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# Obesity and overweight in children and adolescents as a risk factor of glucose homeostasis disturbances and their complications

Otyłość i nadwaga u dzieci oraz młodzieży jako czynnik ryzyka zaburzeń homeostazy glukozy i ich powikłań

## ABSTRACT

The excessive body mass prevention should be conducted from the first months of the child's life. The waist circumference measurement should be obligatorily performed during the routine check-up visits because some children with abdominal obesity do not fulfill the body weight or BMI obesity criterion. Children with positive family history of the cardiovascular diseases, hypertension, lipid disturbances or diabetes ought to be closely monitor for the blood pressure, blood lipids and glycemia abnormalities. (*Diabet. Prakt.* 2011; 12, 5: 180-187)

**Key words:** adipose tissue, adipokines, insulin resistance, metabolic syndrome, metabolic memory

## Introduction

Adipose tissue nowadays not only is regarded as an energy depot but is also recognized as a source of endo- and paracrine substances. The fat tissue is additionally a place where receptors for many hormones, cytokines, lipoproteins and growth factors as well as adrenergic receptors occur [1-6].

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A change in adipose tissue mass causes a change in the endocrine function. Leptin and resistin secretion become increased and adiponectin secretion decreases. These alterations affect other biologically active substances that take part in important metabolic processes as well (i.e. TNF- $\alpha$ , IL-6) [7-9].

Retinol binding protein 4 (RBP4) is a novel adipocytokine that may link obesity and insulin resistance. RBP4 is a marker of adipose tissue mass and obesity already evident in children. The association of RBP4 with metabolic and cardiovascular sequelae of obesity appears to be secondary to the underlying relationship with body fat [10].

An opinion is being put forward that insulin resistance and its related conditions affect people with abnormal functions of fat tissue which is termed adiposopathy [11].

This adipose tissue disease typically presents as adipocyte hypertrophy, visceral obesity and ectopic fat accumulation in other tissues. In the conditions of positive energetic balance the size of the cells increases at first which is then followed by generation of new adipose cells from preadipocytes. If this continues, adipose tissue cells undergo further hypertrophy with accompanying angiogenesis abnormalities. This will escalate fat tissue dysfunction.

Adipose tissue excess can produce a number of metabolic disturbances in the organism. Because the increase in adipocyte number is irreversible the

excessive amount of these cells that develops in the childhood can result in obesity in the adulthood. For several years obesity in childhood was considered as a cosmetic defect only, rather than a health issue. In the eighties of the last century a growing number of reports about the impact of obesity on the adolescents' health were beginning to appear. One has started to pay attention to its accompanying symptoms like hypertension, dyslipidemia or glucose tolerance disturbances [12].

At first the observations were made in the populations with high rate of marked obesity. Subsequently it was noted that these kinds of abnormalities are abundant also in other groups of patients including Caucasian adolescents. It is confirmed also by some Polish studies [13–16].

To assess the excess body weight different indexes are used. The DEXA method (dual-energy X-ray absorptiometry) is currently considered a reference method in the evaluation of the body composition. It is a low-invasive examination allowing the assessment of the bone mineral density as well as lean body mass and body fat [17].

Waist circumference (WC), waist/hip ratio (WHR) and waist/height ratio (WHtR) are easy indirect markers helpful in assessment of the abdominal obesity. The result of waist circumference measurement in children should be compared with the existing percentile charts or tables with normative values that include sex and age. That kind of standards have been created for Polish developmental population by Ostrowska-Nawarycz et al. [18].

### The causes of obesity

Three major factors modulate body weight: metabolic factors, diet, and physical activity, each influenced by genetic traits.

### Genetic factors

Performed international and multicenter studies allowed to identify 18 new gene loci, which influence the general obesity and 13 new loci connected with the adipose tissue distribution. The published studies throw a light on the reasons why some people are prone to obesity while some are not [19].

Similar studies concerning genetic background of obesity have been conducted also in children [20, 21].

The mentioned issue was also the subject of Prof Krętownski's lecture during this year's PTD (Polish Diabetes Society) meeting [22].

Clinical observations showing higher prevalence of obesity in children from families with overweight parents (that are overweight) have led to the search for obesity gene [23].

It is considered that genetic factors are responsible in 25–45% for the development of obesity.

