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A review of current knowledge regarding insulin resistance among the pediatric population

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Abstract
One of the key roles in maintaining the body's homeostasis is played by insulin. The presence of insulin receptors in almost all cells of the body reflects the importance of this hormone. Insulin resistance is a state of impaired glucose homeostasis resulting from a decreased sensitivity of peripheral tissues to insulin, despite normal or elevated serum levels. The purpose of this paper is to present the current state of knowledge on the pathogenesis, risk factors, and diagnosis of insulin resistance at developmental age.

Key words: insulin resistance, insulin, children, childhood

Background
One of the key roles in maintaining the body's homeostasis is played by insulin, taking part in the regulation of carbohydrate metabolism and in lipid and protein metabolism, as well as in ion and amino acid transport [1]. Insulin is also known to play a role in cell cycle control, cell proliferation and differentiation, nitric oxide synthesis and gene transcription [2]. The

presence of insulin receptors in almost all cells of the body (with the largest number on the surface of adipocytes and hepatocytes and erythrocytes), reflects the versatility and diversity of regulatory processes in which insulin is involved [3].

Insulin resistance is a state of impaired glucose homeostasis resulting from decreased sensitivity of peripheral tissues to insulin, despite normal or elevated serum levels [1]. Taking into account the pathomechanism, there are three types of disorders leading to insulin resistance [3]: pre-receptor - associated with abnormal insulin structure; receptor - caused by receptor damage; post-receptor - resulting from impaired insulin-receptor coupling or improper function of intracellular glucose transporters [1].

An example of pre-receptor insulin resistance is the so-called mutant insulin syndromes, in which the defective structure of insulin is genetically determined. In such cases, administration of exogenous insulin abolishes the symptoms of insulin resistance, while this is not the case with endogenous mutant insulin [2]. Receptor-mediated insulin resistance can develop as a consequence of structural or functional abnormalities of the insulin receptor. The gene for this receptor is located on the shorter arm of chromosome 19. The insulin receptor is a glycoprotein composed of 2 α subunits and 2 β subunits that undergo autophosphorylation upon binding to the α subunits, which initiates endocytosis of the receptor and initiation of the intracellular protein phosphorylation cascade. The receptor then undergoes intracellular degradation or moves back to the cell surface able to attach further insulin molecules. To date, about 50 mutations of the gene encoding the insulin receptor have been described, leading to polymorphic forms of insulin resistance [1]. These include, for example, type A insulin resistance (OMIM ID: 610549), Rabson-Mendenhall syndrome (OMIM ID: 262190) or Donohue syndrome so-called leprechaunism (OMIM ID: 246200). The latter two are severe genetic syndromes with poor prognosis; patients do not live to adulthood [3] These mutations result in impaired binding of the receptor to insulin, reduced tyrosine kinase activity, impaired membrane and intracellular transport of the receptor, and abnormal synthesis of its molecule [1].

Post-receptor insulin resistance, which occurs most frequently in children and adolescents, is associated with excess adipocytes, as well as poorer glucose utilization in skeletal muscle cells [1]. These processes are closely related to the exponentially increasing scale of obesity and inappropriate physical activity in this age group [2]. A distinction is made between peripheral and hepatic forms of insulin resistance. In the former - peripheral, there is impaired glucose uptake and utilization in skeletal muscle and increased lipolysis in adipose tissue. Hepatic insulin resistance, on the other hand, is characterized by increased gluconeogenesis and glycogenolysis and the production of triglycerides and VLDL cholesterol [4]. There is a close association of insulin resistance with obesity and type 2 diabetes mellitus (T2DM- type 2 diabetes mellitus) in children; it can precede impaired glucose tolerance for many years. It has been recognized as an important risk factor for cardiovascular disease, including atherosclerosis [3].

The purpose of this paper is to present the current state of knowledge on the pathogenesis, risk factors and diagnosis of insulin resistance in developmental age.

Pathogenesis of insulin resistance in children

Overweight and obesity, and consequently excess adipose tissue, are a major cause of

insulin resistance in developmental age. Visceral adipose tissue is hormonally active, and ongoing chronic inflammation of moderate severity and the associated excessive production of pro-inflammatory cytokines that reduce cellular sensitivity to insulin is a key mechanism of IR in this group of patients [4]. This phenomenon is relevant from the earliest years of a child's life and is responsible for a number of complications, including cardiovascular complications in adulthood. Both low and high birth weight, as well as diabetes of the pregnant mother, are proven risk factors for overweight, obesity and metabolic disorders in the child. Gillman et al. proved that a 1 kg increase in birth weight in a term newborn was associated with a 30% increase in the risk of overweight in an adolescent [5]. On the other hand, suboptimal energy supply (maternal malnutrition, diseases associated with placental insufficiency) directly affect later body composition, i.e. decreasing lean mass and increasing fat mass [6]. Among other things, maternal protein malnutrition can cause abnormal development of pancreatic islands in the fetus, and consequently, their improper functioning in postnatal life [7]. In turn, children of mothers with diabetes during pregnancy have a high birth weight, and with it an increased likelihood of obesity, insulin resistance and type 2 diabetes [8]. This is because a high fetal glucose load stimulates the pancreas to increase the secretion of insulin, which is a potent growth promoter in fetal life. A cohort study by Dalrymple et al [9] on a group of pregnant women demonstrates a close correlation between maternal BMI in early pregnancy and the child's BMI and nutritional status; also, pIGF concentrations in the study population correlated with the nutritional status of the newborn. Elevated maternal pIGF concentrations have a direct role in programming risk factors for childhood obesity by modifying placental function. Rolland-Cashera et al [10] demonstrated a strong link between childhood obesity and adult obesity. In their study, they found that most obese infants typically lose excess body fat around the age of two, a period when their physical activity increases. In subsequent years, there is a resurgence of fat gain, called "rebound obesity." Weight gain usually occurs around the age of 8, and at later ages most children maintain their weight at the same percentile until they complete their growth [11]. A significant proportion of children who gain weight before the age of 6 remain overweight into puberty. The earlier "rebound obesity" occurs, the greater the final body weight is observed in the study group. Oliveira-Santoz et al [12] showed that elevated BMI as early as age 2 correlates positively with increased inflammation and insulin resistance in adolescence. The TC/HDL ratio is associated with BMI from age 5, and BMI in adolescence correlates closely with cardiometabolic parameters, with overweight adolescents showing higher inflammatory, HOMA-IR and TC/HDL scores than normal-weight adolescents.

