Insulin resistance and obesity in childhood
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Abstract
Childhood obesity is a significant health problem that has reached epidemic proportions around the world and is associated with several metabolic and cardiovascular complications. Insulin resistance is a common feature of childhood obesity and is considered to be an important link between adiposity and the associated risk of type 2 diabetes and cardiovascular disease. Insulin resistance is also a key component of the metabolic syndrome, and its prevalence in the paediatric population is increasing, particularly among obese children and adolescents. Several factors are implicated in the pathogenesis of obesity-related insulin resistance, such as increased free fatty acids and many hormones and cytokines released by adipose tissue.
Valid and reliable methods are essential to assess the presence and the extent of insulin resistance, the associated risk factors and the effect of pharmacological and lifestyle interventions. The two most common tests to assess insulin resistance are the hyperinsulinemic euglycemic clamp and the frequently sampled i.v. glucose tolerance test utilizing the minimal model. However, both these tests are not easily accomplished, are time consuming, expensive and invasive. Simpler methods to assess insulin resistance based on surrogate markers derived from an oral glucose tolerance test or from fasting insulin and glucose levels have been validated in children and adolescents and widely used. Given the strong association between obesity, insulin resistance and the development of metabolic syndrome and cardiovascular disease, prevention and treatment of childhood obesity appear to be essential to prevent the development of insulin resistance and the associated complications.

Childhood obesity: dimension of the problem
Childhood obesity is reaching epidemic proportions and represents the most important chronic disease in this age group (1). In the USA 15.8% of children between 6 and 11 years and 16.1% of adolescents have a body mass index (BMI) in the range of overweight (2). Similar trends have also been observed in many European countries, where, based on the latest International Task Force criteria, overweight and obesity are present in 31.8% of school-aged children (3). Furthermore, the recent phenomenon of ‘nutritional transition’ with a ‘westernization’ of food, typical of many developing countries, has caused a significant rise in obesity even among populations that were unaware of this problem until some years ago (4).
Childhood obesity is associated with an increased risk for several metabolic complications, such as insulin resistance, glucose intolerance and type 2 diabetes mellitus (T2DM). In particular, insulin resistance is the most common metabolic alteration related to obesity (5), and it represents an important link between obesity and other metabolic as well as cardiovascular complications (5) (Fig. 1).
Data from the Bogalusa Heart Study clearly show that almost 20% of obese children have adverse levels of at least one cardiovascular risk factor (hypercholesterolemia, hyperinsulinemia, hypertriglyceridemia, hypertension) and the presence of multiple risk factors is strongly associated with early stages of atherosclerosis (6). As cardiovascular disease is the first cause of morbidity and mortality in adulthood, the epidemic of childhood obesity will cause a real burden for the future of the society (1).
Obese children are also at risk of developing psychological problems, orthopaedic and respiratory disorders and also certain malignancies (7). Furthermore, childhood obesity frequently tracks into adulthood (8), thus representing a major contributor to the adult obesity epidemic and to the increased cardiovascular morbidity and mortality in adult life. All these data are alarming and underline how obesity is a real threat for the health of children and adolescents.
Obesity-related insulin resistance

**Insulin resistance: definition and pathogenesis**

Insulin resistance is a state in which a given amount of insulin produces a subnormal biological response (9, 10). In particular, it is characterized by a decrease in the ability of insulin to stimulate the use of glucose by muscles and adipose tissue and to suppress hepatic glucose production and output (10). Furthermore, it accounts for a resistance to insulin action on protein and lipid metabolism and on vascular endothelial function and genes expression (11).

Several defects in the insulin signalling cascade have been implicated in the pathogenesis of insulin resistance, such as reduced synthesis or increased degradation of components of the system, an increased inhibitory serine phosphorylation of the insulin receptor or the insulin receptor substrates, the interaction of components of the system with inhibitory proteins or an alteration of the ratio of the different proteins of the signalling cascade (10–12).

Insulin resistance is believed to have both genetic and environmental factors implicated in its aetiology (10, 13). The genetic component seems to be polygenic in nature, and several genes have been suggested as potential candidates (10). However, several other factors can influence insulin sensitivity, such as obesity, ethnicity, gender, perinatal factors, puberty, sedentary lifestyle and diet (13).

