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Early Insulin Resistance, Type 2 Diabetes, and Treatment Options in Childhood

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Insulin resistance · Type 2 diabetes · Obesity

Abstract
Background: Type 2 diabetes (T2D) represents just the tip of the iceberg of the complex metabolic alterations associated with obesity and other clinical conditions associated to impaired adipose tissue storage. ***Summary:*** Available data have suggested the presence of a continuous spectrum of metabolic alterations developed in the progression from insulin resistance (IR) to T2D, most of which are likely preventable through the early characterization of all the multiple risk factors involved. Therefore, the complete characterization of the natural history of the disease and the major modifiable factors represents a milestone in the daily care of young subject at risk for the development of impaired glucose metabolism early in life. This review will focus on the main components defining the risk of IR and T2D in childhood with a specific focus on the main aspects of treatment options available in children and adolescents. ***Key messages:*** Impaired adipose tissue storage documented in obesity results in a continuous spectrum of metabolic alterations ranging from IR to T2DM. These metabolic alterations are mostly likely preventable through the early characterization of all the multiple risk factors involved. The complete characterization of the disease and of the major modifiable factors represent a milestone in the daily care of young subject at risk for the development of impaired glucose metabolism early in life.

Introduction

Type 2 diabetes (T2D) mellitus is no longer considered an entity confined only in the elderly. Moreover, during the last decades, several reports showed a persistently increasing prevalence of the disease also in childhood, mostly in those subjects affected by obesity [1]. Insulin resistance (IR), considered as an impaired balance between an abnormal cellular response and insulin actions together with a relative pancreatic β-cell insufficiency, is one of the leading causes of T2D. As well, IR strongly correlates with other different dysmetabolic conditions, such as dyslipidemia, fatty liver disease, hy-

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pertension, hyperinsulinemia and obesity, representing the milestones of the metabolic syndrome (MetS). Cardiovascular diseases are often due to this cluster of disorders, which determines precocious chronic complications in adolescents who develop T2D [2]. T2D represents just the tip of the iceberg of the complex metabolic alterations associated with obesity. In fact, available data have suggested the presence of a continuous spectrum of metabolic alterations developed in the progression from IR to T2D, most of which are likely preventable through the early characterization of all the multiple risk factors involved. Obesity per se represents one of the major factors explaining the risk of IR documented in obese children and adolescents. Particularly, visceral adiposity and ectopic fat accumulation, like into the liver and muscles, strongly affect the development of metabolic alteration in obese subjects. However, several studies have also shown risks specifically related to race, gender, and age for developing T2D [3]. Besides obesity, additional risk factors might be involved including genetic, family history, lifestyle, and perinatal factors. Therefore, all these components need to be evaluated in order to properly contrast the progression of metabolic alteration related to obesity and those state of impaired adipose tissue storage.

Discovery of Insulin

According to the constant increasing prevalence of both obesity and T2D all over the world, IR and its related consequences have then gained further relevance. Hence, the knowledge of insulin, its roles and complex processes, is essential to explain the resulting chronic diseases [4].

In 1889, Minkowski and von Mering discovered the development of an impaired metabolic status characterizing a state of severe diabetes, following the hypothesis that the metabolic control of the human body was mediated by a substance released by the islets of Langerhans. In the following years, the pancreatic islet mediator was named as "insuline"; only in 1921, insulin was isolated and accessible for therapeutic use and a significant restoring of glucose levels was registered in dogs, which underwent a pancreatectomy, treated with intravenous insulin administration. Furthermore, insulin showed to be able to restore hepatic glycogen depots and normalize ketonemia. In 1922, insulin was first dispensed in humans as treatment for diabetes, registering the resolution of symptoms [5].

Islet of Langerhans and Biochemical Structure of Insulin

α-Cells and β-cells are the most numerous cells described in the islets of Langerhans, respectively, responsible for glucagon and insulin production, two hormones with distinct and opposite functions. Insulin has a lowering effect on blood glucose values; instead, glucagon tends to increase glucose levels in the circulation [6]. Somatostatin is also produced by islet of Langerhans, in particular by delta cells, and realizes a glucose homeostasis regulation by carrying out an inhibitor action of both glucagon and insulin release [7].

In 1928, insulin was recognized as a polypeptide and its complete amino acid sequence was identified in 1952 [8]. Specifically, insulin is a 51 amino acid dipeptide consisting of two chains, A and B containing, respectively, 21 and 30 amino acids, linked by disulphide bridges originated from cysteine residues, with a total molecular weight of 5,802 μ. Insulin is encoded by the short arm of chromosome 11 and derives from its original precursor, preproinsulin, characterized by the set of a signal peptide, the B chain, the A chain, and a connecting peptide (C-peptide), for a total of 100 amino acids. With the removal of the signal peptide, proinsulin is formed in the rough endoplasmic reticulum, with the C-peptide connecting the N-terminus of the A chain to the C-terminus of the B chain through dibasic residues at its extremities (Arg-Arg and Lys-Arg) [9]. From rough endoplasmic reticulum, proinsulin is then transferred via secretory vesicles to the Golgi apparatus that presents an environment rich in calcium, facilitating synthesis of soluble zinc-containing proinsulin hexamers. Thanks to the trypsin-like endoprotease enzymes, insulin and C-peptide are then created outside the Golgi from proinsulin, after the removal of the dibasic residues. Blood vessels receive an equimolar ratio of insulin and C-peptide, released by β-cells via exocytosis [10]. Of this secretion, proinsulin and zinc represent about 6%. Insulin is stored in mature granules as hexamers containing zinc ions in the center and with the peculiarities of hydrophobicity and stability as crystals at pH 5.5.

Release of Insulin

Insulin plays an important role in the preservation of a normal metabolism, by following the metabolic requests of healthy subjects (Fig. 1). Glucose is considered the most important regulator of insulin secretion by se-

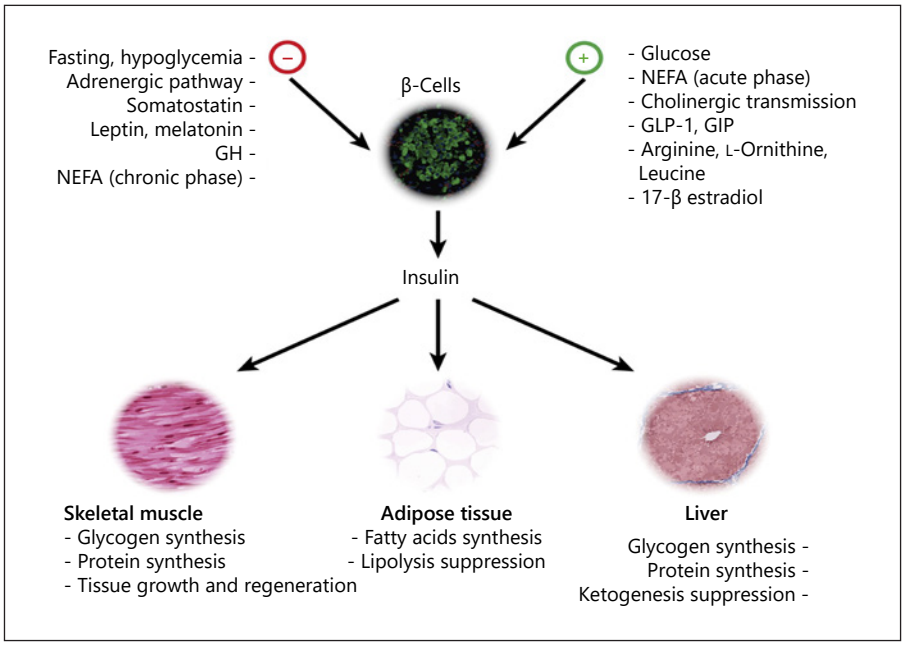

Fig. 1. Major regulator of insulin secretion and main metabolic effects of insulin on target tissues. NEFA, Nonesterified fatty acids; GH, growth hormone; GLP-1, glucagon-like peptide 1; GIP, gastric inhibitory peptide.

cretory granules in the pancreatic β-cells. Skeletal muscle and adipose tissue are the main insulin target tissues by stimulating glucose uptake to preserve blood glucose homeostasis. Insulin reaches the same result by interrupting glucose production by the liver.