A critical period in the development of insulin resistance is sexual maturation. According to Tanner, at stages II-IV, there is a nearly 30 percent reduction in peripheral tissue insulin sensitivity and a significant increase in fasting insulin and glucose concentrations. Insulin resistance during this period of life appears selective for glucose metabolism and does not involve protein metabolism, which contributes to the increased anabolic effect of insulin and growth hormone GH during the growth spurt [13]. The reasons for the reduced insulin sensitivity of tissues during this period are believed to include hormonal game changers. During puberty, there is a periodic increase in GH, and consequently in IGF1 and IGF2 [14]. Growth hormone contributes to the deterioration of insulin sensitivity of tissues and affects the increase in lipolysis and free fatty acid concentrations [15]. The increase in insulin

resistance during adolescence is probably not due to an increase in adipose tissue or steroid hormone concentrations.

Risk factors for insulin resistance in children

Studies have shown that there are many important risk factors for IR in children, including obesity and visceral obesity, race/ethnicity, puberty, family history of type 2 diabetes, gender, and gestational obesity or prematurity [16]. However, obesity is a critical risk factor for IR in children. More than 50% of obese adolescents in the US have IR [17]. Tissue sensitivity to insulin is about 50% genetically determined; the other 50% depends on the degree of obesity and physical activity. In obese children, excessive accumulation of visceral adipose tissue is responsible for reduced insulin sensitivity of peripheral tissues, and insulin sensitivity of tissues is inversely proportional to the area of visceral adipose tissue. Several studies have attempted to identify conditions that predispose to insulin resistance, and thus identify risk groups, especially during the developmental period, for early detection of metabolic disorders and subclinical arteriosclerosis.

One of the many risk factors for insulin resistance in healthy individuals is a first-degree relative with type 2 diabetes according to Abdaly et al [18]. This group shows a higher risk of insulin resistance and pancreatic beta-cell disorders during adolescence, although they often remain asymptomatic. Clinical signs of metabolic disorders and atherosclerosis will appear earlier in the FDR group with T2DM, who have a sedentary lifestyle and obesity, compared to the control group. Low intrauterine growth and increased postnatal growth rate also predispose to the development of insulin resistance in later life. A study by Wickramasinghe et al [19] in an analysis of a group of children 5-15 years old found that children born small but obese had the highest risk of developing insulin resistance.

Visceral obesity is a primary driver of tissue insulin resistance, as endocrine function of adipose tissue and ongoing chronic moderate inflammation associated with the production of pro-inflammatory cytokines leads to impaired insulin sensitivity of peripheral tissues and the liver. A study by Fang et al[20] confirms that obese adolescents showed increased levels of insulin, HOMA-IR, elevated levels of inflammatory markers and triglycerides, and reduced HDL-C and adiponectin compared to normal-weight adolescents. Obesity-related anthropometric markers (WC, BMI) positively correlated with insulin resistance and levels of inflammatory markers as well as dyslipidemia, which unequivocally increased the risk of ischemic heart disease CHD and the development of T2DM diabetes in early adulthood.

In a cohort study by Hosking et al [21] called Earlybird, analyses of associations between individual serum metabolites and homeostatic model assessment (HOMA) and insulin resistance (HOMA-IR) were conducted. It was shown that insulin resistance was higher in girls than in boys and was closely related to BMI; at the same time, a direct association of insulin resistance with reduced concentrations of branched-chain amino acids (BCAAs), 2-ketobutyrate, citrate and 3-hydroxybutyrate, and higher concentrations of lactate and alanine was proven. These studies demonstrate the biochemical consequences of insulin resistance on intermediary metabolism, ketogenesis and pyruvic acid oxidation.

A study by Dursun et al. showed an association between insulin resistance in children and thyroid dysfunction. They showed that obese adolescents with non-autoimmune thyroiditis were more likely to have insulin resistance. This finding supported the hypothesis that insulin resistance may affect thyroid function. In analyses by Caprio et al. it was found

that in patients with thalassemia and Turner syndrome, insulin resistance and increased insulin secretion are very early metabolic defects that appear many years before the development of diabetes [22]. Fasting hyperinsulinemia and , inferring from animal studies, enlargement of pancreatic islets and beta-cell mass, promotes abnormal fasting blood glucose (IFG), viz. >6.1mmol/l a <7.0mmol/l [110-126mg/dl, respectively] and abnormal tissue glucose tolerance (IGT) and also leads to dysregulation of basal insulin secretion with impairment of particularly slow oscillations of insulin release, loss of the first phase of insulin secretion after a carbohydrate stimulus and impaired insulin formation. This is indicated by an increase in the ratio of circulating proinsulin to insulin. Tissue sensitivity to insulin correlates inversely with BMI and body fat percentage. Insulin resistance does not necessarily show progression to open IGT; in fact, most obese adolescents with insulin resistance will never develop type 2 diabetes. The development of glucose intolerance requires the occurrence of pancreatic islet beta cell dysfunction and loss of insulin output after a glucose stimulus, probably as a familial or genetically determined trait. Chronic elevation of free fatty acid (FFA) levels is a major contributor to pancreatic beta cell damage [23].

Diagnosis of insulin resistance in children

Direct and indirect methods are used to diagnose insulin resistance in children. The direct method, which is the so-called gold standard, is the hyperinsulinemic, euglycemic metabolic clamp. This method, developed by Andres et al. and refined by De Fronzo et al. involves measuring the amount of glucose required to maintain glycemia at a constant level under conditions of experimentally obtained hyperinsulinemia (within the limits of physiological postprandial concentrations). The test includes a variable intravenous infusion of 20 percent glucose, a constant intravenous insulin infusion, measurement of blood glucose every 5 minutes in venous blood, and evaluation of changes in the amount of glucose needed to keep glycemia constant relative to constant amounts of insulin administered [24]. With exogenous insulin infusion, complete blockade of insulin production by the pancreas and glucose production by the liver is achieved. The rate of glucose uptake by the body's cells per unit time is defined as the M value (expressed in mg/kg/min or mmol/kg/min). The reproducibility of this method is very high with a coefficient of variation of 10%. Unfortunately, this method is costly, labor-intensive and burdens the patient with prolonged intravenous infusions of glucose and insulin; it is only used for clinical trials.

In everyday practice, indirect methods are used, determining the so-called indices of insulin resistance. These methods can be divided into those in which fasting glucose and insulin levels are determined and after intravenous provocation with glucose or insulin administration.

