Insulin Resistance And The Risk Of Diabetes

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Gianpaolo De Filippo
Pediatric Endocrinology & Adolescent Medicine Unit,
Bicêtre Hospital, Paris 11 University, France

Introduction

Insulin resistance (IR) is one of the most common metabolic alterations related to obesity, representing a key element of metabolic syndrome. Mechanisms linking obesity to IR and diabetes are multiple, sharing several molecular and genetic bases (1).

Both obesity and type 2 diabetes are associated with insulin resistance (2), but fortunately, most obese, insulin-resistant individuals do not develop hyperglycemia. Under normal conditions, pancreatic islet β-cells increase insulin release sufficiently to compensate the reduced efficacy of insulin action, allowing the maintain of normal glucose tolerance (3). For obesity and insulin resistance to be associated with type 2 diabetes, β-cells must be unable to compensate fully for decreased insulin sensitivity. β-cell dysfunction exists in individuals who are at high risk of developing the disease even when their glucose levels are still normal (4).

Thus, children predisposed to insulin resistance are also at risk for type 2 diabetes (5). The true incidence of type 2 diabetes in children and adolescents is still debated. North American and European studies show contrasting results, the former indicating an impressive rise in the incidence of type 2 diabetes in obese children and adolescents (6,7), an observation not completely shared in European cohorts (8).

Physiopathology

Fluctuations in insulin sensitivity occur during the normal life cycle, and insulin resistance is typically observed during puberty (8) and pregnancy (10).

On the other hand, lifestyle changes such as increased physical activity (11) and increased (but not restricted) carbohydrate intake are associated with enhanced insulin sensitivity (12).

Adipose tissue is considered an endocrine organ; it modulates metabolism by releasing Non –Esterified Fatty Acids (NEFAs), glycerol, hormones (including leptin and adiponectin), and proinflammatory cytokines (13).

In obesity, production of many of these products is increased, inducing a delicate balance between factors that promote and factors that protect from IR. For example, Retinol-Binding-Protein-4 (RBP4) induces insulin resistance in muscle and enhances gluconeogenesis in the liver through a retinol-dependent mechanism (14). By contrast, adiponectin acts as an insulin sensitizer, stimulating fatty acid oxidation in an AMP-activated protein kinase (AMPK)- and peroxisome proliferators activated receptor-a (PPAr-a)-dependent manner (15,16). This delicate balance can be impaired in obese children and adolescents (17).
In addition to adipocyte-derived factors, some studies showed that increased release of tumor necrosis factor alpha (TNFa), IL-6, monocyte chemoattractant protein-1 (MCP-1), and additional products of macrophages and other cells that populate adipose tissue might also play a role in the development of insulin resistance (18), as well as all components of the IL-6 biological system, including soluble IL-6 receptor and sgp 130 (19).

Pathways involving the induction of suppression of cytokine signaling (SOCS) proteins (20) and

inducible nitric oxide synthase (iNOS) (21) may be involved in mediating cytokine-induced insulin resistance. Secretion of these proinflammatory proteins, particularly MCP-1 by adipocytes, endothelial cells and monocytes, increases macrophage recruitment and thereby contributes to a self-mantaining inflammatory mechanism (22). While products of adipose tissue induce IR, other factor diminish insulino-sensitivity. The release of NEFAs may be the most critical factor in modulating insulin sensitivity. Increased NEFA levels are associated with the insulin resistance observed in both obesity and type 2 diabetes (23). It has also been proposed that increased NEFA delivery or decreased intracellular metabolism of fatty acids results in an increase in the intracellular content of fatty acid metabolites which, in turn, activates a serine/threonine kinase cascade leading to serine/threonine phosphorylation of insulin receptor substrate-1 (IRS-1) and insulin receptor substrate-2 (IRS-2) and a reduced ability of these molecules to activate PI(3)K(24). Events downstream of insulin-receptor signaling are subsequently diminished. The distribution of body fat is itself a critical determinant of insulin sensitivity. Whereas simple obesity is typically associated with insulin resistance, insulin sensitivity also varies markedly in lean individuals because of differences in body fat distribution (25). Lean individuals with a more peripheral distribution of fat are more insulin sensitive than lean subjects who have their fat distributed predominantly centrally. Furthermore, independent of visceral fat, liver fat content is a key determinant of global insulin resistance, which involves liver, muscle, and adipose tissue (26) (see corresponding chapter on non alcoholic fattly liver disease in children).