When glucose levels in blood vessels arise, a specific glucose transporter protein (GLUT)2 determines the uptake of glucose by facilitated diffusion into the β-cell, guaranteeing a high glucose inflow thanks to its low substrate affinity. GLUT2 tends to maintain the intracellular glucose concentration as the one present in the extracellular fluid [11]. Glucokinase acts as a glucose sensor and monitors its speed of utilization. Once inside the β-cell, glucose is phosphorylated by glucokinase, creating glucose-6-phosphate that is subsequently processed through the glycolysis and the tricarboxylic acid cycle (TCA cycle or also called Krebs cycle), thus generating ATP [12]. The increased ATP/ADP ratio induces the closure of ATP-dependent K+-channels, whose structure is divided into four small internal subunits binding ATP, called Kir6.2, and four major external subunits, called SUR1, where sulfonylureas bind. The binding to one of the subunits depolarizes the cellular membrane and the consequent opening of the voltage-dependent Ca^{2+}-channels. The increase in intracellular Ca^{2+} activates the insulin secretory granules to fuse with plasma membrane and release insulin as hexamers. Other modulators of insulin secretion, such as acetylcholine and cholecystokinin, act on the pathways G-protein associated to phospholipases and protein kinase C, while α- and β-adrenergic stimulations and glucagon-like peptide 1 (GLP-1) act on the pathways G-protein connected to adenylyl cyclase and cAMP [13].

Regulation of Insulin Secretion

Insulin secretion shows a pulsatile pattern, represented by the summation of secretory spurts deriving from highly numerous pancreatic islet cells (Fig. 1). Glucose action determines a biphasic insulin release, with a transient rapid first phase, followed by a less intense but more continuous secretion of insulin [14]. In particular, by administering intravenous glucose, a rapid insulin secretion lasting 10 min and a peaking at 3–5 min is registered; it represents the already synthesized insulin. The second part of insulin release does not appear for 10 min after the glucose bolus, but has the same duration as the hyperglycemia state and shows a proportional concentration to the initial glucose value. This represents both stored and recently synthesized insulin. A different condition is seen in case of oral glucose administration: gastrointestinal motility and hormones have an effect on glucose absorption and subsequent insulin secretion that is protracted after taking glucose [15].

Glucose is responsible not only for insulin release but also for its synthesis, by increasing the transcription of insulin gene [16]. Nevertheless, other biological substances, such as humoral factors, hormones, macronutrients, and

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neural transmission, may have a role in this reaction. In response to the sight or smell of food, a variable amount of insulin is produced representing the so-called cephalic phase mediated by vagus nerve stimulation. So, cholinergic transmission has a positive effect on insulin secretion; however, conditions as fasting or hypoglycemia do not facilitate this releasing system. On the contrary, adrenergic pathway mediated by catecholamines, interacting with α2-adrenoreceptors, realizes an inhibition of insulin release, during stressful situations [17]. Receiving stimulations by nutrient load, the gut controls the secretion of peptide hormones, among which somatostatin and GLP-1 stand out, that respectively inhibit and activate insulin actions. GLP-1 and gastric inhibitory protein are incretin, whose role is activating a greater secretion of glucose-induced insulin. An inhibitory effect on insulin secretion is also exerted by leptin, an adipokine released by adipocytes influencing insulin action especially in fat tissue and hepatic cells [18, 19]. Amino acids are one of the nutrients that most stimulate insulin secretion, such as arginine and leucine, thanks to their insulinotropic effect. Insulin release in response to intravenous arginine shows a proportional level to the basal glucose and appears 2–10 min after the injection [20]. Generally, insulin is secreted according to the types, proportions, and specific components of the ingested foods [21]. Nonesterified fatty acids act differently in the context of acute or chronic elevation: in the first case, they provoke the rise of insulin secretion stimulated by glucose, while in the second case they reduce both the release as well as the synthesis of insulin.

Insulin Receptors

The active form of insulin is the monomer. It determines the stimulation of a complex cascade of signal transduction binding to receptors. The first characterization of insulin receptor was in 1971 as belonging to the class of the tyrosine kinases receptors [22]. The gene encoding for the insulin receptor is situated on the short arm of chromosome 19. The receptor is a hetero-tetramer at the level of cell membrane, consisting of 2 α and 2 β glycoprotein subunits, held together by disulfide bonds between them and synthesized from a single mRNA comprising 22 exons and 21 introns. According to whether the splicing of exon 11 is realized or not, two receptor isoforms are present: the insulin receptor A does not have the exon 11, instead insulin receptor B shows it. These two forms are similar, except for a minor difference in their affinity for insulin [23]. The extracellular portion of the receptor is made up of the α-chain and 194 residues of the β-chain. In addition to this, the β-chain contains a single transmembrane part and the tyrosine kinase activity domain in the cytoplasm. The binding part of the receptor is the extracellular α subunit, which provokes a conformational change, allowing ATP to bind the intracellular portion of the β unit. The result is the phosphorylation of the β unit and the tyrosine residues of intracellular substrate proteins, after their recruitment. These proteins, also called insulin-responsive substrates (IRS), are then useful to activate signaling pathways involved in the expression of additional insulin actions. The most characterized substrates are IRS-1–4 [24].

A minor characterization has been realized for IRS-3 and IRS-4 that show a specific distribution, respectively, in the fat tissue, the liver, β-cells and the thymus, the brain, and kidneys. IRS-1 and IRS-2 can be found in the same types of tissue, but IRS-1 is considered the main IRS present in skeletal muscle, while liver host IRS-2 as the major one. IRS-1 organizes the release of insulin based on glucose blood values, facilitates insulin mitogenic effects and receives phosphorylation not only by insulin receptor but also by insulin-like growth factor-1 receptor. Instead, insulin actions in the peripheral districts and β-cell development are mediated by IRS-2 [25].

A phosphorylated tyrosine residue of IRS-1 becomes the anchoring point of src-homology-2 domain, housed by different proteins with enzymatic activity, such as phosphatidylinositol 3-kinase (PI 3-kinase) and phosphotyrosine phosphatase SHPTP2 (or Syp). IRS proteins, once phosphorylated, bind other proteins that do not present enzymatic activity: an example is Grb2, an adaptor protein, which determines the activation of RAS signaling system. In particular, PI 3-kinase and RAS are characterized by realizing different aspects of the insulin action. PI 3-kinase pathway activates a signaling cascade including protein kinase B, also known as Akt, responsible for translocation of the GLUT4, activation of glycogen synthase and other enzymes leading to metabolic effects of insulin. RAS pathway includes downstream activation of mitogen-activated protein kinase and extracellular signal-regulated kinases 1 and 2, that provide for mitogenic effects, such as cell growth (Fig. 2) [26].

