OBESITY AND METABOLIC SYNDROME

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ABSTRACT

Obesity is a state of the body, when the amount of energy delivered from food exceeds its consumption by the body. The concept of metabolic syndrome (MS) is determined by the coexistence of the clinical condition with connects risk factors for cardiovascular disease of atherosclerotic character and type 2 diabetes. Metabolic syndrome consists of: increased waist circumference, fasting blood glucose, hyperinsulinemia, lipid disorders, including reduced HDL cholesterol, hypertension, proinflammatory and prothrombotic states. The etiology of metabolic syndrome can be related to two reasons: “adipose-centric” and “diabetes-centric”. The basis of all these metabolic changes is an increased fat mass, a fundamental element of the pathogenesis of insulin resistance. Lack of physical activity, caloric and highly processed diet are not without significance for the development of MS. The paper discusses the influence of adipose tissue in the development of metabolic syndrome and the common denominator that links obesity to insulin resistance, which results in inflammation. In addition, the indicators reveal the prevalence of obesity and metabolic syndrome in Poland and in the world on the basis of the available literature. Additionally, the principles of dietary treatment and its importance in reducing the risk of cardio-vascular patients with metabolic syndrome are discussed. Data from studies conducted around the world confirm that we are dealing with an epidemic of the XXI century in the form of obesity and its complications, including metabolic syndrome.
BACKGROUND

Obesity is a condition characterized by excessive accumulation of fat by the growth of hypertrophy and/or hyperplasia of the adipocytes. This growth occurs not only in the subcutaneous adipose tissue, but also in internal organs (in men over 25%, and in women over 30%) [1,2]. Adipose tissue is not only a reservoir of energy, but it is also an endocrine gland of an endocrine and paracrine character. The number of adipocytes is genetically determined. After 16 years of age in lean individuals - their number does not change, while in the obese it progressively increases in both size and number [3, 8]. The epidemic of overweight and obesity is the result of profound lifestyle changes in society. The progress of civilization has considerably reduced the need for mobility, and increased food rations, rich in saturated fats, carbohydrates, and low in dietary fiber and fruits [4]. The World Health Organization (WHO) estimates that worldwide obesity concerns 20% of people, which is confirmed by numerous clinical studies [5].

Excessive accumulation of fat, particularly in the abdominal cavity, is associated with the onset of various disorders such as insulin resistance and impaired glucose tolerance leading to type 2 diabetes; increased triglycerides and decreased HDL cholesterol (dyslipidemia); high blood pressure and activation of proinflammatory and prothrombotic states [7,8]. These complications of obesity referred to as metabolic syndrome, increase the risk of cardiovascular disease. The frequency of the detection of adults but also in developmental age, in recent years, is assumed as an epidemic [6,8]. Causes of metabolic syndrome are not sufficiently understood [8]. Among the causes of metabolic syndrome pathomechanism two directions may possibly be distinguished: the first one indicates that the main cause of MS is obesity, and the second - insulin resistance [9]. Research conducted in recent years indicated a connecting link in the metabolic pathways between insulin resistance and compensatory hyperinsulinemia with atherosclerosis and hypertension - which is an inflammatory condition. Recently attention has been drawn to the current obesity in the course of oxidative stress [8]. "Non-infectious" inflammation correlates with insulin resistance and the risk of cardiovascular disease [7]. These etiological factors of MS are associated with environmental factors (caloric, atherogenic diet and lack of physical activity) and individual factors (age, sex, ethnic and racial conditions) [9] and disorders in organogenesis of fats, the pancreas and vascular system (fetal malnutrition during fetal life). These factors are described as "common background" which is formed on the substrate and cardiac angiotoxic dependent disorders alongside with atherosclerosis [7].

Weight loss through an appropriate diet significantly improves the quality of life of patients with metabolic syndrome and reduces the risk of disease atherosclerosis. Implemented prevention programs should include education, health and nutrition tailored to the capabilities and the age of the recipients [10].