The simplest way to assess insulin resistance is to calculate the quotient of insulin concentration (expressed in mIU/l) to glucose concentration (expressed in mg/dl). A quotient higher than 0.3 speaks for insulin resistance. This test can be performed under basal conditions, as well as 1 hour after administration of 75g of glucose. This result determines the degree of insulin resistance, provided there is normal insulin secretion in the pancreas.

The insulin tolerance test, which involves a single intravenous injection of insulin at a dose of 0.1 units/kg body weight, followed by repeated measurements of serum glucose levels. In insulin-resistant subjects, the drop in serum glucose is relatively slight, while in

insulin-sensitive subjects, serum glucose levels drop to 50% of baseline glycemia. This test is fraught with the risk of excessive hypoglycemia and may pose a health risk to test subjects, mainly young children. Nowadays, the mathematical model for assessing insulin resistance HOmeostatic Model Assessment (HOMA) is widely used [25]. In this model, based on serum glucose and insulin concentrations under basal conditions, the insulin resistance index is calculated according to the following formula:

FI (fasting insulin) [IU/ml] x FG (fasting glucose) [mmol/l] /22.5;

FI (fasting insulin) [IU/ml] x FG (fasting glucose) [mg/dl] /405,

with normal being < 2.5; insulin resistance > 2.5. The value of this index under physiological conditions is 1.0. Higher values argue for peripheral insulin resistance or hepatic origin. The mathematical formula for the original HOMA-IR index (HOMA1) was developed in 1985 by Matthews et al [26]. Unfortunately, this index has not been included in tabulated values or centile channels, which makes its use in children and adolescents difficult, while its calculation makes sense, especially in monitoring the patient's condition.

Nowadays, the HOMA2-IR index, modified in 1996 by Levy et al. It estimates steady-state beta cell function (%B) and insulin sensitivity (%S) as percentages of a normal reference population, is also used. In 2004, the HOMA2 Calculator was released. This index is calculated by a computer program (software available free of charge for non-commercial use from the source www.ocdem. ox.ac.uk). The HOMA-IR index correlates closely with the insulin sensitivity index determined by the standard euglycemic clamp ($p<0.0001$), with fasting insulin concentrations ($p<0.0001$) and the hyperglycemic clamp ($p<0.01$) [23]. In addition, it has been shown that the HOMA-IR index can also be used to assess insulin resistance in children with chronic kidney disease.

The QUICKI index is very similar to the HOMA-IR. To calculate it, the glucose and insulin results from the first measurement of the OGTT test are sufficient. It is less commonly used because the formula is complicated.

1/(log fasting insulin [IU/ml] + log fasting glucose [mg/dl],

That's why diagnosticians use calculators available online. In the case of Quicki, there is a relationship that the lower the value, the stronger the insulin resistance. With a value less than 0.34, insulin resistance is diagnosed.

Some authors emphasize the low usefulness of a single fasting insulin determination due to the cyclic nature of its basal secretion in pulses every 5 minutes or so, but Galli-Tsinopoulou et al [13] found significantly higher fasting insulin concentrations in obese children and adolescents than in their lean peers, and reduced FGIR in 88% of obese children and in all obese adolescents. A normal fasting insulin concentration should be <15 mIU/l, at 120 minutes of an oral glucose load test <75 mIU/l, and at other time intervals always <150 mIU/l. This method of assessment is useful in both adults and children, and is based on the observation that the primary measure of insulin resistance is fasting hyperinsulinemia, not leading to hypoglycemia.

A study by Suzuki et al [27] showed a direct correlation of insulin resistance with a certain amino acid profile; they found that HOMA-IR was positively correlated with valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, threonine, lysine, alanine, tyrosine, glutamate, proline, arginine or ornithine. In addition, blood uric acid levels were positively correlated with leucine and glutamate, and negatively correlated with serine, glycine and asparagine. Determination of the amino acid profile is therefore a useful marker reflecting impaired glucose tolerance and hyperuricemia in the early stages of obesity in both children and adults. In contrast, Ilyes et al [22] showed that insulin binding to erythrocytes (IB) decreases markedly in obese children compared to controls. The reduction in IB was due to a decrease in the number of receptors for insulin. Strong negative correlations were found between BMI and IB and between insulin resistance and IB, while a positive correlation was observed between BMI and insulin resistance. These results confirm the association between excess body weight, hyperinsulinism and insulin resistance in childhood obesity.

Clinical significance of insulin resistance in children

Insulin resistance plays a key role in the development of so-called atherogenic dyslipidemia in obese children with metabolic syndrome. In children with insulin resistance, especially those with dysfunctional insulin secretion, meal administration results in a state of prolonged postprandial hyperglycemia and hyperlipidemia. Both absolute and relative (insulin resistance) insulin deficiency contributes to the inhibition of lipogenesis, increasing lipolysis and thus increasing the concentration of triglycerides as well as free fatty acids in the blood. At the level of hepatocytes, insulin resistance leads to increased lipogenesis, increased synthesis of very-low-density lipoprotein VLDL and increased degradation of high-density cholesterol HDL. Hypertriglyceridemia is a consequence of both excess food-derived chylomicrons and excessive liver synthesis of very-low-density lipoprotein (VLDL-1). In addition, the reduced activity of plasma lipoprotein lipase (slowed catabolism of VLDL-1 and chylomicrons) associated with insulin resistance contributes to the increased number of circulating TGs. Under these conditions, a mechanism of cholesterol ester exchange with TG via cholesterol ester transport proteins is initiated in LDL and HDL particles. Thanks to the increased activity of hepatic lipase, the originally TG-enriched LDL and HDL particles quickly get rid of them, reducing their size and increasing their density. Small dense lipoproteins more easily penetrate the vascular wall, undergo oxidation and have reduced affinity for the receptor for LDL. In contrast, small dense HDLs, depleted in Apo-AI and Apo-AII, are much less efficient in the reverse transport of cholesterol from peripheral tissues to the liver, undergo more rapid catabolism and lose their endothelium-protective properties.