Actions of Insulin

Insulin is considered a strong anabolic hormone that facilitates the storage of substrates and inhibits their release (Fig. 1). Insulin exerts actions at different cellular

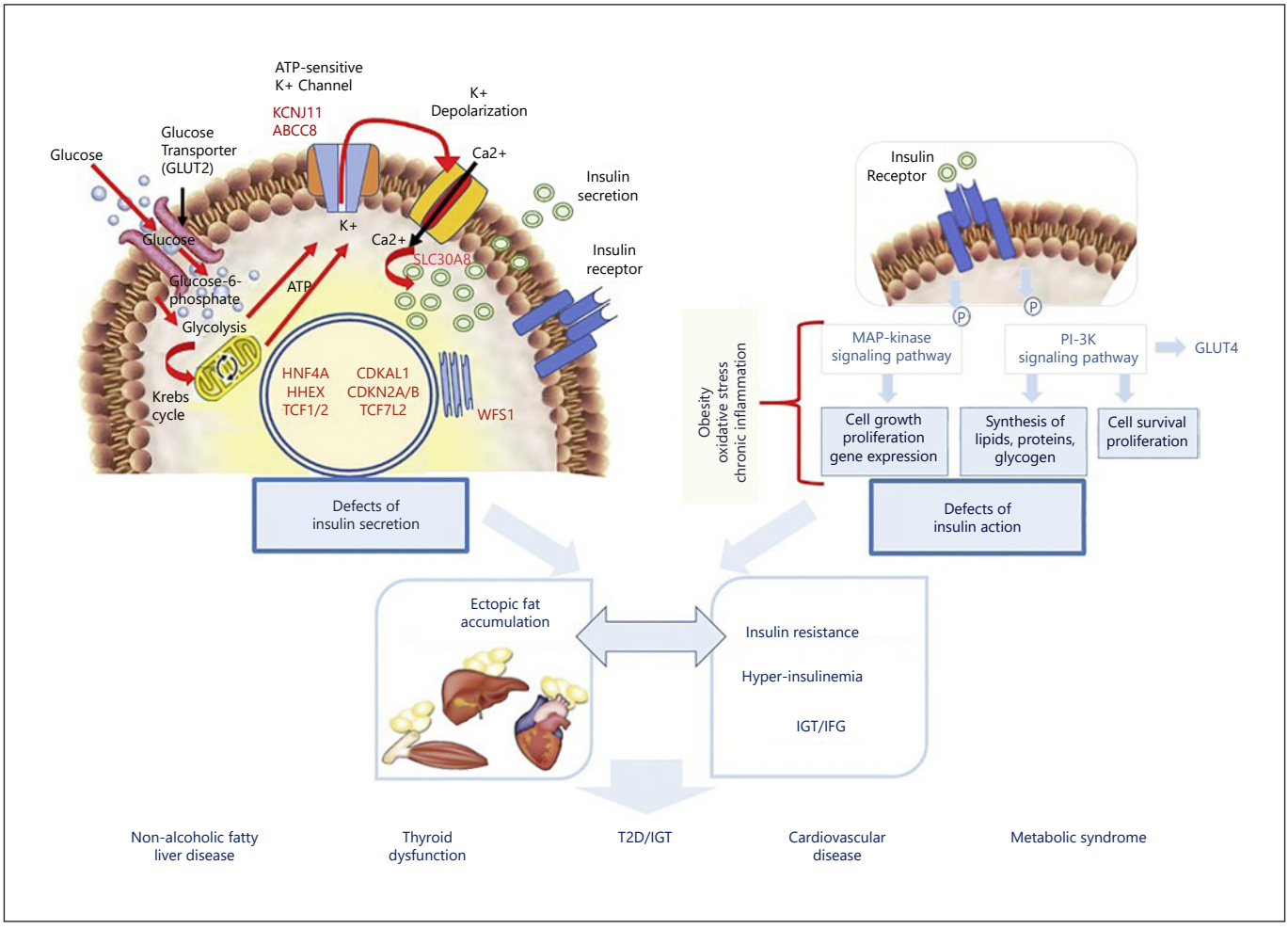

Fig. 2. The complex pathway linking the alterations of insulin secretion and/or insulin action affecting ectopic fat accumulation and alteration of glucose metabolism related to obesity and obesity-related complications in children.

levels, accomplishing a metabolic control. Glucose, lipid, and protein metabolisms are strictly coordinated by insulin actions directly on the liver, skeletal muscle, and adipose tissue that represent the insulin targets tissues [27]. Therefore, factors affecting both insulin secretion and insulin action are directly related to ectopic fat accumulation and alterations of glucose metabolism leading to obese related complications (Fig. 2).

Glucose transport into cells is different according to their nature and is mediated by GLUTs, which differ in their affinity for glucose (*Km*) according to the subtype and to the regulation of insulin. So far, at least 5 subtypes of GLUT transporter have been recognized. In skeletal muscle and adipose tissue, insulin incites glucose transport from the plasma to the cytoplasm, where it receives phosphorylation. Specifically, GLUT4 is the major GLUT in cells belonging to adipose and muscle tissues. Its translocation from intracellular to extracellular into the plasma membrane of muscle cells and adipocytes is a consequence of PI 3-kinase's activation [28]. GLUT4 shows insulin dependence and low affinity for glucose (high *Km*), characteristics that can be sustained thanks to the great amount of energy stored in fat tissue, that allows glucose to enter into cells in response of elevated glucose levels. Once entered, glucose stimulates fatty acids and glycerol synthesis and indirectly through insulin action lipolysis suppression. On the contrary, during fasting, which is characterized by low glucose and insulin levels, no current of glucose entering is registered and lipolysis is then stimulated. After a meal, glucose transport into muscle cells enables glycogen synthesis (Fig 2).

Glucose Metabolism

Glycogen metabolism is the result of the actions exerted by protein phosphatase I: glycogenolysis can be inhibited by inactivating phosphorylase kinase and phosphorylase A or facilitated through the activation of glycogen synthase B. In the liver, insulin increases the interaction between protein phosphatase I and glycogen, resulting in the stimulation of glycogen synthesis. In case of high glucose blood levels, insulin tends more to carry out glycogen storage instead of releasing glucose. All these effects are rejected if glycemic values are low, and in return, antagonistic and self-regulatory mechanisms are actuated. Furthermore, insulin may control the activity of key enzymes related to glycolysis and gluconeogenesis, with the result of a major stimulation toward the first cascade [29, 30].

New methods have been developed to identify and quantify the fraction of glucose formed from all potential gluconeogenic precursors. It has been realized by using labelled glucose and glycerol (the latter deriving, together with free fatty acids, from the hydrolysis of triglycerides (TG) and then converted into glucose in the liver, as a source of energy), respectively [U-13C]-glucose and [2-13C]-glycerol [31, 32]. Mass isotopomer distribution analysis is used to examine the biosynthesis and turnover of complex polymers. The administration of a labelled precursor subunit in a sufficient mass provides the accurate measurement of the relative concentration of isotopomers, i.e., polymers with the same chemical formula and nominal mass but with different isotopic positions, by the use of mass spectrometry. The structure of glucose derived from gluconeogenesis contains two three-carbon subunits (triose phosphates), so Hellerstein et al. [31] adapted this technique to define the fractional synthesis of glucose from a three-carbon precursor by administering [3-13C]-lactate or [2-13C]-glycerol, which labelled the triose phosphate pool and then glucose. Nevertheless, the loss and exchange of carbon within the tricarboxylic cycle as well as lactate oxidation led to an incomplete lactate labelling. In the light of such variable and underestimated rates of gluconeogenesis by using labelled lactate methods, correction equations were developed to account for the loss of carbon [33].