**The role of fatty acids and adipocytokines**

Obesity represents the major risk factor for the development of insulin resistance in children and adolescents (14), and insulin resistance/hyperinsulinaemia is believed to be an important link between obesity and the associated metabolic abnormalities and cardiovascular risk (5). Approximately, 55% of the variance in insulin sensitivity in children can be explained by total adiposity, after adjusting for other confounders, such as age, gender, ethnicity and pubertal stage (14). Obese children have hyperinsulinaemia and peripheral insulin resistance with an ~40% lower insulin-stimulated glucose metabolism than non-obese children (15). In a recent population-based study conducted in American adolescents, insulin resistance was detected in ~50% obese subjects (16) and adiposity was also confirmed to be the most important factor affecting insulin sensitivity.

Adipose tissue seems to play a key role in the pathogenesis of insulin resistance through several released metabolites, hormones and adipocytokines that can affect different steps in insulin action (17) (Fig. 1).

Adipocytes produce non-esterified fatty acids, which inhibit carbohydrate metabolism via substrate competition and impaired intracellular insulin signalling (17–19). In children, as in adults, several ‘adipocytokines’ have been related to adiposity indexes as well as to insulin resistance.

Adiponectin is one of the most common cytokines produced by adipose tissue, with an important insulin-sensitizing effect associated with anti-atherogenetic properties (20, 21). Whereas obesity is generally associated with an increased release of metabolites by adipose tissue, levels of adiponectin are inversely related to adiposity (17). Therefore, reduced levels of this adipocytokine has been implicated in the pathogenesis of insulin resistance and metabolic syndrome (17). Decreased levels of adiponectin have been detected across tertiles of insulin resistance in children and adolescents (22), where it is a good predictor of insulin sensitivity, independently of adiposity (23).

Adipose tissue also produces tumour necrosis factor-α, an inflammatory factor, which can alter insulin action at different levels in the intracellular pathway (17). Interleukin-6 (IL-6) is another inflammatory cytokine released by adipose tissue and its levels are increased in obesity (17). IL-6 stimulates the hepatic production of C-reactive protein and this can explain the state of inflammation associated with obesity, and could mediate, at least partially, obesity-related insulin resistance (17). Data based mainly on animal studies also suggest that increased levels of resistin, another molecule produced by adipose tissue, could impair insulin sensitivity (17). There are also data showing a close relationship between leptin levels and insulin resistance in children (24). Recently, it has also been shown that serum levels of retinol-binding protein 4 (RBP4) correlate with insulin resistance in subjects with obesity as well as in those with impaired glucose tolerance (IGT) or T2DM, therefore suggesting that it could be useful in assessing insulin resistance and the associated risk for complications (25). A study
conducted in normal weight and overweight children has shown that serum RBP4 is independently related to obesity as well as to components of the metabolic syndrome (26).

In obese children, diet composition might be an additional factor promoting and/or worsening insulin resistance. Animal and human studies suggest that a high energy intake as well as a diet rich in fat and carbohydrates and low in fibre could increase the risk of developing insulin resistance (27).

The role of fat distribution

An altered partitioning of fat between s.c. and visceral or ectopic sites has been associated with insulin resistance (5). Visceral fat has a better correlation with insulin sensitivity than s.c. or total body fat (28), in both obese adults and children. Based on the ‘portal theory’, this could be related to a higher lipolytic activity of visceral when compared with s.c. fat, and therefore to a greater amount of free fatty acids and glycerol carried directly to the liver (10). Studies conducted in the paediatric population have shown that in girls the amount of visceral fat was directly correlated with basal- and glucose-stimulated insulin levels and inversely correlated - with insulin sensitivity and the rate of glucose uptake (28). By contrast, no correlation was found between abdominal s.c. fat and these metabolic indexes (28).

Ectopic deposition of fat in the liver or muscle can also be responsible for insulin resistance in obese subjects, as the accumulation of fat in these sites impairs insulin signalling, with a reduced glucose uptake in the muscle and a decreased insulin-mediated suppression of hepatic glucose production (5).