Under conditions of excessive blood glucose concentrations, there is an aggravation of already existing abnormalities in the lipid profile on the one hand, and qualitative changes appear on the other. These are associated with the processes of glycation, oxidation, methylation and tyrosylation. They characterize the chronic inflammation typical of diabetes, metabolic syndrome and atherosclerosis. The smoldering inflammatory response is associated with endothelial dysfunction, which initiates vascular pathology. Physiological protective mechanisms for the endothelium include antioxidant, anti-inflammatory and anticoagulant HDL-cholesterol molecules. HDL-c molecules are characterized by high heterogeneity. Thus, the HDL-2 (so-called "good") subclass consists of large molecules with lower density, while

the small and dense HDL-3 ("bad") molecules are characterized not only by smaller size and higher density, but also have significantly less surface antioxidants (Apo-AI). As a result of chronic inflammation, HDL-2 particles lose their anti-inflammatory properties. The unfavorable modification of HDL-cholesterol molecules is aggravated by processes of non-enzymatic protein glycosylation. Atherogenic dyslipidemia is observed in more than half of obese children [16]. Serum levels of total TC cholesterol, LDL cholesterol and TG triglycerides are significantly higher in obese children than in lean controls. LDL-C is particularly fraught with atherogenic potential [28]. Body weight above the 85th - percentile increases the risk of abnormal levels of total cholesterol 2.4-fold, LDL fraction cholesterol 3-fold, HDL fraction cholesterol 3.4-fold, triglycerides 7.1-fold, and hypertension 4.5-fold [29]. It has been proven that dyslipidemias in childhood significantly increase the risk of cardiovascular events in adulthood. In a comprehensive assessment of the risk of atherosclerotic changes, the plasma atherogenicity index (AIP), calculated as the logarithm of the quotient of TG and HDL-C concentrations, is applicable. AIP values above 0.5 indicate an increased risk of atherosclerotic cardiovascular disease. Risk categories according to AIP have also been defined for the pediatric population:

- low: AIP <0.11,
- AIP averages 0.11-0.21,
- high: AIP> 0.21

AIP was found to correlate with the thickness of the intima-media complex of the carotid arteries in patients with diabetes. A study by Sapunar et al [30] involving more than 200 adolescent children analyzed the prevalence of dyslipidemia and assessed the risk of atherosclerosis by calculating AIP. 38% of the subjects had dyslipidemia, irrespective of gender and Tanner's stage of sexual maturation. In contrast, the prevalence of dyslipidemia was significantly higher in children with obesity (54%; $p<0.1$) and waist circumference >90th percentile (61%; $p<0.1$). Children with obesity also had higher CT / cHDL, cLDL / cHDL and AIP. According to AIP, 54% of children had a high risk of atherosclerosis, and this was associated with changes in anthropometric parameters (BMI, WC) and insulin resistance. All anthropometric parameters and indices of insulin resistance were significantly correlated with AIP.

Recent studies have shown an association between obesity and chronic inflammation with low-grade CLGSI. It has been recognized that inflammation is responsible for obesity-related complications such as insulin resistance, type 2 diabetes, and the inflammation-induced effects of obesity may be systemic, causing metabolic abnormalities and altering cellular functions. Obesity-related low-grade inflammation appears to originate mainly from macrophage infiltration in adipose tissue. Thus, the interplay between monocytes/macrophages and inflammatory mediators may play a key role in the pathogenesis of obesity and the metabolic syndrome. An exponent of inflammation is an increase in acute-phase proteins such as CRP protein or fibrinogen and also elevated levels of cytokines such as IL-1, IL-6, TNF-α, PAI-1, leptin, resistin or transforming growth factor β (TGF- β). Increased biosynthesis of cytokines is a consequence of visceral obesity and leads to a prothrombotic state, impaired endothelial function and increased tissue insulin resistance. The source of cytokines responsible for the development and maintenance of inflammation are

macrophages, found within adipose tissue. Adipocytes, which die as a result of hypertrophy, are surrounded by macrophages, which, in an attempt to remove the dead cell, secrete large amounts of cytokines.[31] In the metabolic syndrome, we see increased biosynthesis of TNF-α , which contributes to insulin resistance, and induces inflammation [32] TNF-α, by blocking tyrosine kinase phosphorylation of the β-receptor subunit for insulin, contributes to the development of receptor-mediated insulin resistance. As a result, once insulin attaches to the receptor, glucose transport into the cell via GLUT transporter 4 is impaired. TNF also has an inhibitory effect on PPAR-γ transcriptional receptors in adipocytes, resulting in a decrease in triglyceride synthesis and an increase in free fatty acids.

Increased expression of interleukin-6 has broad implications in the pathogenesis of obesity and its complications. IL-6, by increasing the synthesis of acute phase proteins in hepatocytes, affects vascular endothelial function. As a result, the formation and progression of atherosclerotic lesions occurs, mainly through a mechanism of increased adhesion of monocytes to endothelial cells. A number of studies have shown a positive correlation between IL-6 levels and classical factors in the development of atherosclerosis.[33] The induction of insulin resistance by IL-6 is caused by direct inhibition of lipoprotein lipase activity, which leads to the accumulation of free fatty acids and triglycerides. TGF-β, which enhances fat cell proliferation and stimulates the release of other pro-inflammatory cytokines, is also involved in the inflammatory processes associated with obesity.[34] In the course of obesity, there is an increase in the concentration of adhesion molecules ICAM-1 and VCAM-1, allowing monocytes to interact with the endothelium, which is considered to be an important element initiating atherosclerotic plaque formation. [35]. Obese patients also show an increase in leptin levels, and its involvement in the formation and maintenance of inflammation is still the subject of much research. Leptin affects cells of the immune system - activates macrophages, monocytes, induces phagocytosis, stimulates the expression of other adipokines especially interleukin 6, interleukin 12 and TNF-α. It has an inhibitory effect on the proliferation of immune memory lymphocytes. [36,37]. Resistin also plays an important role in the pathogenesis of inflammation.

Clinical consequences of insulin resistance in children

Obesity in children is associated with an early risk factor for high adult morbidity and mortality. While children rarely experience cardiovascular events, early signs of accelerated atherogenesis can be detected in children. Children who remain obese as adults have a significant risk of developing type 2 diabetes, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. This group of diseases and disorders is collectively known as metabolic syndrome (MetS). In addition to type 2 diabetes and cardiovascular disease, the metabolic syndrome is associated with a number of clinical conditions, including chronic low-grade inflammation, oxidative stress, hyperuricemia, hypertension dyslipidemia, hyperandrogenism and polycystic ovarian syndrome, hepatic steatosis, impaired glucose tolerance, obstructive sleep apnea, hypogonadism, vascular dementia and Alzheimer's disease, and some forms of cancer. This concept, is defined as a number of interrelated factors of a metabolic nature, the co-occurrence of which increases the risk of developing atherosclerotic cardiovascular disease and type 2 diabetes [38]. Insulin resistance is considered one of the main pathogenetic factors of metabolic syndrome. Genetic and environmental factors play an

important role in the pathogenesis of metabolic syndrome. This is demonstrated by cases of familial occurrence of metabolic syndrome. In genetic studies, most data point to the importance of polymorphisms of genes related to nuclear peroxisome proliferator activated receptors g (PPAR; peroxisome proliferator activated receptors), among others that regulate adipogenesis and increase insulin sensitivity. Other genes include the gene for calpain 10, a cytoplasmic protease involved in metabolism, the gene for resistin, an adipose tissue hormone that affects insulin resistance, and genes related to the synthesis of glucose transporters in cells. The primary environmental factors relevant to the development of metabolic syndrome are physical inactivity and poor diet leading to overweight and obesity. Overweight and obesity, especially the visceral type, lead to insulin resistance and compensatory hyperinsulinemia.