Lipid Metabolism

Insulin is responsible for the transport of circulating fatty acids, together with those released by circulating TG, into adipocytes by increasing lipoprotein lipase activity. In the adipose cells, a new esterification is made; lipids are then stored as an energy reserve. The opposite action, that is lipolysis of stored TG, is performed by insulin as well and mediated by inhibitory action of hormone-sensible lipase. The consequence is the suppression of fatty acids release from adipocytes and their use by other tissues [34]. As in the liver insulin arises α-glycerol phosphate level, fatty acids are addressed to sites of esterification, but not to β-oxidation. Therefore, insulin negatively affects the production of β-hydroxybutyrate and acetoacetate, expressing a strong antiketogenic action. In addition, insulin stimulates fatty acids synthesis from glucose throughout the activation and augmented phosphorylation of acetyl-CoA carboxylase and fatty acid synthetase. HMG Co-A reductase is the key enzyme for cholesterol metabolism: an activation and dephosphorylation of the enzyme lead to cholesterol synthesis, while an inhibition of cholesterol esterase dephosphorylation determines cholesterol ester breakdown. Insulin stimulates the production of α-glycerol phosphate from triose phosphates of the glycolytic cascade because it helps in the esterification of free fatty acids, subsequently stored as TG [35].

Protein Synthesis

In response to high amino acids levels, insulin controls and increases the transcription and translation pathways for protein synthesis, realizing the Na+-dependent transport of amino acids into cells. Some examples of specific proteins are albumin and fatty acids synthase in the liver, while amylase in the pancreas. The anabolic effects of insulin are reinforced by inhibition of proteolysis and release of amino acids that are anticatabolic effects. In the light of protein synthesis, insulin has an important role in growth, in regenerative tissue processes, and in bone remodelling [20, 36].

IR and Assessment

IR is a condition that has a long natural history, appearing earlier than the development of the disease, so it is considered as a key component and the best predictor of T2D development [37]. The available methods can be distinguished into two major groups, namely the direct methods, including the hyperinsulinemic-euglycemic clamp and the intravenous glucose tolerance test (IVGTT), and the indirect methods obtained by fasting or after glucose load measurements. However, among the

methods available for the definition of insulin sensitivity, the gold standard is the hyperinsulinemic-euglycemic clamp. It consists of a continuous infusion of high doses of insulin, in order to get a hyperinsulinemic plasma state, and a contemporary intravenously administration of glucose at a variable infusion rate, to maintain a glucose physiological level. The glucose infusion rate, when a steady state is reached, shows the glucose uptake realized by all the tissues in the human body, so it can be considered as a direct measurement of insulin sensitivity. Therefore, in an IR situation characterized by impaired glucose uptake, blood glucose levels are maintained within the normal range through a low rate of glucose infusion [38]. However, accurate assessment of IR in children is complicated, since there are numerous factors, including physical activity, diet, pubertal state, and menstrual cycle, that can influence the balance between glucose homeostasis and pancreatic β-cell function [39]. Therefore, all the methods utilized for defining insulin sensitivity need to evaluate these confounding factors to properly define IR.

The hyperinsulinemic-euglycemic clamp represents the gold standard method, although this complex technique is characterized by several cons. In fact, although this method is well reproducible and precise, and particularly well correlates with clinical measures of disease (diabetes, MetS), it is too expensive, too invasive, and needs multiple clamp measurements to get information on insulin sensitivity and acute insulin response. Therefore, these aspects strongly minimize its use in the daily clinical setting. Therefore, other surrogate methods have been elaborated. Among them, the glucose tolerance test (GTT) consists of the delivery of glucose via oral, intraperitoneal, or intravenous administration and the recording of exogenous glucose effects on the systemic clearance of glucose [40]. The IVGTT provides an intravenous bolus of a standard dose of glucose and frequent blood samples at a specific timing in the hours after the injection; the outcomes are not affected by the consequences derived from oral glucose administration, making more consistent the test [41].

Throughout intraperitoneal administration of insulin is realized the insulin tolerance test (ITT) that analyzes the systemic glucose clearance; its results may be considered not reliable when counterregulatory responses interfere with the state of hypoglycemia often encountered [40]. In contrast to these more invasive and complex techniques, the oral GTT (OGTT) is performed by administering glucose orally and realizing blood samples in the following 2–3 h. It represents the physiological way of taking carbohydrates, so it is widely used in the clinical practice.

Bergman et al. [42] in 1979 developed an indirect measure of metabolic insulin sensitivity/resistance based on glucose and insulin data derived during a frequently sampled IVGTT, called the minimal model. It consists of the administration of an intravenous bolus of glucose over 2 min starting at time 0, after an overnight fast. A modified frequently sampled IVGTT is recently used and involves the infusion of exogenous insulin over 5 min beginning 20 min after the intravenous glucose bolus [43, 44]. The oral minimal method allows the estimation of insulin sensitivity, β-cell function, and hepatic insulin extraction from an oral glucose test, either a mixed-meal tolerance test or an OGTT. These oral tests are more physiologic and easier to perform than those based on an intravenous administration. In addition, mixed-meal tolerance test has shown to be superior to OGTT as it includes other macronutrient components, such as proteins and fat [45].

In the last decades, new methods of insulin sensitivity assessment have been developed, considering the ratio of plasma glucose to insulin concentration during the OGTT. The Matsuda index or Insulin Sensitivity Index composite, discovered by Matsuda and Defronzo [46] in 1999, is simple to calculate and offers a realistic approximation of whole-body insulin sensitivity from the OGTT. It represents the combined effects of insulin, at baseline and after ingestion of a glucose load, on the stimulation of peripheral glucose uptake and suppression of hepatic production of glucose. This index, unlike that provided by the minimal model technique, correlates intensely with the direct measure of insulin sensitivity derived from the euglycemic insulin clamp [46, 47].

By adopting fasting and post oral glucose loads, simple surrogate indices of insulin sensitivity that have been validated to and shown to correlate well with hyperinsulinemic-euglycemic clamp have been proposed. Among these, fasting plasma insulin is a way to determine insulin sensitivity, compensatory hyperinsulinemia, and liver insulin metabolism by the measurement of insulin levels during a fasting state [48].

Another surrogate index of IR is homeostatic model assessment for IR (HOMA-IR), that uses fasting values of both insulin and glucose and is directly proportional to the degree of IR. Compared to fasting plasma insulin, HOMA-IR is considered a more reliable method of measurement, since it allows the joint evaluation of glucose and insulin fasting levels, realizes an estimate of β-cell function in the light of insulin sensitivity, and is performed by a single blood sample that can be easily repeat-

ed several times. Aside from the original index HOMA-IR, in these last years, a new model has been proposed, the HOMA2-IR, representing the updated computer model and the version that is preferred to compare with others [49, 50]. A study conducted in Mexico on a large cohort of 6,100 children has demonstrated that HOMA-IR changes throughout childhood, so it has published age-based pediatric HOMA-IR norms [51]. Similarly, an Italian multicenter study has elaborated a percentile reference for HOMA-IR values [52]. In a recent study, HOMA-IR has been shown to be a useful tool for identifying IR associated MetS among children and adolescents. In fact, as reported by authors, independently of the definition of MetS used HOMA-IR cut point to avoid MetS risk ranged from 2.30 to 3.59 [53].