New lines of evidence show that other factors such vitamin D deficiency (27) and excess dietary salt intake (28) could play a substantial role in the development of IR. Poor vitamin D status is associated with future risk of type 2 diabetes and metabolic syndrome in obese individuals. The biological mechanisms by which vitamin D influences glycemic control in obesity are not well understood but are thought to involve enhancement of peripheral/hepatic uptake of glucose, attenuation and/or regulation of insulin synthesis/secretion by pancreatic β-cells. Excess salt intake is linked not only to increased blood pressure but also to defective insulin sensitivity and impaired glucose homeostasis (29).

Progression from insulin resistance to type 2 diabetes

Type 2 diabetes onset is progressive and the onset of type 2 diabetes is usually a slow process that takes many years. One of the main factors responsible for this characteristic is the continued decline in β-cell function, as discussed above (4). Decreased insulin release results in disordered regulation of glucose levels by decreasing suppression of hepatic glucose production and reducing the efficiency of glucose uptake in insulin-sensitive tissues. As a result of β-cell dysfunction and inadequate insulin secretion, postprandial and subsequently fasting glucose levels increase owing to incomplete suppression of hepatic glucose production and decreased efficiency of liver and muscle glucose uptake. Decreased insulin output could also impair adipocyte metabolism, resulting in increased lipolysis and elevated NEFA levels. Elevations in both NEFAs and glucose levels can occur simultaneously with an amplification of deleterious effects (29,30). Even mild impairments of insulin release may have central effects on metabolic homeostasis. Insulin acts in the hypothalamus to regulate appetite, and impaired insulin signaling is associated with changes in food intake and body weight (31).

The magnitude of the reduction in β-cell function in type 2 diabetes is consistent with a failure of the cell to respond adequately to secretagogue stimulation, an important contributor to reduced insulin release.

This conclusion is based on a number of observations. β-cells loose progressively the capacity to release insulin rapidly in response to intravenous glucose (4). Second, delivery of non-glucose secretagogues is able to acutely increase insulin release but does not result in responses equivalent to those seen with similar stimulation in healthy subjects (4). Third, although the number of β-cells is clearly reduced by about 50% in type 2 diabetes (32,33), this degree of β-cell loss cannot fully account for the change in secretory function, because by the time diabetes can be diagnosed, the cell is operating at 25% or less of its functional capacity (34).

The extremely elevated blood glucose levels frequently observed in diabetes might contribute to further disease progression through glucotoxic effects on the β-cell and harmful effects on insulin sensitivity, both of which can be ameliorated by therapeutically lowering the glucose level (35). By contrast, the acute raise of the blood glucose level experimentally induced for 20 hours in healthy subjects has exactly the opposite effect: it improves insulin sensitivity and enhances β-cell function (36). These observations suggest that a pre-existing, and perhaps genetically determined, risk is crucial for β-cell dysfunction to occur. It is this pre-existing abnormality that results, with time, in a progressive impairment in insulin release and, ultimately, an increase in glucose levels, the latter of which further aggravates the situation and contributes to β-cell failure. A second metabolic disturbance that might contribute in a feed forward manner to progressive loss of β-cell function is elevated plasma NEFA concentrations. Although NEFAs are critical for normal insulin release, chronic exposure to NEFAs *in vitro* and *in vivo* is associated with marked impairments in glucose-stimulated insulin secretion and decreased insulin biosynthesis (37,38).

Recent studies have described trajectories in plasma glucose, insulin sensitivity, beta cell function, and subclinical inflammation related to diabetes before the disease is diagnosed. These population-level growth curves contribute to etiological and pathophysiological understanding but may somewhat oversimplify the complex and heterogeneous disease mechanisms responsible for type 2 diabetes (39-41).

Given that β-cell function is decreased by about 75% when fasting hyperglycemia is present, assessment of β-cell function in individuals at risk of developing diabetes has been of interest to better understand the physiopathology of diabetes progression. Even when the glucose level is still within the normal range, β-cell function decreases progressively with a corresponding increase of fasting glucose (42). First-degree relatives of individuals with type 2 diabetes, who are genetically at increased risk, also have impaired β-cell function, even though they may still have normal glucose tolerance (43). Data from groups of first-degree relatives with different ethnic backgrounds suggest that common processes underlie the development of type 2 diabetes — namely, insulin resistance and β-cell dysfunction — and that the degree of abnormality of insulin release is the dominant determinant of differences in glucose tolerance between individuals (44)).