### Environmental factors

The genetic predisposition is overlapped by very important environmental factors. It is known that obesity may appear as a result of disturbances of the genes controlling body mass, however this factor solely is not sufficient to cause it. In the circumstances of facilitated food access and limitation of physical activity the expression of genes responsible for body mass build-up leads to obesity. The influence of the environment is the strongest in the childhood when all the alimentary habits are forming. Not only is the ingested calories excess important but also the incorrect meal composition. They cause postprandial hyperglycemia(s) which stimulate insulin secretion as well as may lead to the endothelium damage [24].

Decreased physical activity plays crucial role in the processes leading directly and indirectly to the excessive body mass gain. Diminished energetic expense causes disturbance of the energetic balance of the organism [25].

### Consequences of obesity

#### Insulin resistance

Obesity and overweight promotes insulin resistance [4, 26]. It particularly applies to the abdominal obesity which is strongly connected with that phenomenon [27, 28].

In the visceral adipose tissue adipocyte hypertrophy occurs. Fat accumulation in the liver, skeletal muscles but also in the kidneys, pancreas and heart is essential for the development of insulin resistance. In the process of adipocyte hypertrophy a number of alterations promoting lipolysis emerge which in turn cause an increase of free fatty acids (FFA) concentration in the blood. Raised FFA influx decreases insulin sensitivity through the gluconeogenesis augmentation and weakening of inhibitory action of insulin on the glucose production in the liver. In the skeletal muscles a stop in glucose transport to the cells, reduction of glucose oxidation and glycogen synthesis occurs. Fat accumulation is present also in other organs. In the islets of pancreas,  $\beta$ -cell dysfunction and disturbed insulin secretion can be found. The

experimental studies showed that the increased FFA inflow in kidneys can cause tubulo-interstitial lesions. Moreover, the accumulation of fat in the heart may lead to the cardiomyocytes necrosis and promote contractility disturbances. In the clinical setting a relationship between insulin resistance and heart muscle hypertrophy was observed. The increased accumulation of the adipose tissue in the perivascular space is also of note. It is considered that obesity appears in people who have a genetic predisposition and when a favourable environmental conditions are present i.e. it has an **epigenetic background**. Epidemiological studies that document different prevalence of insulin resistance in different populations as well as those revealing familial predisposition(s) to the development of disorders connected with it, suggest **genetic background**. Currently it is considered that genetic factors are responsible for the development of insulin resistance in 46–80% [29].

Low physical activity and high-caloric diet rich in foods with high glycemic index are regarded main environmental factors associated with the development of insulin resistance. The coexistence of those factors leads to the increased prevalence of overweight and obesity [30].

Abnormalities of the fetal development are also mentioned as one of the environmental factors. In children born **small for gestational age** (SGA) compared to those with normal birth weight, insulin resistance and other features of metabolic syndrome are more frequently observed [31–35].

The precise mechanism of this phenomenon is not known. A few hypotheses try to explain it i.e. “thrifty fenotype hypothesis”, “foetal insulin hypothesis” or “foetal salvage hypothesis” [36].

On the contrary, children born with abnormally high birth weight are prone to develop obesity and insulin resistance as well [37].

Decreased physical activity is an important factor magnifying insulin resistance [38, 39].

As 70–80% of glucose is utilized in skeletal muscles they form one of the main effector organs for the peripheral action of insulin [40].

In skeletal muscles, as results of the studies show, post receptor signaling disturbances leading to GLUT4 translocation abnormalities and in effect causing decreased glucose transport to myocytes are the main reasons of insulin resistance. Mitochondrial defect is also related to the insulin resistance in muscles. It causes decreased fatty acids oxidation and accumulation of the intracellular acetyl-CoA and other toxic products of lipid metabolism (i.e. diacyl-

glycerols and ceramides). Studies performed in children display that insulin sensitivity depends on physical activity with its increase related to the intensity of the activity. The insulin sensitivity’s improvement while performing physical activity is connected to the increased  $\beta$ -oxidation of fatty acids which in turn leads to the increased lipid turn-over in myocytes (IMCL intramyocellular lipids) and decreased lipid peroxidation.

As one of the outcomes of insulin resistance the excessive  $\beta$ -cells stimulation leading to endogenous insulin’s over-secretion in order to maintain glucose homeostasis occurs. A gradual loss of  $\beta$ -cell mass with glucose tolerance impairment is a result of this process.

Several indices are used to determine sensitivity to the action of insulin. The hyperinsulinemic euglycemic metabolic clamp is regarded as “a gold standard”. Being the most accurate method the clamp is also complicated and used mostly for experimental purposes.

In persons with preserved insulin secretion, much easier indirect methods are used in the population based studies. They are based on the relation between blood insulin and glucose concentrations in the fasting state or during the oral glucose tolerance test (OGTT) [41, 42].