Type 2 diabetes mellitus - T2DM in children is the final result of a process of metabolic decompensation that evolves over months or years and its main pathogenetic factor is tissue insulin resistance. The type 2 diabetes phenotype is characterized by decreased insulin production, relative and absolute hypoinsulinemia, reduced beta cell mass and amyloid deposits in pancreatic cells. The risk of developing T2DM in people of developmental age depends on congenital predisposition, environmental and dietary factors, and energy expenditure. The incidence rises sharply during adolescence, due to the antagonistic effect to insulin of growth hormone and sex steroids. This risk is subject to modification by prenatal determinants - T2DM develops more often in children of mothers with diabetes and children born at low birth weight. There is a notable difference between the development of T2DM in girls and boys. In the former, especially in girls burdened with hyperandrogenism and PCOS, type 2 diabetes develops more frequently. Pre-pubertal girls with adrenarche are also a group at increased risk of developing T2DM. Impaired glucose tolerance is an intermediate step in the natural history of type 2 diabetes and is a risk predictor for the development of diabetes and cardiovascular disease. However, children and adolescents with impaired glucose tolerance have a high spontaneous conversion rate from IGT to normal glucose tolerance within 3-5 years. This normalization has been attributed to changes in insulin resistance at the end of adolescence. After puberty, the basal and stimulated insulin response declines. Studies of the HEMP hyperinsulinemic-euglycemic buckle have shown that tissue insulin sensitivity is on average 30% lower in adolescents between Tanner stages II and IV compared to prepubertal children and young adults. Increased secretion of growth hormone during adolescence is said to be responsible for insulin resistance during this period. Given this information, it is not surprising that the peak age at onset of type 2 diabetes in children coincides with the usual age at mid-adolescence. The mere formation of insulin resistance in diabetes is not sufficient and inadequate insulin secretion by β-cells is necessary. Patients with type 2 diabetes have both insulin dysfunction and insulin secretion failure. Elder et al [39] in both oral and intravenous glucose load tests observed three times lower insulin sensitivity in obese adolescents with T2DM than in a group of obese adolescents without T2DM.

Macrovascular lesions in children are less common than in adults; arteriosclerosis is a time-dependent phenomenon, so the absolute time from diagnosis to the development of pathological cardiovascular lesions can be many years - in this sense, these children may be protected by age, as they do not have pre-existing age-related cardiovascular disease.

However, adolescents with type 2 diabetes have already been shown to have increased carotid intima-media thickness, which is a predictor of myocardial infarction and stroke.

Available studies have shown increased thickness of the intima-media membrane IMT complex. Urbina et al [40] analyzed ultrasound parameters of carotid artery evaluation in normal-weight, obese and T2DM groups of children, finding a thickening of the IMT complex in children with T2DM compared to obese and normal-weight patients, and an increase in the beta stiffness index of the arteries in both the obese and T2DM groups. Total myocardial mass was also found to positively correlate with BMI, systolic and diastolic blood pressure and fasting blood glucose; with fasting insulin levels and insulin resistance not being associated with left ventricular hypertrophy in healthy, but only in obese children [41].

In contrast, microvascular complications are a feature of hyperglycemia diagnosed at a young age. Data from population-based studies in Japan and India demonstrate the presence of microvascular changes already at the time of diagnosis. In the Japanese material, retinopathy was present in 36% of children at diagnosis, while microalbuminuria was present in as many as 39% at 2-year follow-up. Among Indian children, 22% had microalbuminuria, and by the age of 20-29 years, already 60% had microalbuminuria and 17% had macroalbuminuria. In contrast, in European studies, adolescents had no retinopathy and only 5% had microalbuminuria , suggesting a strong influence of genetic factors on the development of organ complications in diabetes [42]. Subjecting children and adolescents with T2DM to a systematic evaluation of metabolic status and verification of possible vascular complications seems to be an essential preventive measure. It is believed that once a year the following should be performed: ophthalmologic examination with fundus evaluation, determination of urinary microalbumin concentration. Systematic blood pressure monitoring is mandatory.

Insulin resistance is associated with the development of non-alcoholic fatty liver disease NAFLD, and can lead to fibrosis and cirrhosis of this organ. NAFLD is estimated to occur in 50-90% of adults who are obese or have type 2 diabetes, and at least 20% of those with insulin resistance will develop cirrhosis, liver failure or liver cancer in the future. Among obese children, hepatic steatosis can be found in 20-50% [43]. The risk of fatty liver lesions is significantly increased by dyslipidemia in the form of high TG and low HD fraction cholesterol. Elevated levels of aminotransferases, especially ALT, as a marker of liver cell damage, are found in 10-25% of obese children, and ultrasound features of steatosis are found in up to 52% of obese children. In most patients, non-alcoholic steatosis clinically has a benign course. However, it is a risk factor for increased liver fibrosis and cirrhosis. NAFLD occurs in a wide spectrum of liver diseases from asymptomatic steatosis to steatohepatitis. NAFLD is considered a hepatic manifestation of the metabolic syndrome, and a body of evidence suggests that children with NAFLD exhibit one or more features of MetS. The pathogenetic mechanisms explaining the links between hepatic steatosis and MetS are not fully understood. Although central obesity and insulin resistance appear to be at the core of the pathophysiology in both diseases, genetic susceptibility and environmental factors are emerging as key elements promoting the development of NAFLD and MetS in children [44].