Intramyocellular lipid (IMCL) accumulation has been shown as a factor related to decreased insulin sensitivity (29, 30). Obese insulin sensitive children and adolescents present lower levels of visceral fat and IMCL when compared with obese insulin resistant children (31). Furthermore, higher IMCL has been reported in obese children with IGT when compared with normal glucose tolerance (32), suggesting a pathogenetic role of IMCL in the development of insulin resistance and IGT.

Accumulation of fat in the liver has also been associated with insulin resistance, independently of adiposity (33, 34). Recently, it has also been suggested that deposits of fat around blood vessels can produce several cytokines and therefore contribute to the development of insulin resistance, through a so-called ‘vasocrine’ effect (35).

Insulin resistance and associated complications

Insulin resistance in obesity is strictly related to the development of hypertension (36, 37), dyslipidemia (38), IGT (39), hepatic steatosis (40), as well as to the combination of these factors, also known as metabolic syndrome (41). Furthermore, insulin resistance is associated with systemic inflammation, endothelial dysfunction, early atherosclerosis and disordered fibrinolysis (42) (Fig. 1). It is alarming that these metabolic and cardiovascular complications are already found in obese children and adolescents (1). The presence of these alterations in prepubertal children (36, 40, 43) is then particularly worrying, as insulin resistance and related complications might be further exacerbated by the influence of puberty, due to the physiological decrease in insulin sensitivity associated with normal pubertal development (44).

Obese children with a similar BMI can differ on the basis of the degree of insulin resistance in the risk for complications. In fact, those with a more impaired insulin sensitivity show, for example, a greater risk for T2DM and cardiovascular disease (45).

It has also been clearly shown that insulin resistance in childhood can track in adult life (46). A recent study has shown that insulin resistance at the age of 13 years predicts insulin resistance at age 19, independently of BMI, and is also associated with cardiovascular risk in adulthood (46).

The fundamental role of insulin resistance in human disease was already recognized in 1988 by Reaven (47) who emphasized its role in the development of a grouping of metabolic abnormalities, which he defined as syndrome X. Later studies strengthened the concept of insulin resistance as a key component of the metabolic syndrome, a cluster of IGT, dyslipidemia, hypertension, hyperinsulinemia, associated with an increased risk of T2DM and cardiovascular disease (41). The prevalence of the metabolic syndrome is not particularly high in the overall paediatric population (0.4%) but it is as high as 30–50% among overweight children and adolescents (22, 48). The presence of obesity, mainly visceral obesity and reduced insulin sensitivity are the main mechanisms implicated in the development of the syndrome. A direct correlation between the degree of obesity and insulin resistance and the prevalence of the metabolic syndrome has been reported already in obese youths (41).

In obese children and adolescents, insulin resistance is the best predictor for the development of IGT (39) and T2DM (49). T2DM is a progressive disease with a gradual increase in insulin resistance associated later with a decline in insulin secretion with fasting hyperglycemia. Over the last decade, there has been an alarming increase of T2DM in youth, concomitant with the rise of obesity in this age group (49) and in the USA T2DM now accounts between 8 and 45% of all cases of diabetes diagnosed among children and adolescents (49).

Low insulin sensitivity is also a well-known contributor of high blood pressure in children (36, 37, 50). Whereas in some studies, this has been attributed to the effect of obesity itself, in others insulin resistance has
emerged as a predictor of blood pressure, independent of BMI (36, 37, 50). An insulin-mediated effect on the sympathetic nervous system and on renal sodium reabsorption are the main mechanisms suggested as potential links between insulin resistance and increased blood pressure (51–53).

In obese children, insulin resistance is also associated with an abnormal lipid profile, characterized by hypertriglyceridemia, hypercholesterolemia, low HDL-cholesterol, which increase the risk of developing early atherosclerosis (54).

Increased levels of plasminogen activator inhibitor-1 and fibrinogen have also been associated with insulin resistance, and they might contribute to the enhanced coagulability and the risk of cardiovascular diseases related to obesity and insulin resistance (17).

In obese children, increased levels of inflammatory markers, such as C-reactive protein and IL-6, have been shown to progressively increase with insulin resistance (22), and some of them have been suggested as additional components of the metabolic syndrome (22).