## Type 2 diabetes and metabolic syndrome

Diabetes and glucose tolerance impairment are the outcomes of insulin resistance. On this basis it is crucial to perform the glucose concentration assessment as a screening in obese people including children and adolescents, especially when other type 2 diabetes risk factors are present. Most of the published data come from the studies from outside Europe [43–52].

However, the increasing number of studies describing glucose metabolism disturbances in children and adolescents with obesity and overweight have been performed appear in the European countries [53–56].

The observations made in Polish centers confirm these reports [57–60]. Recently published results of the study in 78 obese children showed hyperinsulinemia in 53.8% and the increase of the R-HOMA index in 62.3% of the study group [60].

Von Berghes et al. [61] point at insulin’s secretion abnormalities in obese children. Kleber et al. [54] performing a study in a group of 169 obese European children, after a year of follow-up, revealed impaired glucose tolerance (IGT) in 11.2% and

impaired fasting glycemia (IFG) in 2.4% of them. A study conducted by Italian authors in 530 children with obesity/overweight the presence of glucose metabolism disturbances in 12.4% of patients, most commonly IGT — 11.2%. Only in two adolescent patients (0.4%) a disorder named “silent T2DM” was identified. The endogenous insulin’s concentration and HOMA-IR were higher in patients with IGT than in subjects with normal glucose tolerance. The authors suggest that OGTT may be warranted as the screening test in all obese and overweight European children.

Studies performed in Germany in 520 children with BMI > 97<sup>th</sup> percentile by Wabitsch et al. [56] were the impulse to form a conclusion about a need to diagnose the insulin resistance and glucose homeostasis disturbances also in Caucasian children that live in Europe.

Insulin resistance plays a role not only in the development of type 2 diabetes but also in the pathogenesis of other disturbances regarded the components of metabolic syndrome [62, 63].

### Metabolic syndrome

In the year 2007 IDF introduced the definition of metabolic syndrome in children which considered three age groups [64].

According to this guidelines metabolic syndrome can only be diagnosed in adolescents. It is, however, underlined that younger children with abdominal obesity and especially with positive family history of the insulin resistance relating diseases, should be regularly tested for the glycemia, lipid and blood pressure abnormalities [65]. Being regarded an important insulin resistance indicator, the waist circumference criterion was particularly highlighted [66].

The recent IDF-MS criterion in children represents a more severe definition and appears to identify a group of children with higher fasting insulin than the adapted-MS definition which uses age-related thresholds (90<sup>th</sup> percentile). It is urgent to establish a consensus on MS definition to allow early identification of adolescents at risk and the development of prospective studies to define what cut-offs are the best indicators of future morbidity [67, 68].

Long-term survivors of childhood cancer appear to have an increased risk for the metabolic syndrome, subsequent type 2 diabetes and cardiovascular disease in adulthood compared to healthy children [69, 70].

The rise in the prevalence rates of overweight and obesity may explain the emergence of nonalco-

holic fatty liver disease (NAFLD) as the leading cause of liver disease in pediatric populations worldwide.

NAFLD is closely associated with abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance and impaired glucose tolerance, which are all features of the metabolic syndrome [71–73].

### Insulin resistance in type 1 diabetes

Because of the proved contribution of the insulin resistance also in type 1 diabetes the current division into two main types of diabetes is now being questioned [52, 74–76].

Wilkin [77] in his hypothesis formed an opinion about both types of diabetes being the same disease differing only in the rate of  $\beta$ -cell function loss and the underlying mechanisms responsible for it. Insulin resistance is one of them. The  $\beta$ -cell apoptosis is significantly increased by the autoimmune destruction of the islets of pancreas.

### The role of obesity in diabetes type 1

It was formerly considered that the developing insulin deficit resulting from the progressing  $\beta$ -cell auto-destruction is the essence of type 1 diabetes. The insulin sensitivity was regarded intact. Currently it is known that even in diabetes type 1 insulin resistance occurs [78].

It is connected with various factors including the stage of onthologic development as during the adolescence period a “physiologic insulin resistance” appears. Overweight plays also a role in the increase of insulin resistance in those patients. In persons with type 1 diabetes the prevalence of overweight is growing. It results from the aspiration of the patients to acquire better glycemia control with increasing the dose of insulin instead of dietary limitations and the physical activity.

According to the “overload hypothesis” the insulin resistance leads to the overproduction of insulin which in turn stimulates the cellular antigens expression. It induces the autoimmune processes and together with augmented apoptosis cause the destruction of  $\beta$ -cells [79].