Genes and environment

Genetics and heritability play a role in childhood insulin-resistance and future development of diabetes. Many genes, together with their interactions with the environment, are involved in the development of obesity and diabetes. In the case of obesity, the most frequent mutation is that in the melanocortin-4 receptor gene, which accounts for up to 4% of cases of severe obesity. Other rare causes include mutations in leptin and the leptin receptor, prohormone convertase 1 (PC1) and pro-opiomelanocortin (POMC) (45). At the state of knowledge, these genes are associated with obesity but do not seem to enhance directly the susceptibility to diabetes. The gene variant most commonly associated with insulin sensitivity is the P12A polymorphism in PPAR γ, which is associated with an increased risk of developing diabetes (46,47). A number of genes associated with β-cell dysfunction have been identified, and include hepatocyte nuclear factor-4α and 1α — genes known to cause the monogenic disorder maturity onset diabetes of the young (MODY), the E23K polymorphism in the islet ATP-sensitive potassium channel Kir6.2 (encoded by KCNJ11), two non-coding single-nucleotide polymorphisms in transcription factor 7-like 2 (TCF7L2) and mutations in the mitochondrial genome that are also associated with neurosensory hearing loss. Other genes, including calpain 10, adiponectin, PPAR-γcoactivator 1 (PGC1) and the glucose transporter GLUT2 are interesting candidates (1,47).

Diagnosis of IR

Identification and diagnosis of insulin resistance usually relies on clinical and biochemical features.

Clinical features

Acanthosis nigricans (AN) (figure) is so closely linked with IR that is has been called a clinical surrogate for laboratory-determined hyperinsulinemia (48). AN is characterized by the presence of visible posterolateral neck pigment and/or texture and visible axillary pigment and/or texture. In one study (49), the reproducibility of palpable texture was limited, and visible texture grading seemed to be more reproducible. Considering that the onset of hyperglycemia is usually slow and symptoms such as polyuria and polydipsia are often subtle and may go unrecognized by the patient. Thus, the presence of AN, associated with obesity could be the unique clinical sign of incipient (or present) type 2 diabetes).

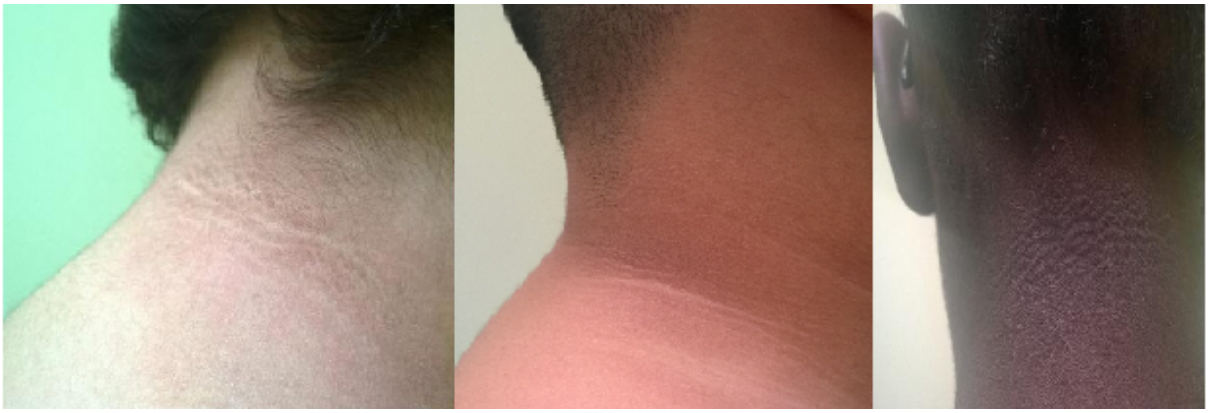

Figure 1: visible acanthosis nigricans on the neck of a Caucasian boy (a), a North-African boy (b), and a Black-African girl (c)

Biochemical features

To date, there is still a lack of adequate reference data for markers of insulin resistance, and thus, there is no universally accepted biochemical definition of IR in children and adolescents. Several methods have been proposed, stemming from reports of adult cohorts (table). The gold standard method to measure insulin sensitivity (the hyperinsulinemic euglycemic clamp) is very labor- and time-intensive and thus not feasible in epidemiological research.