It is known that all obese girls have insulin resistance and secondary hyperinsulinism. Elevated androgen levels are associated with increased conversion of ovarian and adrenal

precursors in visceral adipose tissue and hyperinsulinemia. Insulin, acting through receptors targeting IGF-1, stimulates ovarian androgen synthesis by increasing the activity of 17α - hydroxylase, an enzyme that determines the conversion of progesterone to 17-OH progesterone and then to androstendione. As a consequence of hyperinsulinism, synthesis of growth factor-binding protein 1 (IGF-BP 1) is reduced, so the synergistic effect of IGF-1 with insulin is increased. Reduced concentrations of sex hormone binding globulin (SHBG; sex hormone binding globulin) further increase the concentration of the free androgen fraction. About 50% of testosterone in young women may come from adipose tissue. Excessive androgen secretion causes ovulation disorders and the formation of cystic lesions in the ovaries. PCOS (polycystic ovary syndrome) is the most common endocrinopathy diagnosed in obese girls and young women of reproductive age. It is characterized by polycystic ovaries and menstrual dysfunction accompanied by chronic ovulation failure and hyperandrogenism, which can coexist with obesity. The first description of enlarged, smooth polycystic ovaries was attributed to Chereau in 1844. In the 19th century, wedge resection of the ovary became the recommended therapy, although Stein and Leventhal first reported that the clinical features of menstrual regularity and infertility could be improved by removing parts of both ovaries. As a result, the constellation of enlarged, sclerocystic ovaries often associated with hirsutism, menstrual irregularity, obesity and infertility became known as Stein-Leventhal syndrome. In recent decades, PCOS has become the preferred terminology . About 60% of women have hirsutism, which is the most common clinical sign of hyperandrogenemia. In addition, irregular menstruation is associated with a 1.5-fold increased risk of coronary heart disease and a 1.9-fold increased risk of fatal myocardial infarction [45]. Already in young women with PCOS, subclinical signs of atherosclerosis can be found in the form of increased coronary calcification, increased vascular stiffness and dysfunction, as well as increased left ventricular mass up to and including hypertrophy [45].

One of the manifestations of insulin resistance is acanthosis nigricans, found in as many as 51% of obese African-Americans and 8% of obese Caucasians. It is characterized by the presence of thickened, hyperkeratotic, papillary and excessively pigmented brown skin. The lesions are localized around the axillae, neck and hands. It can appear around the nipples, elbow fossa, navel and perineal area. The pathogenesis of keratosis annulare is not well understood, but the molecular basis is believed to be the excessive proliferation of keratinocytes in response to various growth factors (EGF, TGF - α, insulin) and also receptors (EGFR, IGFR, FGFR).

Prevention and treatment of insulin resistance in children

A key role in the non-pharmacological treatment of insulin resistance is played by a properly balanced diet and appropriate levels of physical activity. As insulin resistance is a metabolic disorder and not a disease entity, there is a lack of recommendations on therapeutic dietary guidelines for IR. Taking into account the fact that untreated hyperinsulinemia and insulin resistance may be the cause of type 2 diabetes in the first place, it seems reasonable to compose dietary recommendations in accordance with the recommendations for the nutritional treatment of type 2 diabetes, updated annually by the Polish Diabetological Association, as prevention of this disease entity [46]. The phenomenon of reduced tissue sensitivity to insulin affects not only overweight children, but also those of normal weight.

Nevertheless, it affects the former much more often. The main reason for the increasing scale of obesity is the over-consumption of highly processed, energy-dense foods, their variety, easy access and affordability, consumption of ready-made, processed meals with lower vitamin and mineral content compared to freshly prepared meals, dining at fast food bars, drinking sugary drinks, too much time spent sitting and in immobility, and sleep deprivation. Less sleep increases ghrelin and decreases leptin, resulting in increased cravings, eating more food and consequently increasing body weight [53,54]. For young children and adolescents with excessive body weight, it is recommended that:

- In children aged 2-4 years, limit weight gain to 1kg for every 2cm of height gain if overweight,
- When obesity is diagnosed in children under the age of 4, the goal is to keep weight constant, which, with gains in body length, has the effect of reducing BMI values.
- In older children, over 4 years old, if overweight, it is recommended to keep the weight at the same level,
- In the case of obesity, reducing weight by 1-2kg per month[53].

Total energy expenditure per current body weight should be calculated according to the formula recommended by WHO/FAO/UNU experts:

*for boys $310.2 + 63.3 \times W - 0.263 \times W^2$;
*for girls: $263.4 + 65.3 \times W - 0.454 \times W^2$,

Where W- current body weight [55].

Then, it is necessary to subtract by 300-400kcal per day, from the result obtained, to obtain the expected weight loss of about 0.45 kg/week, in the case of obese children. Note that it is not recommended to excessively reduce calories and, consequently, macronutrients in the diet of children, due to the intensive developmental processes [56].

The number of meals per day should be determined individually for each child, depending on his lifestyle, taking into account, for example, additional physical activity. Most often, 4-5 meals a day are recommended. The habit of eating between meals should be eliminated, which stimulates the body for further insulin secretion by the ß-pancreas islands.

It is recommended that breakfast be eaten as soon as possible after getting up, preferably up to 1h after waking up. This is to prevent the accumulation of calories consumed in the afternoon and uncontrollable hunger (especially for carbohydrates, usually simple ones) in the second part of the day.

The interval between meals should be 2.5-4 hours, so as not to overburden the stomach with continuous digestion and lingering food after meals eaten. For school children, attention should be paid to where lunches are eaten. It is not recommended to eat two lunches in a day (for example, at the school cafeteria and later at home), due to the excessive amount of calories consumed with two lunches. Dinner should be eaten 2-3 h before bedtime. It is inadvisable not to eat dinner or to eat it shortly before bedtime.

To treat insulin resistance and prevent type 2 diabetes, dietary patterns such as the Mediterranean diet and the DASH (Dietary Approaches to Stop Hypertension) diet are most commonly recommended, in addition to the 2021 PTD recommendations. Both diets combine

recommendations for a high intake of vegetables, fruits, whole grain cereals, fatty seafood, while limiting sweets, confectionery, sugary drinks and highly processed foods. The foods recommended for consumption are characterized by a low to medium glycemic index (GI) and glycemic load (GL) [57].

After eating meals that include carbohydrates, blood glucose levels rise. Not all products containing carbohydrates cause the same response from the body after consumption. Based on differences in the body's response to changing blood glucose levels (its rate of increase and decrease), an index called the glycemic index was developed.