On the other hand insulin resistance overlapping the decreased insulin secretion can directly accelerate the onset of type 1 diabetes. Since, the accompanying resistance to insulin’s action is an additional factor disrupting the glucose homeostasis. Nowadays the insulin sensitivity abnormalities in patients with type 1 diabetes are being observed more frequently than before [78]. It is the rationale to diagnose “double diabetes” in those patients [80].

The role of obesity in triggering processes leading to diabetes type 1 onset is lately being paid more attention to. The importance of insulin resistance in starting the autoimmune processes was highlighted by Wilkin [81].

Insulin resistance being regarded one of the possible factors accelerating the clinical revelation of diabetes may be responsible for increasing morbidity of type 1 diabetes in progressively younger age groups [82, 83].

Other authors pointed out the role of overweight during the first period of child's life in increasing the risk of acceleration of the autoimmune processes and the risk of type 1 diabetes development [84].

The extensive review of the results of multicenter studies about obesity as type 1 diabetes risk factor in children was recently shown by Verbeeten et al. [85].

The other authors also underline the significant role of overweight and insulin resistance in the development of diabetes type 1 [86, 87].

Knerr et al. [83] presented a comprehensive study about the role of overweight in acceleration of type 1 diabetes occurrence in children. The authors performed an analysis in a group of 9,248 patients from 116 centers in Austria and Germany. (While) Not all authors are in agreement with the increase of body weight being the accelerator in diabetes (including type 1 diabetes) [88]. This issue remains under discussion [86, 89].

Although overweight is one of the basic factors leading to the development of type 2 diabetes, it is not neutral for the patients with type 1 diabetes [78, 90].

The primary cause in this case is the autoimmune destruction of the  $\beta$ -cells of pancreas. The substitution with exogenous insulin preparations is the cornerstone of the treatment. The increase of adipose tissue mass leads to insulin resistance also in these patients. Hence it is crucial to maintain the appropriate body mass by means of proper diet and physical activity in type 1 diabetes as well. Overweight in type 1 diabetes patients is frequently the outcome of hyperinsulinism resulting from chronic insulin overdosing. The patients try to keep near normoglycemia by increasing the doses of insulin. It creates the vicious circle. Insulin dosage increase without calories restriction leads to the adipose tissue expansion which in turn magnifies the insulin resistance. The augmented insulin resistance produces a need for further rise in insulin dose. To break this vicious circle one needs to reorganize their nutrition and the whole daily routine. Restrictions in

the amount of calories intake and the energy expense enhancement by physical activity increase are necessary [91, 92].

### **Cardiovascular complications and arterial hypertension**

As a result of persistent chronic hyperglycemia a non-enzymatic protein glycation increase and subsequent AGEs (advanced glycation end products) accumulation can be observed. These processes produce a number of endothelium disturbances causing arterial stiffness which leads to the elevation of systolic blood pressure. In the course of hyperglycemia an increased activity of renin-angiotensin-aldosterone system is observed also leading to the rise in blood pressure. Insulin resistance plays an important role in the development of angiopathy in patients with carbohydrate metabolism disturbances as well [93].

Thickening of the intima-media complex of the carotid artery is a risk factor for the development of lesions in the cardiovascular system. Hypertension can be a sign of changes in this system but one should remember that even very slight blood pressure elevation can already be a signal of abnormalities [94].

The values of blood pressure in the area of upper normative value for age require a thorough analysis and usually introduction of treatment. The blood pressure measurement in children needs to be performed with a high degree of precision and its result should be referred to the percentile charts [95].

Interpreting the blood pressure measurement results one should take into account not only the age, sex and height but also the body weight if the anthropometric data exceed 90<sup>th</sup> percentile for age. Pietrzak et al. [96] presented a study in adolescent patients with type 1 diabetes which pointed at an association of the blood pressure values with BMI and the percentage of body fat.

The results of the studies in adolescents with diabetes type 1 presented by Dutch authors showed significant increase of the cardiovascular risk factors in patients with overweight or obesity compared to those with appropriate body mass [97].

English authors performed an analysis of the late outcomes of obesity in children. They found that the presence of overweight and obesity during childhood and adolescence significantly increases morbidity during adulthood [98].

### **Epidemiological studies**

Because of the dangers that obesity brings all over the world epidemiological studies are perfor-



med to determine the scale of that phenomenon [99, 100].

Poland is also one of the sites of a large-scale studies on this issue. The developmental population is being studied among others as the aim of the OLAF program [101–105].

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