In obese children, as in adults, evidence exists on an association between insulin resistance and hepatic accumulation of fat (40). This has been related to a reduced effect of insulin action on adipose tissue, with a consequent lack of suppression of lipolysis and thus an increased flux of free fatty acids to the liver (55). This effect, together with an increased hepatic lipogenesis related to hyperinsulinemia, is responsible for the accumulation of triglycerides in the hepatocytes and the development of steatosis (55). Increased levels of liver enzymes, particularly alanine aminotransferase (ALT), increase with worsening insulin sensitivity (56). Based on the association of steatosis and IGT in obese adults and children, steatosis has been suggested as the hepatic manifestation of the metabolic syndrome (56, 57).

Insulin resistance has also been associated with the development of polycystic ovary syndrome (PCOS), an ovulatory dysfunction associated with hyperandrogenism not due to other causes (58). Obese girls with PCOS have an ~ 50% lower insulin sensitivity than obese-matched controls together with a 40% lower first-phase insulin secretion (59), and have a significantly increased risk of progression to T2DM, if they are left without intervention. A screening of adolescents with PCOS demonstrated that 30% had IGT and 4% already had diabetes (60).

Insulin resistance has also been suggested as a potential risk factor for the development of respiratory problems, such as asthma, in severe obese children and adolescents. In fact, obese children with asthma have a higher degree of insulin resistance than obese children without this respiratory problem, and the state of inflammation associated with insulin resistance has been suggested as a possible mediator of this relationship (61).

Assessing insulin resistance

Valid and reliable methods are essential to assess the presence and the extent of insulin resistance, the associated risk factors and the effect of lifestyle and pharmacological interventions. Different methods to assess insulin resistance are currently available and they include fasting measurements of insulin and glucose, the OGTT, the insulin tolerance test, the hyperinsulinemic euglycemic clamp and the frequently sampled i.v. glucose tolerance test (FSIVGTT) (62).

The two most common tests to measure insulin sensitivity are the hyperinsulinemic euglycemic clamp and the FSIVGTT utilizing the minimal model (62). These methods are accurate and, when labelled glucose tracers are used, they also allow differentiation between hepatic and muscular insulin resistance (62). Furthermore, the use of stable isotopes also permits the assessment of protein and lipid metabolism together with insulin sensitivity (62). However, both these tests are difficult to perform, time consuming, expensive and invasive (62).

Simpler methods based on surrogate markers derived from fasting insulin and glucose or from an OGTT have been suggested as potential alternatives. These surrogate measures include: fasting insulin, fasting glucose to fasting insulin ratio (FGIR), the homeostasis model assessment of insulin resistance (HOMA-IR), the quantitative insulin sensitivity check index (QUICKI). These indices have been validated and proposed for the purpose of screening in large populations of adults (62). Validation studies have also been performed in children and adolescents with normal glucose tolerance, with good correlation coefficients, when compared with the results derived from the clamp or FSIVGTT methods (63–65). In children and adolescents, the simple use of fasting insulin, in presence of normoglycemia, could be an estimate of insulin resistance as good as HOMA-IR, QUICKI or FGIR (66). However, the validity of these conclusions in children with IGT or T2DM remains to be determined. Furthermore, it is also important to acknowledge that there are some limitations in the use of these surrogate indexes related to the variability in insulin measurements across laboratories, with a consequent difficulty in comparing results obtained in different centres (62). However, these fasting indexes could be of particular relevance for screening purposes in populations at high risk of diabetes, such as obese children and adolescents.