The quantitative insulin-sensitivity check index is a mathematical transformation of fasting blood glucose and insulin levels, and it has been shown that is useful to study the role of IR in hypertension [54]. In addition, also non-insulin- or glucose-derived measures have been validated in children and adolescents. Among them, the TG/ high-density lipoprotein-cholesterol (HDL-C) ratio has been shown to offer a good definition of IR and β-cell function in different ethnic groups. It well documented that in overweight and obese children with IR, TG levels are high, while HDL-C decreased. TG:HDL-C ratio has been proposed to be an alternative approach for estimating IR, registering a strict correlation with IR when is ≥3 [55]. In a study conducted in a large multiethnic population of obese and overweight children and adolescent, an increased TG/HDL-C ratio has been associated with a worsening of glucose metabolism defined by the 2 h glucose levels and the AUC 2h glucose values during the OGTT [56]. In fact, the higher is the ratio, the higher are the 2h glucose levels and the AUC 2h glucose levels in all the three ethnic groups. Similarly, the TG/HDL-C ratio has been associated with a worsening of IR defined by the WBISI and worsening of β-cell function defined by the disposition index (DI) values. Therefore, the higher is the TG/HDL-C ratio, the lower are the WBISI and the DI values. This index might offer some advantages mainly related to the assay utilized for the measurement of TG and HDL compared to insulin measurement. In fact, this assay has the advantage to be more standardized, thus more reproducible, and less variable between different laboratories. However, it is affected by diet during the day before the measurement that might negatively affect its definition.

All these surrogated markers are easy to use, inexpensive, and relatively noninvasive, thus represent useful tools in the daily clinical setting. However, they are also associated to some specific contra and particularly, they are less reproducible, less accurate in states of glucose intolerance, and a less informative regarding the risk of diabetes. Therefore, all these pros and cons need to be evaluated in the process of definition of IR in order to properly characterize insulin sensitivity in daily practice.

Clinical Conditions Associated with IR in Childhood

IR may be the result of a lacking response by the target tissues to insulin actions. It does not always demonstrate the same clinical features, but these change according to body districts involved, the etiological factor involved, and the grade of severity [50].

The etiology of IR is varied and can be divided into acquired and genetic. The most frequent conditions that determine IR in the young are the acquired, such as excess dysfunctional adipose tissue, prolonged use of glucocorticoids or growth hormone and other medications, reduced physical exercise, nutritional imbalance, glucose, and lipid toxicity, the latter derived from the great number of free fatty acids in the circulation, ethnicity, and puberty [57]. In particular, African-American, Hispanic, Pima Indian, and Asian children have shown to be less insulin sensitive than young Caucasians [58]. These ethnicity-related risks similarly affect the risk of T2D. In fact, some ethnic groups, such as Afro-American and Hispanic children, are more likely to develop T2D since the compensatory insulin secretion during pubertal spurt is not sufficient [59, 60]. As a matter of fact, puberty is a physiological condition characterized by a decrease of about 25–50% of insulin sensitivity, reversible with the end of the pubertal development.

Although most of these pathological entities can be found in young obese children, obesity is certainly considered the major cause of IR, thus represents one of the most relevant risk factors associated to IR and the risk of T2D [2]. However, similarly to the excess of adipose tissue, the depletion of fat storage mimics several of metabolic alterations documented in obese subjects [61]. Therefore, adipose tissue is now considered a real and complex endocrine tissue able to strongly affect the body metabolism [62].

IR and Obesity

Obesity is a complicated matter involving children across all ages, with increasingly worrying data. BMI universal data derived from 200 countries have shown an

increase from 4% to 18% in the years 1975–2016 of the pediatric obesity prevalence. In this same time frame, obesity registered an arise from 5 million to 50 million girls and from 6 million to 74 million boys. While the childhood obesity trend has reached the plateau in the industrialized countries, it continues to rise in the developing countries [63].

Obesity is the result of the combination of various factors, such as genetic pattern, everyday socioeconomic context, environmental exposures, and behavior. In the light of the relevant environmental changes occurred in the last decades, children have deeply modified their eating habits. For instance, children tend to eat less healthy food because of the development of fast-food industries that lead also to a higher number of meals throughout the day [64, 65].

Along with an improper diet, physical activity is deeply reduced among children, since they spend more time on TV, play more video games instead of outdoors, and motorized bicycles and scooters have become the favorite way to get around [64]. Furthermore, both energetic imbalance and sedentary life have been emphasized by the spreading of COVID-19 pandemic, due to the need for social isolation and restriction of sporting and recreational activities [66].

Additionally, obesity is determined by genetic causes that can either be monogenic or polygenic types. Monogenic obesity is usually rare, related to mutations in leptin/melanocortin pathway in the hypothalamus that is responsible for the regulation of food intake/satiety, body weight, and energy metabolism [67]. Other monogenic forms are linked to genetic syndromes, such as Prader-Willi syndrome, Alström syndrome, and Bardet-Biedl syndrome, presenting both severe obesity and other typical features, including cognitive impairment and typical facial characteristics [68]. Different genetic variants interact each other to define polygenic obesity that has been elected as the most common form, derived from the interface between genetic pattern and environment. Epigenetics that is the alteration of gene expression without varying the DNA sequence has recently emerged as a factor that might play a role in the increase of risk for chronic conditions, as obesity [69].

The increasing prevalence of childhood obesity represents an important public health issue, as it facilitates the development of chronic noncommunicable diseases and underlies numerous risks that must not be underestimated [70, 71]. In the long-term, obese children might present a high risk of being obese becoming adults, getting cancer, dying early, and being disabled in adulthood. Instead, in the short term, they may be affected by hypertension, cardiovascular disease, fractures, psychological issues, and IR [72]. Nevertheless, not every obese child acquires all of these risk factors over time, presenting instead promising metabolic profiles. Recent studies have explained a potential cause of IR based on the "adipose expandability hypothesis." According to this theory, when the subcutaneous adipose tissue is no longer able to host lipids, a transfer of lipids towards the visceral adipose tissue and nonadipose tissues is accomplished, finally determining lipotoxicity and IR [73, 74].

So, the specific types and proportion of lipids in fat depots, and not the total body fat, are responsible for the metabolic risk [75]. Recent findings show that the development of hepatic steatosis and metabolic implications are due to an increased turnover of TG and mature adipocytes in subcutaneous adipose tissue, instead of decreased TG storage or proliferation of new adipocytes [76].

The accumulation of lipids in the insulin-responsive organs, such as the skeletal muscle, liver, and adipose tissue, leads to a condition of selective IR that involves only the glucose metabolism pathways, determined by intracellular fatty acids derivates [77]. In particular, the skeletal muscle realizes a reduced glucose uptake through a lower transportation of GLUT4 to the cell membrane. In addition, gluconeogenesis is no more inhibited, so in the liver, occurs a greater glucose production, while in the adipose tissue is registered an increased lipolysis, determining a flux of free fatty acids into both skeletal muscle and liver [75]. A severe degree of IR has been found early in obese children characterized by impaired glucose tolerance and by a greater abdominal and muscles fat deposition, as well as in those with an important hepatic steatosis [78, 79]. As consequence of lipidic imbalance, a cardiometabolic risk status is established. The presence of nonalcoholic fatty liver disease (NAFLD) in obese children ensures a higher IR [80], together with elevated prevalence of prediabetes, T2D, and dyslipidemia, than those who do not present NAFLD, as shown in recent studies [81].

