific cutoff values are available to make the diagnosis of IR with accuracy. Thus, IR is a spectrum, and while we can suspect IR we do not yet know which thresholds to use in youths for future disease risk prediction. Appropriate therapeutic options are beyond the scope of this review but promotion of a healthy diet and activity program during infancy and childhood are key factors to prevent the development of IR, especially in children at risk.

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