The fasting insulin level and the homeostasis model assessment to quantify insulin resistance (HOMA-IR, [glucose (mmol/l) x insulin (µUI/ml)/22.5]) (50) have been suggested among others as surrogate markers for screening adults, As the HOMA-IR varies among populations, there is no agreement on HOMA-IR cutoffs (51), its utility in pediatric age is still controversial and apparently it does not offer any diagnostic advantages over fasting insulin in euglycemic children (52)

Several authors have published data on the distribution of insulin, glucose and HOMA-IR values in pediatric populations, and some also suggested cut-off values for insulin and HOMA-IR (52, 53). However, the majority of these studies were limited to national study populations, and the sample sizes were mostly too small for statistical modeling of reference values. The IDEFICS (Identification and Prevention of Dietary and Lifestyle Induced health effects in children and infants) study, the characteristics of which are detailed in another part of this book (see corresponding chapter), present age- and sex-specific reference values for insulin, glucose and HOMA-IR based on a population of normal-weight prepubertal children from eight European countries (54). In this study, the 5th and 95th percentiles of insulin levels in 3 to < 3.5-year-olds were 4.2 and 49.3 pmol/l, respectively, in girls, and 3.5 and 41.0 pmol/l, respectively, in boys. In 10.5 to < 11-year-olds, the 5th and 95th percentiles were 25.7 and 100.7 pmol/l, respectively, in girls and 19.4 and 88.2 pmol/l respectively, in boys.

For HOMA-IR, the 5th and 95th percentiles in 3 to < 3.5-year-olds were 0.1 and 1.5, respectively, in girls and 0.1 and 1.3, respectively, in boys. In 10.5 to < 11-year-olds, the 5th and 95th percentile HOMA-IR values were 0.8 and 3.4, respectively, in girls and 0.6 and 3.0, respectively, in boys.
It is reasonable to state that a HOMA value > 3.5 indicates a state of IR.

In 2000, a new simple insulin sensitivity check index (QUICKI: 1/(log (insulin µUI/ml)) + log (glucose mg/dl) - values in normal subjects are about 0.4) was proposed (55). Despite initial reports that QUICKI seemed to correlate better than HOMA to the minimal model and euglycemic clamp, HOMA is more often used in epidemiological studies.

Table 1: Derived indexes of IR from fasting blood samples

Index	**Formula**
HOMA-IR	Fasting insulin (µU/ml) x fasting glucose (mmol/l)/22.5
QUICKI	1/(log fasting insulin [µU/ml] + log glucose [mg/dl])
HOMA –b%	20 x fasting insulin (µU/ml)/ (fasting glucose [mmol/l] - 3.5)
FGIR	Fasting glucose (mg/dl)/fasting insulin (µU/ml)

HOMA – IR : homeostasis model assessment for insulin resistance
QUICKI : quantitative insulin-sensitivity check index
HOMA-b% : HOMA of percent b cell function (assuming that normal young subjects have 100 % b cell function)
FGIR : fasting glucose-to-insulin ratio

Diagnosis of Diabetes

The adaptive response of healthy β-cells to insulin resistance involves changes in both function and mass and is so efficient that normal glucose tolerance is maintained. But when there is β-cell dysfunction, impaired glucose metabolism and finally type 2 diabetes results. Yet only a small fraction of obese individuals with insulin resistance progress to type 2 diabetes (56). Generally, the onset of type 2 diabetes in an obese adolescent progresses slowly. Initial clinical manifestations are difficult to detect. This scenario deeply contrasts with the dramatic onset of the classical form of type 1 diabetes of the young, in which the clinical onset is always evident. A pitfall has to kept in mind: a rapid weight loss in an obese adolescent (who may be happy of this unexpected situation and try to hide his polyuro-polydipsia) is in some cases the first alarming feature of ketoacidosis and later diabetic coma. Type 1 diabetes cannot be ruled out in obese children and adolescents although type 2 diabetes is the commonest form associated to obesity.

A high proportion of cases of type 2 diabetes, that should be routinely assessed, appears to be initially undiagnosed.

The diagnostic criteria for diabetes mellitus are shown in table 2.