IR and T2D

T2D is a pathological condition presenting hyperglycemia, derived from IR and compromised insulin secretion not due to autoimmune β-cell destruction, as instead happens in type 1 diabetes [82]. The incidence of T2D has increased among children all over the world in the last decades. In the USA, an incidence of about 5,000 new

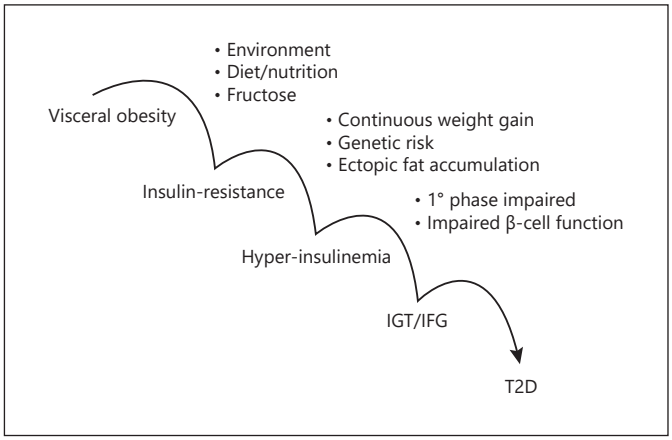

Fig. 3. The snaky way to T2D. IGT, impaired glucose tolerance; IFG, impaired fasting glucose; T2D, type 2 diabetes.

cases of T2D has been registered [83]. Thanks to the use of the SEARCH database, the Centers for Disease Control and Prevention have predicted a quadruplication of T2D prevalence, considering a rise of 2.3% annually, in people under 20 years in a period of 4 decades [84].

A relevant number of obese children with this disorder might experiment a free-symptoms period of prediabetes, which includes impaired fasting glucose (IFG: fasting glucose between 5.6 and <7 mmol/L) and impaired glucose tolerance (IGT: 2-h glucose levels between 7.8 and <11.1 mmol/L on the 75-g OGTT) (Fig 3) [85]. It has been shown that the conversion from IFG/IGT to T2D does not always have a linear progression and is faster in children and adolescents than it happens in the adults, appearing within 12–21 months [86]. The development of T2D is definitely controlled by the balance between IR and insulin secretion, in turn determined by β-cell mass and secretory capacity, both dependent on hereditary and acquired factors. Hyperglycemia causes an inflammatory state that worsens the underlying IR condition by stimulating apoptosis of more β-cells [87]. The more elevated levels of global insulin secretion found in young people with T2D, on the contrary of diabetic adults, are then decreased in obese children during the progression from normal glucose tolerance (NGT) to IGT to T2D [88].

IR in Leanness and Syndromes Associated with IR

During the last decades, a large amount of data has clearly shown a key role of adipose tissue in the development of cardiovascular diseases as a result of its endocrine function [89–92]. In fact, by synthesizing several endocrine molecules, adipose tissue affects metabolic status or determines important antiatherogenic, anti-inflammatory, and antidiabetic effects, which in turn have relevant cardiovascular effects [93]. Therefore, adipose tissue excess as well as depletion has been shown to be associated to an increased morbidity and mortality for cardiovascular disease [89–92]. Of note, these effects, already during the childhood, lay the metabolic groundwork for adult cardiovascular disease contributing to the development of atherosclerosis in adulthood [6]. Moreover, a comparable negative effect of both lower and higher adipose tissue storage on early markers of endothelial function has been documented in constitutional lean and severe obese prepubertal children. In fact, Giannini et al. [61] have shown an increased oxidative stress, impaired inflammation and insulin sensitivity in prepubertal lean and obese children, which in turn result in similar increased values of carotid intima-media thickness, an early signs of atherosclerosis in childhood.

Similarly to constitutional leanness, other genetically determined conditions induce a similar effect on metabolic status and, among them, lipodystrophy certainly represents one of the major hereditary condition associated with IR and dysmetabolic status. Lipodystrophies are a collection of rare heterogenous disorders characterized by generalized or partial lack of adipose tissue without evidence of nutrition deprivation or a catabolic state. Lipodystrophies represent a group of syndromes, etiologically divided into congenital or acquired, linked to severe metabolic complications, such as dyslipidemia (characterized by high TG and low HDL-C concentrations), NAFLD, and impaired insulin sensitivity. Although lipodystrophic patients are usually nonobese or lean, these syndromes show the same clinical features of the MetS found in the obesity [94]. Furthermore, in these subjects, the compromised metabolic profile is the result of a greater loss of adipose tissue. In the light of the rarity and heterogeneity, lipodystrophy may be often unrecognized or misdiagnosed, with the consequence of progression of the disease without any intervention, leading to complications potentially life threatening. Therefore, the diagnosis is still challenging and so is the clinical management [95].

The most prevalent forms of lipodystrophy, among both inherited and acquired syndromes, are the congenital generalized lipodystrophy (CGL), the familial partial lipodystrophy, the acquired generalized lipodystrophy, and the acquired partial lipodystrophy [96]. By contrast, the other lipodystrophic variations, such as mandibuloacral dysplasia, autoinflammatory lipodystrophy, progeroid syndromes linked to lipodystrophy, are even more rare.

Focusing on CGL, which records a prevalence of about 1 in 10 million, it presents at birth or early in life and shows a near total lack of adipose tissue, along with a paradoxical muscularity. There are four subtypes of CGL, each related to a mutation of a specific gene. Diagnosis is based on clinical and anthropometric evaluation; MRI is usually performed to better investigate the distribution of the adipose tissue, and in the last years, genotype studies are realized to reach a diagnosis of certainty. Affected patients may present acromegaloid features, prominent superficial subcutaneous veins, an avid appetite that is usually referred to a severe hypoleptinemia. Umbilical prominence or hernia can derive from splenomegaly and/or hepatomegaly, the latter due to hepatic steatosis, which can develop into steatohepatitis, fibrosis, and then cirrhosis, finally requiring a liver transplantation. A frequent finding is hyperinsulinemia that tends to set diabetes mellitus with resistance to ketosis. Xanthomas and pancreatitis can be often found, as results of hypertriglyceridemia. In addition, low HDL levels are typical. Cardiovascular involvement, especially cardiomyopathy, focal segmental glomerulosclerosis, and/or mental retardation are common features [97]. Other findings might be acanthosis nigricans and in females hirsutism, clitoromegaly, amenorrhea, polycystic ovaries, and sometimes, sterility [98]. The absence of bone marrow fat determines focal lytic bone lesions; a great risk of pathological fractures in the long bones and advanced bone age are registered in these patients.

The metabolic complications are caused by the ectopic accumulation of excess TG in the liver and skeletal muscle, due to the significantly lack of adipose tissue. Therefore, similarly to obesity, the ectopic depots of TG induce IR and its metabolic consequences. The ectopic accumulation of TG is further worsened by the hypoleptinemia [98].

The therapeutic approach includes at first diet and exercise, as in the obesity, and then the specific treatment for each metabolic complication that appears; injectable fillers, plastic, and bariatric surgery are often valid alternatives. Recently, the use of a recombinant leptin, metreleptin, has been accepted as a therapy to treat metabolic complications in the context of leptin deficiency [99].