Indexes derived from the OGTT have also been developed (67). Some of them, such as the whole body insulin sensitivity index and the insulin sensitivity index have been validated also in obese children and adolescents, and a strong correlation between these two indexes and the euglycemic clamp has been reported (64). These indexes could have the advantage over fasting indexes to detect earlier reductions in insulin sensitivity, mainly related to an impairment of stimulated insulin to increase peripheral glucose uptake (64). The OGTT can also offer the advantage of

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diagnosing IGT or overt diabetes, and to estimate first-phase insulin responses to a glucose challenge, and thus to evaluate the relationship between insulin secretion and insulin sensitivity (64). Therefore, the OGTT could be used as a screening test to assess insulin resistance mainly in severely obese children or in those with other risk factors associated with obesity, such as a family history of T2DM and cardiovascular diseases, who are at particular risk not only for insulin resistance but also for impaired β-cell function and IGT (39). Recently, insulin growth factor binding protein-1 (IGFBP-1) has been suggested as a new potential plasma marker to assess insulin resistance (68). IGFBP-1 seems to have a good correlation with FSIVGTT assessment of insulin sensitivity, particularly in children younger than 10 years (68). However, further studies are required to validate the utility of this marker.

Prevention of obesity and insulin resistance

Prevention of obesity and insulin resistance includes strategies that need to be started early in life, already during pregnancy and the perinatal period (69). It is important to strongly recommend breast feeding and offer guidance for appropriated food choice, caloric intake and exercise for children (69). The first step of prevention must aim towards maintaining normal BMI (69). A rapid weight gain must be avoided during the first years of life as it causes an early adiposity rebound, which is a well-known risk factor for future persistence of obesity (70). When obesity is already developed, a programme of secondary prevention is required, in order to reverse or at least to avoid progression of obesity and reduce the risk of co-morbidities (69).

Control of body weight is also particularly important during adolescence, another important period for the development of obesity (1). Puberty is a delicate period, associated with physiological insulin resistance and hyperinsulinemia. Therefore, the presence of obesity in this phase, represents an additional stress for the body, with an increased risk for complications (1).

Preventive strategies need to be further intensified in presence of other risk factors, such as a family history of obesity, T2DM or cardiovascular disease, or the presence of other risk factors for insulin resistance, such as ethnicity (71).

A recent meta-analysis of studies investigating the effect of prevention of obesity in children and adolescents has shown that these interventions are often of limited success (72), thereby suggesting a need of major efforts in preventing childhood obesity. However, the same meta-analysis, as well as another systematic review, have shown that interventions to prevent obesity are at least associated with improved dietary habits and physical activity (72, 73).

Treatment of obesity and insulin resistance

A balanced diet and increased physical activity are generally the cornerstone of the treatment of obesity and insulin resistance in children and adolescents. Decreases in body weight have been associated with a significant improvement in insulin sensitivity (74). A recent study has shown that in obese children, an 8-week exercise training programme increased insulin sensitivity and was associated with an improvement in cardiorespiratory fitness but was independent of measurable changes in body composition (75).

In children and adolescents, there is not a wide experience with weight loss medications or with insulin sensitizers. Metformin has been shown to improve insulin sensitivity and BMI in non-diabetic obese adolescents with fasting hyperinsulinemia and a family history of T2DM (76). A similar efficacy of metformin on insulin sensitivity and BMI has been found in two other small studies conducted in obese normoglycemic adolescents (77, 78).

Sibutramine seems to have a good efficacy in reducing body weight in children and, in some studies, a positive effect on glucose and lipid metabolism has also been shown (79). However, this drug has been associated with an increase in blood pressure and heart rate, thereby posing limitations for its wide use in the paediatric population (79).

Orlistat is a weight loss drug, which has been investigated in children and has been associated with a significant weight loss, even though several side effects have been associated with its use (80); mainly gastrointestinal disturbances, but also multiple vitamin deficiencies (80). No significant effects on glucose metabolism have been reported with this drug (80).

In adults thiazolidinediones have also been shown to have a good efficacy in improving insulin sensitivity (81); however, their use in children has not been yet approved, based on the lack of relevant studies in this age group.

Further controlled trials are required in order to have a better assessment of the safety and efficacy of drugs to contrast obesity and insulin resistance in children and adolescents, and to clarify which group of subjects really needs pharmacological interventions.

Conclusions

Insulin resistance represents a serious and common complication of obesity during childhood and adolescence. A timely diagnosis and an appropriated prevention and treatment of obesity and insulin resistance are required in order to reduce the associated risk of metabolic and cardiovascular complications. Greater efforts are therefore required in order to avoid obesity and the associated insulin resistant status seriously compromising the health of our children and the future of our societies.
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