Table 2. Criteria for the diagnosis of diabetes (from 57)

FPG ≥126mg/dL (7.0 mmol/L). OR Two-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an OGTT OR In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L). OR HbA1C ≥6.5%.

FPG : fasting plasma glucose
OGTT : oral glucose tolerance test
HbA1c : glycated haemogloblin

Clinical impact

Most of the observations concerning the progression from impaired glucose tolerance to diabetes over time and the possibility of preventing or delaying progression have been made in adult populations. It is questionable whether the entire body of evidence is applicable to children and adolescents. The American population seems more prone to develop type 2 diabetes in the context of severe obesity, even if the heterogeneity of the studied populations should does not allow definitive conclusions. A recent study (5) showed that the prevalence of type 2 diabetes among youth aged 10 to 19 years showed a relative increase of 35% from 2001 to 2009, increasing from 0.34 per 1000 in 2001 to 0.46 per 1000 in 2009. A statistically significant increase was seen in both sexes, in those aged 10 through 14 years and 15 through 19 years, and in white, black, and Hispanic youth. No significant changes were seen in Asian Pacific Islander or American Indian youth. The prevalence was somewhat lower than that reported in the Studies to Treat or Prevent Pediatric Type 2 Diabetes33 (STOPP-T2D) involving eighth-grade students, which documented a 0.5% prevalence of elevated screening glucose levels; however, only a single screening test was used (7). In a primary care-based study of free-living children and adolescents, a 30.8% overall prevalence of metabolic syndrome was observed. Of the entire cohort, 16.6% had fasting hyperglycemia, defined as a fasting glucose value ≥ 5.5 mmol/l (7). As an epidemiological study on presumably healthy individuals, OGTT was not performed for economic and ethical reasons. A glucose value ranging from 5.6 to 6.9 mmol/l allows classifying the individual as being at high risk of diabetes (i.e. in a prediabetic state) (57). This body of evidence indicates that type 2 diabetes in adolescents is an emerging problem in Europe not only in ethnic minority groups, but also in multiethnic, mostly Caucasian, European populations.

Therapeutics

Despite the fact that the treatment of type 2 diabetes in children and adolescents is an area of active research, actually, there is no recommended systematic pharmacological treatment for isolated IR. When hyperglycemia appears, standard approaches to the treatment of IR associated with obesity include weight loss and drug therapy. Therefore, screening for IR is not justified in the clinical setting for children, including those with obesity. The mere presence of obesity should call for intervention to lower weight and consequently improve insulin sensitivity without an imperative need to measure insulin levels (52).

Even in adults with overt type 2 diabetes, interventions should initially be aimed towards improvement in tissue insulin sensitivity. While lifestyle changes are a cost-effective method of delaying the progression of impaired fasting glucose to diabetes mellitus, implementation is often difficult in the clinical setting. When a pharmacological choice is made, the first step is to administer metformin, a biguanide that is thought to reduce hepatic glucose production and improve IR (58). While its approved use is for the treatment of diabetes, it has been largely used off-label for the management of IR in children and adolescents (59) (for a more detailed discussion, please refer to corresponding chapter). A recent meta-analysis of 14 clinical trials studying the efficacy of metformin for weight loss among obese children and adolescents found a statistically significant reduction in BMI after 6 months, with the effect fading to non-significance by 12 months (60). The choice of therapeutic management should be individualized, taking in account all behavioral and clinical aspects.

A more detailed discussion on therapeutic approach can be found in the corresponding chapter.

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~ About the Authors ~

Gianpaolo De Filippo

Gianpaolo De Filippo is pediatric endocrinologist at Paris Sud University, France.

He received his medical degree, completed Pediatrics residency and received PhD in Clinical Physiopathology and Experimental Medicine from the University of Naples « Federico II ». He completed his academic formation with fellowship at Saint Vincent de Paul Hospital in Paris and obtained degrees in Pediatric Endocrinology and Diabetology and Basic and Fundamental Hormonology from the Réné Descartes University in Paris.

Actually, he is the responsible of clinical and research programs concerning severe obesity of children and adolescents at Paris Sud University, with particular regard to metabolic complications of severe obesity and bariatric surgery.

He is an active member of several scientific societies (Italian and French societies for pediatric endocrinology, European Society of Endocrinology), author of papers on metabolic complications of severe obesity, sparing from childhood to adult age and reviewer for themes of endocrine and metabolic diseases.

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