Spectrum of Alterations of Glucose and Insulin Metabolism

T2D onset in children is very heterogeneous in terms of onset and progression (Fig 3) and is considered as a progressive phenomenon, in which overt diabetes is anticipated by a continuous spectrum of glucose-related phenotypes, characterized by a progressive dysfunction of β-cell. All these conditions identify a clinical manifestation known as prediabetes that is very common in obese youth and, as T2D, typically derives from a poor glucose metabolism. Blood glucose regulation and its clinical significance are based on the following key points: the liver acting as a buffer for blood glucose concentrations, insulin and glucagon working together to maintain glucose concentration, and CNS controlling blood glucose levels thanks to the activation of the sympathetic nervous system by hypothalamus, growth hormone, and cortisol that avoid hypoglycemia by increasing fat utilization and decreasing the rate of glucose used by cells. After a meal, high blood glucose levels as well as contemporary elevated secretion of insulin from the pancreas are registered, the latter determining glucose to deposit as glycogen in the liver. When blood glucose decreases, the liver releases glucose back in the vessels, stopping gradually fluctuations, and glucagon secretion is then stimulated, which in turn causes blood glucose elevation. Therefore, in case of liver dysfunction, blood glucose concentration is not possible to be maintained and diabetes mellitus is the result of impaired and insufficient insulin secretion [100–102]. Alterations in glucose metabolism lead to the development of metabolic and cardiovascular disease, occurring already in children, especially in the presence of obesity [103]. Although obesity is certainly the most important risk factor for the development of T2D, not all obese children develop T2D: in fact, this condition can be identified also in children with moderately lower BMI matched to their peers, thus suggesting a predisposition role of genetic and particularly some susceptibility genes. Several studies have evaluated the genetic risk of prediabetes and T2D in obese and overweight children and adolescents compared to healthy children. In 2017, Cropano et al. [104] demonstrated that rs7903146 variant in the TCF7L2 gene increases the risk of prediabetes/T2D in obese adolescents by impairing β-cell function and hepatic insulin sensitivity and, therefore, predicts the advance of IGT and T2D. In addition, by evaluating simultaneously different genes related to cell function, other authors have shown an additive effect of the co-occurrence of risk genes related to impaired glucose metabolism. In fact, Giannini et al. [105] in a large multiethnic cohort of youth have shown an increased risk of prediabetes and T2D in childhood directly related to the co-occurrence of risk alleles linked to 5 genes regulating insulin secretion (*TCF7L2* rs7903146, *IGF2BP2* rs4402960, *CDKAL1* rs7754840, *HHEX* rs1111875, and *HNF1A* rs1169288). In detail, au-

thors have shown that the increase of risk alleles was associated with a progressive worsening of insulin secretion mainly due to an impairment of the dynamic phase of insulin secretion. Therefore, the higher the number of the risk alleles, the higher the chance of progression from NGT to IGT/T2D. Also, for those who were IGT at baseline, a higher risk score was associated with a lower odd to revert to NGT.

Therefore, β-cell dysfunction associated with IR is the major pathogenetic factor that plays a key role in the progressive deterioration of glucose homeostasis in obese youth. As known, glucose is the most important signaling for the release of insulin. Normal glucose metabolism depends on the dynamic interaction between insulin secretion and insulin action in order to progress from NGT towards prediabetes and overt T2D. β-cell produces and secretes insulin at a basal level and in reaction to a modification of glucose concentration, with a bi-phasic model. The evaluation of phasic insulin dynamics is essential in order to identify alterations in insulin secretion which predicts a condition preceding the progression towards overt diabetes [106]. In fact, obese youths with prediabetes have lower insulin secretion in first phase than patients with normal glucose metabolism [107]. Instead, change in second phase of insulin secretion appears as subsequent event expression of combined IFG/IGT or manifest T2D [108]. Therefore, a two-hip defect state defines the natural history of T2D characterizing an initial alteration of first-phase insulin secretion, followed by an impaired second phase insulin secretion, documenting the failure of β-cell function to counteract increased glucose levels leading to overt T2D. Interestingly, although similarities have been shown in the natural history between adults and youths, data have clearly shown some peculiarities in children and adolescents. Particularly, data have shown that adolescents have a more rapid decline in insulin secretion than adults. In fact, the progression from prediabetes toward T2D in adults has been estimated of 10 years with a lowering of about 7% per year of β-cell function. In contrast, in adolescents this rate increases to 20–30% per year with a time of 2.5 years [109, 110]. In the recent RISE study, authors have shown a progressive decline in β-cell function after stopping treatment in youth in contrast to β-cell function in adults that remained stable despite an increase in HbA1c over time [111]. Furthermore, the deterioration of β-cell function and its related defects in insulin secretion are associated to a more profound IR state in obese children. Moreover, the action of insulin in tissues and organs is impaired in obese children with IGT compared to obese children with normal glucose metabolism [112]. Although obese children with IGT show evidently IR, insulin sensitivity levels ranging from extremely sensitive to significantly resistant have been described in obese children with NGT. This state of a lower insulin sensitivity results in an ectopic lipid storage, such as into the visceral fat, or intrahepatic, and intramyocellular. Moreover, obese children respond to low insulin sensitivity raising insulin concentrations and determining an actual glucose tolerance state through increased insulin secretion and decreased insulin clearance by the liver. This mechanism determines an increased fasting and post absorptive glucose levels in order to stimulate the β-cell to release enough insulin [113].

Over time, an index of β-cell function in relation to insulin sensitivity has been identified, called DI. This index is one of the major predictive factors of progression towards diabetes over time. In fact, reduced DI levels have been identified in obese with impaired glucose metabolism compared to obese with NGT, describing β-cell dysfunction that anticipates development of hyperglycemia on diabetic range [113]. Continuous stimulus to increased insulin secretion is needed to determine a correct β-cell compensation and reduced insulin sensitivity or alteration of DI can increase fasting and 2-h glucose levels, remaining in the NGT range. These aspects establish that great dysfunction of β-cell can occur in obese with values close to the upper portion of the normal levels of 2-h glucose. Thus, it is considered a good predictor of the risk of developing prediabetes or T2D over time.

Fasting and 2-h glucose levels during an OGTT not only are used to identify T2D, but can also be adopted in the clinical setting to identify those subjects at the highest risk for developing T2D and prediabetes. However, over time, growing attention has been developed to identify biomarkers and models for early prediction of metabolic risk alterations. In fact, recent studies have demonstrated that the shape of the OGTT-glucose response curve can identify the increased risk for T2D. In particular, the risk associated to monophasic glucose curve compared with biphasic glucose curve is associated to lower insulin sensitivity levels and to a poorer β-cell function, the two major biomarkers of T2D risk in nondiabetic obese youth [114].

More recently, Olivieri et al. [115] have confirmed these data demonstrating that monophasic OGTT-glucose shape is associated with unfavorable glucose metabolism independently of 2-h glucose level and therefore, children with monophasic shape curve and normal-high 2-h glucose have an IGT-like glucose metabolism.

Several studies have shown that obesity and prediabetes are linked to the development of ectopic fat accumula-

Table 1. The most important risk factors related to the development of IR in children

Risk factors promoting IR in children
Obesity and long-lasting obesity
NAFLD
Inactive lifestyle
Diet high in carbohydrates
Fructose ingestion
Puberty onset
Gender
Genetics and heritability
Family history of diabetes
Polycystic ovary syndrome
Ethnicity (African-American, Hispanic, Asian)
Prolonged use of corticosteroids
Prolonged growth hormone therapy
Adipose tissue depletion
Ectopic fat mass accumulation (mainly into the liver and muscles)

tion that modifies insulin signaling pathway on insulin-responsive tissues and organs, thus increasing IR. Liver IR can increase hyperinsulinemia and further hepatic lipid accumulation [80, 116]. In fact, a longitudinal study has shown that hepatic lipid accumulation is related to alteration on glucose metabolism and 2-h glucose, as well as to insulin sensitivity and insulin secretion after 2 years of follow-up [117]. Thus, T2D represents the end of a spectrum of a complex and progressive alteration of glucose metabolism defined by a continuous and progressive decrease in insulin secretion and insulin sensitivity during which different risk factors might act as step on facilitators (Table 1). In fact, adolescence is a phase of high susceptibility to the onset of diabetes in children, because of rapid endocrine alterations and a variable background of genetic risk. The molecular pathway linking genetic risk factors, weight gain, and puberty to the risk of developing diabetes, to date, is steel poorly known. Deciphering these pathways is of fundamental to understand the progression of the disease in children and how prediabetes could be detected at an earlier stage to enable preventive measures to be taken to tackle the worldwide epidemic of diabetes.