The definition of GI is: "The glycemic index is the area under the blood glucose curve formed within 2h after ingestion of a specific product in an amount that contains 50g of assimilable carbohydrates and is expressed in comparison to the area of the glycemic curve formed after ingestion of a standard product such as glucose or white bread by the same person. The GI of glucose is 100" [58,59].

Depending on the glycemic index value, we divide foods into those with:

- low GI ≤ 55
- medium GI 56-70
- high GI > 70

GI alone is not an indicator of whether a product is healthy or not. Often, products classified as healthier, have a higher GI than products with a lower GI. For example, the GI of nutella= 33 (low), and the GI of mountain oatmeal cooked in water =58 (medium). Therefore, in 1997, in addition to the definition of glycemic index, the definition of glycemic load was also introduced. It is the product of the GI of the consumed product and the amount of carbohydrates in it. The result obtained should be divided by 100.

The following breakdown for GL for a portion of the product was adopted:

- low GL ≤10,
- medium GL 11-19,
- high GL ≥ 20.

You can also count the GL for a whole-day ration by adding up the GL of all the foods eaten during the day. The interpretation of the result obtained is:

- low GL < 80,
- medium GL 80-120,
- high GL >120.

Frequent consumption of foods with high GI and GL can cause frequent feelings of hunger, excessive caloric intake throughout the day, disturbances in glucose and insulin metabolism or the development of cardiovascular disease. A comprehensive meta-analysis by Goff et al. of 28 randomized, controlled clinical trials proved that a low-GI diet helped reduce total cholesterol and LDL cholesterol [60].

The main source of energy in the human diet from carbohydrates is starch - a polymer of α-D-glucose, which is the spare material of plants and products of plant origin (there is no starch in animal products, the spare material in the animal world is glycogen). Starch is stored in the form of grains, consisting of two varieties: amylose and amylopectin. Amylose is made up of glucose chains that are unbranched, so the access of digestive enzymes is limited to the branching sites - amylose digests more slowly, so that glucose from its chains is gradually released into the blood. Amylopectin, is digested much faster compared to amylose, due to its

more branched structure, as digestive enzymes can act simultaneously on multiple bonds at the same time. Products rich in amylopectin definitely raise blood glucose levels faster after they are consumed. Amylopectin-rich foods are primarily cereals, with the exception of barley, while amylose-rich foods include dried pulses with the exception of green peas and broad beans. [61].

Based on the rate of glucose release and absorption from the gastrointestinal tract, starch is divided into three types:

- Rapidly digested starch- starch contained in a product that is digested within 20 minutes of consuming a starchy product, resulting in a rapid rise in blood glucose levels, followed by a rapid drop in blood glucose levels due to the release of large amounts of insulin,
- slow-digesting starch - starch that is completely digested in the gastrointestinal tract, but within 20-120 minutes after ingestion of the product, thus maintaining a normal, more constant postprandial glycemia compared to RDS,
- resistant starch - starch that is not digested.

When starch-rich products are heated (cooking), the starch grains swell and spill over - glueing. When the glue cools down, the starch particles aggregate again and form a gel. After further cooling of starch products, water is pushed out of the gel structure-retrogradation, which results in reduced digestibility of starch, since the resulting structures are resistant to digestive enzymes. Amylose is more easily retrograded than amylopectin [62].

Therefore, it is recommended that starchy products (groats, rice, pasta), after cooking, should be cooled to room temperature and then in the refrigerator at about 4 C, in order for resistant starch to form, so that after consuming these products, blood glucose levels will rise more slowly compared to starchy products eaten immediately after cooking. Reheating these products will not reduce the amount of resistant starch in this product, since the process of retrogradation is an irreversible process.

In addition to lowering the energy value of products containing resistant starch, it has other beneficial effects on the human body-it reduces the amount of insulin secretion after a meal, has a beneficial effect on the human microbiome or increases the bioavailability of calcium, magnesium, zinc, iron or copper [62,63].

The protein supply in the diet of children between the ages of 4 and 18 is recommended at 10-20% of the total daily energy supply. 1 gram of protein provides 4 kcal. For children diagnosed with insulin resistance, protein is recommended to come from such products as lean white meat - chicken, turkey, lean cottage cheese, fish, dry pulses, natural homogenized cheese, natural yogurt, natural kefir and buttermilk, 1.5-2% milk, eggs, smoked fish. Yellow cheeses, such as feta or mozzarella, are also a good source of protein and easily absorbed calcium. However, due to the high content of animal fats and cholesterol, it is recommended to limit the consumption of these products[64].

The total amount of fat in a child's diet should vary between 20-35% of daily energy requirements, taking into account other values of blood test results. 1g of fat provides 9 kcal. What is important is not only the right amount of fat in the diet, but especially the quality and source. Fats of vegetable origin are preferred above all, and fat of zoonotic origin is limited, due to the often high amount of cholesterol in these products. Vegetable fats are a source of essential fatty acids (EFAs) of the omega -6 (n-6) and omega -3 (n-3) family, which must be

supplied with food to the body. However, attention should be paid to the ratio of n-6 to n-3 fatty acids consumed. An excess of n-6 fatty acids can negatively affect health by exacerbating oxidative stress and increasing the risk of obesity. The optimal ratio of n-6 to n-3 acids is 4-5:1. Good sources of n-3 acids in the diet are hemp oil, flaxseed oil, walnut oil, canola oil and grape seed oil [65].

The supply of saturated fatty acids and trans fatty acid isomers should be as low as possible, linoleic acid- n-6 (LA) at 4% of energy, α-linolenic acid- n-3 (ALA) at 0.5% of energy, eicosapentaenoic acid- n-3 (EPA) and docosahexaenoic acid- n-3 (DHA) 250mg/day. The amount of fat in the diet should not be restricted too strictly, due to the consequences of its deficiency: deficiency of fat-soluble vitamins (A,D,E,K), central nervous system (CNS) dysfunction, immune system dysfunction, endocrine and intestinal disorders. Vitamin A and E are counted among antioxidants, and their deficiency in the diet can cause accelerated aging and increased oxidative stress through an excess of unpaired free radical electrons. For children in adolescence, EPA and DHA acids play a special role in nutrition. Sources of DHA acids in the diet are primarily fatty marine fish. There are 2.15g of DHA acids in 100g of salmon, 1.12g of DHA per 100g in mackerel, and only 0.29g per 100g in brook trout. [66].