Treatment Options in Childhood

The early identification of children with derangement of glucose metabolism allows clinicians to intervene and prevent the progression to T2D. The early diagnosis of prediabetes allows to prompt identify and carefully treat obese children at risk to progress towards diabetes. However, several questions remain unresolved. It is very important to know if early interventions might help recover the β-cell function and stop the development from prediabetes towards clear diabetes.

Several studies have reported that the weight status in early childhood is a significant predictor for the weight status and cardiometabolic comorbidities later in life. Consequently, prevention or treatment of childhood obesity should begin as early as possible in life firstly through a multidisciplinary lifestyle intervention [118, 119]. To date, clinical guidelines define two main steps in the therapy of obesity and its related complications including pharmacological and nonpharmacological treatment.

Non-Pharmacologic Treatment

Lifestyle intervention should start as early as possible both in obese nondiabetic and diabetic children associated to pharmacologic treatments. Lifestyle intervention concerns a balanced diet with lower energy-dense, sugar- and fat-rich products, and a growing daily physical activity [120].

Lifestyle intervention consists of four stages: (1) "prevention plus," which focusses on healthy eating and activity habits; (2) "structured weight management," which is based on monthly visits to provide structured approaches to diet counselling and regular physical activity; (3) "comprehensive multidisciplinary intervention," similar to stage 2, but includes weekly visits and additional structured behavioral intervention; and stage (4) "tertiary care intervention," that includes a structured program addressing all modules of stage 3, but it is in addition, considering concomitant disease, medications, severe dietary restrictions, or surgical intervention [121, 122]. In particular, according to the ISPAD guidelines, dietary modification should focus on eliminating sugar, soft drinks and juices, increasing fruit and vegetable intake, reducing the use of processed foods and made to refined sugar, portion control, and reducing meals eaten away from home [123].

Regular physical activity should be associated to dietary intervention. It focused on reduction of sedentary time, screen time should be reduced to less than 2 h a day, and daily exercise should be done [123]. These key treatments need to be strongly reinforced in order to minimize pharmacologic treatments and/or bariatric surgery to the minority of patients. However, although lifestyle intervention is the gold standard and the corner-stone of the

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majority of obese subjects' treatment, several studies have shown to often fail in reaching clinical goals. Therefore, newer approaches need to be tested in order to significantly increase its success rate.

Pharmacologic Therapy

The treatment of youth with T2D is based on hypoglycemic agents and/or insulin, if necessary, associated to lifestyle intervention, in order to improve glycemia and insulin sensitivity, stop metabolic derangement and development of complications, stimulate endogenous secretion, and ameliorate incretin secretion. Not all hypoglycemic agents are approved for use in adolescents, except metformin; in some countries, sulfonylureas have been accepted.

Metformin is the first line of pharmacologic treatment for T2D in adolescents, associated to lifestyle intervention. It is a biguanide derivate that acts reducing hepatic glucose production by decreasing gluconeogenesis and by stimulating peripheral glucose uptake as well as by determining weight loss by anorexic effect. In addition, several trials have demonstrated that insulin sensitivity and 2-h postprandial glucose during OGTT ameliorate with absolute lifestyle intervention. Other agents (i.e., *Thiazolidinedione, α-Glucosidase inhibitors, incretin mimetics: GLP-1, receptor agonists, DPP-IV Inhibitors, Sodium-Glucose Co-transporter 2, SGLT2, inhibitors*) are available for treatment of diabetes in adults, but not approved for children.

Several trials are underway for the treatment of prediabetes or for the preventing of the progression towards diabetes in youth. The Researching Effective Strategies to Improve Insulin Sensitivity in Children and Teenagers study has evaluated obese and overweight subjects with prediabetes or IR, treated with metformin associated to high carbohydrate or moderate carbohydrate plus high protein diet for 6 months and with physical activity from 4th to 6th months. The authors showed significantly reduction of BMI and highly insulin sensitivity, but no differences between the two types of diet have been identified [124]. In a placebo-controlled study, the use of metformin for 12 weeks is associated with major improvement of weight, HOMA-IR, and HbA1c in children with IGT compared to placebo group [125]. McDuffie et al. [126] showed the efficacy of orlistat in ameliorating BMI, lipid profile and IR after 6 months of treatment. In addition, the RISE study evaluated overweight and obese youth with IGT or recently diagnosed T2D (less than 6 months) treated with insulin glargine alone for 3 months, followed by metformin alone for 9 months, or metformin alone for 12 months. Although any significantly differences have been reported between the 2 groups at baseline and at timepoints in terms of β-cell function, both groups showed a progressive decline in β-cell function at 12 and 15 months and after treatment. So, the helpful results of treatment with metformin and glargine insulin on β-cell function highlighted in adults were not confirmed in youth in terms of prevention the progression of diabetes from prediabetes [127]. These results can be explained by the higher IR and hyperinsulinemic response to glucose in youth compared to adult population.

Therefore, ADA guidelines do not suggest the treatment of prediabetes with metformin. As known, recent studies have demonstrated the efficacy of metformin associated to lifestyle intervention improving glucose uptake and fatty acid oxidation, reducing food intake, stopping gluconeogenesis, lipolysis, and insulin secretion. However, it seems that the prolonged use of metformin stimulates orexigenic receptor in hypothalamus determining increase of appetite. So, the anorexigenic effect of metformin is considered short-term. To date, the therapy for prediabetes consists of lifestyle modification with reduction of sedentary, improved nutrition, and activity through a multidisciplinary program, including also dietitian, exercise, and behavioral health specialists with more frequent visits of follow-up [128]. In addition, although metformin is the early regulatory-approved treatment of choice for most youths with T2D, data have clearly shown an early loss of glycemic control if used as monotherapy. Therefore, novel treatments, after proving to be effective and safe in adulthood, have now been explored and approved in children.

Therefore, a large number of oral and injectable agents of different classes are approved for adults [129]. Among them, in youths with T2D liraglutide treatment added to metformin (with or without basal insulin treatment) has shown to be safe and effective. In details, in a recent study authors recruited 10–16-year-old patients, randomly assigned in a 1:1 ratio, to receive subcutaneous liraglutide (up to 1.8 mg per day) or placebo for a 26-week double-blind period, followed by a 26-week open-label extension period. In addition to liraglutide, authors showed significant changes from baseline in the glycated hemoglobin and in fasting plasma glucose levels after 26 weeks. As well, treatment was safe throughout the course of the trial, with no relevant side effects reported and only gastrointestinal adverse events documented [130]. Therefore, the European Medicines Agency approved liraglutide in addition to diet and exercise in adults and children from 10 years of age who have T2D. In addition, liraglutide is used on its own when the use of metformin is not recom-

mended, as well as an "add-on" to other diabetes medicines. Therefore, new studies reporting its efficacy in other metabolic alterations related to T2D in youth will be offered in the very next future.

Conclusions

Impaired adipose tissue storage documented in obesity, as well as in lipodystrophies and constitutional leanness, results in a continuous spectrum of metabolic alterations ranging from IR to T2D. These metabolic alterations are mostly likely preventable through the early characterization of all the multiple risk factors involved. Therefore, the complete characterization of the natural history of the disease and of the major modifiable factors represents a milestone in the daily care of young subjects at risk for the development of impaired glucose metabolism early in life.

Conflict of Interest Statement

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