Another macronutrient in the diet is carbohydrates, the main source of energy (calories) in the diet. The carbohydrate requirement is about 45-65% depending on the level of physical activity (the higher the level of physical activity, the higher the carbohydrate requirement). 1g of carbohydrates is a source of 4kcal [67]. For dietary treatment of insulin resistance, the supply of simple carbohydrates (monosaccharides), which include glucose, fructose and galactose, and disaccharides (disaccharides), which include lactose or sucrose, should be limited. As a source of glucose and fructose in varying amounts, fruit is recommended to be eaten with meals, not between meals or as a separate meal. Before eating fruit, it is advisable to eat a sandwich of whole-grain bread with the right amount of fat and protein and vegetables. The bread will be a source of complex carbohydrates-starch, and dietary fiber. It is not recommended to consume fruit juices, fruit mousses. It is recommended to consume starchy products such as whole-grain bread, groats, brown rice, wild rice, oatmeal, pasta made from legumes or whole grains. For food preparation, it is recommended to use high type flours, such as type 1850 and type 2000, which have a higher ash content compared to lower type flours.

The last macronutrient in children's diets is dietary fiber - food fiber, which is the remains of plant cells that are resistant to human digestive enzymes. However, dietary fiber is partially hydrolyzed by colon bacteria, so 1g of fiber provides only 2kcal. Dietary fiber can promote the prevention and treatment of obesity, by reducing the nutrient density of food, longer residence of fiber-rich foods in the stomach gives a longer feeling of satiety, which allows for longer intervals between meals, has a beneficial effect on blood lipid levels, and promotes the reduction of postprandial hyperinsulinemia. [68,69,70].

Standards for dietary fiber were set at the level of sufficient AI intake and are for children of age:

- 4-6 years- 14g/day
- 7-9 years old - 16g/day
- 10-15 years -19g/day
- 16-18 years 21g/day

An excessive supply of dietary fiber is not recommended, as an excess can cause mineral deficiencies - reduced absorption of minerals from the gastrointestinal tract, such as calcium and iron, and fats, which can be associated with deficiencies of fat-soluble vitamins.[71,72]. Good sources of dietary fiber are whole-grain products: whole-wheat bread, wholemeal bread, brown rice, oatmeal, buckwheat groats, pearl groats, raw vegetables, wheat bran [66].

Adequate hydration and the source of fluids in a child's diet play an important role during the juvenile period. The young body consists of water in greater quantity than the body of an adult. Fluid requirements are calculated individually for each child, based on body weight, using the formula of the Holliday and Segar method:

- 1-10kg b.w.- 100ml/kg b.w.
- 10-20kg b.w.- 1000ml + 50ml/kg b.w.for every kilogram over10kg
- >20kg bw - 1500ml + 20ml/kg bw for every kilogram over 20kg.

Children have a greater need for water than adults on a per body weight basis, which also influences them to dehydrate faster and face greater consequences of water deficiency. Water deficits as low as 2% have been shown to negatively affect cognitive function: deterioration of short-term memory, problems with concentration, prolonged reaction time to stimuli. Dehydration also causes increased cortisol levels [73,74].

It is not recommended that juices in a child's diet serve a hydrating function. Rather, they should be an accompaniment to meals, rather than an unpunished snack between meals. According to the 2017 APP (American Academy of Pediatrics) and ESPHAGAN recommendations, the recommended juice supply was set at:

- <1 year not recommended to be given at all
- 1-3 years old - 120ml of juice/day
- 4-6 years old - 180 ml of juice/day
- In older children and teenagers- 180 ml of juice per day.

It is also not recommended to give children the following: sugary drinks, sodas, fruit nectars, caffeine, sports drinks, sweetened tea, flavored waters and energy drinks, which in addition to caffeine also contain large amounts of simple sugars, possibly sweeteners such as aspartame. School-aged children often ignore the feeling of thirst and forget to drink adequate amounts of water, which may be the result of too little nutritional awareness and a lack of learned habit [75, 76].

In summary, children should primarily consume medium mineralized mineral water, drinking regularly throughout the day. They should not consume black tea with meals, due to its theine and tannin content, which can cause reduced absorption of minerals from meals, such as iron.

The search is on for an effective and safe drug that can be used in pediatric patients. One of the products being investigated is metformin, an antihyperglycemic drug. Metformin is currently registered in Europe and the U.S. for use in pediatric patients (>10 years of age) for the treatment of type 2 diabetes. In addition to reducing cardiovascular risk and lowering inflammatory exponents, weight loss has also been reported in adults taking the drug. In contrast, data on the effect of metformin on body weight in children and adolescents are limited [74]. Metformin is a first-line drug in carbohydrate metabolism disorders with mild to moderate hyperglycemia (fasting blood glucose 100-126mg/dl). It inhibits gluconeogenesis

and lipogenesis in the liver, and lowers serum insulin levels while increasing peripheral insulin sensitivity. It has proven that it can induce satiety by increasing the synthesis of a glucagon-like protein. In addition to improving the metabolic profile, metformin also affects the hormonal profile, improving endocrine function in girls with PCOS [75].

Insulin is used in disorders of carbohydrate metabolism with high glycemia (fasting glycemia>126mg/dl or incidental glycemia>200mg/dl) and in diabetes of acute onset and especially running with ketoacidosis [75,76].

Summary

Insulin resistance is called a state of reduced insulin action on target tissues, despite normal or elevated serum insulin levels, resulting in impaired metabolic function and homeostasis of carbohydrate, lipid and protein metabolism. The result of which is type 2 diabetes, PCOS, metabolic syndrome. Nutrition in the prenatal, early postnatal, and pubertal periods is crucial to the development of insulin resistance and its consequences. Prenatal environment and fetal nutrition appear to condition metabolic programming in later life. The type of dietary carbohydrates, glycemic index, protein, fat and micronutrient content of maternal nutrition may also affect the insulin sensitivity of the newborn. The impact of breastfeeding on the child's metabolism and eating behavior later in life is invaluable. A well-balanced diet and learning proper eating habits are the key to dietary management of metabolic disorders, including insulin resistance. Dietary changes should be made gradually so that children are not discouraged from taking on the challenge of limiting snacking between meals, reducing their intake of sweets, sweetened, sugary drinks and salty snacks. It should be emphasized that diet in insulin resistance is not short-term, the habits developed during the dietary intervention should be continued even after the reduction of excessive weight or normalization of blood test results. Eating habits and diet quality during adolescence can prevent the onset of pathological insulin resistance through proper distribution of macro- and micronutrients, a diet rich in fiber and vegetables and low in saturated fats, proteins and sugars.

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