DEFINITIONS AND CLASSIFICATIONS OF OBESITY

In humans there are two types of fat: brown and white. Brown adipose tissue is richly vascularized and its triglycerides contained in the adipocytes are burnt on-site - and are not intended for export. White adipose tissue is very metabolically active. Mature adipocytes after reaching a critical value, which is approx. 0.8 mg stimulate adipoblasts (stem cells to adipocytes) to be converted by the new preadipocyte adipocytes. Obese people have an almost unlimited ability to increase the number of adipocytes [3].

Depending on fat accumulation, obesity can be divided into gynoidal (breech-femoral) and visceral (abdominal), which is typical for the deposition of fat in the abdominal cavity [11]. Differentiation of the arrangement number and size of adipocytes associated with the area of the body seems to be clearly marked by gender differences. In women adipocytes in the buttocks are, on average, 20 percent higher than in men, and fat around the thighs of women exhibits a nearly 90 percent greater number of adipocytes per unit volume than in men [3]. Interesting are the differences between subcutaneous fat and visceral one. The first releases its products to the general bloodstream and there are higher levels of leptin and adiponectin than visceral tissue and lower concentrations of IL-6 and -1 PAL and glucocorticoid receptors and androgen. Hormones secreted by abdominal adipose tissue are secreted into the portal vein directly to the liver, affecting its activity [6].

The most commonly used indicator of population studies to identify and assess the degree of obesity is body mass index BMI (body mass index, Quetelet index). It is calculated by dividing body weight (kg) by height squared. According to the World Health Organization (WHO), obesity in adults is recognized as the value of BMI≥30.0 kg/m² (Table 1).

Quetelet index divides obesity into classes but does not answer how fat is distributed, particularly the visceral fat. To evaluate it a simple anthropometric measurement was introduced: WHR (waist to hip ratio) or the ratio of waist circumference (narrowest place in it) to hip circumference (at its widest point). WHR is a measure of simple central obesity or an excessive accumulation of fat in the abdominal region [1]. Abdominal obesity is defined, if the value of WHR exceeds 0.85 in women and 1 in men, or waist circumference (WC) in women is > 88 cm, and > 102 cm in men (Table 2).

The risk of metabolic complications increases with a waist circumference [10]. However, this measurement becomes useless when BMI ≥ 35 kg/m². This applies to both sexes as the risk associated with the degree of obesity becomes sufficiently high.

In the NHANES III study, it was recommended that waist circumference is a better indicator of cardiovascular risk than BMI. Therefore, the rate of waist obesity was adopted and incorporated into the guidelines for the diagnosis of metabolic syndrome (both in the Adult Treatment Panel III (ATP III) and International Federation of Diabetes (IDF) [11].
REASONS FOR OBESITY

Obesity is the result of a positive energy balance, whose formation is influenced by many factors: innate (genetic), environmental (acquired) and the hormonal state of the body.

Genetic variation.

We detect more than 360 genes that shape a predisposition to the development of obesity. However, so far not a single one has been identified as the principal gene or mutations which would be the direct cause of the development of obesity. Mutations can affect the genes governing the collection of food, adipocyte maturation and metabolism.

Monogenic obesity is rare and analyzing it, one can explore mechanisms, eg. the control of appetite, leptin gene and its receptor and the gene encoding another protein melanocortin pathway: proopiomelanocortin (POMC), proconvertase 1 (PC1) and proteins involved in the functioning of the neural network of the hypothalamus. At the moment, there are around 200 described, confirmed cases of monogenic conditioned obesity. Obesity determined by multiple genes, is of more clinical significance to understanding the mechanisms of obesity due to its higher prevalence. Polymorphism of multiple genes reflected in population regards propensity to accumulate excess body fat in a specific environment (i.e. "obesogenic" environment). Obesity is not the result of specific mutations or aberrations of chromosomes (as in the above-mentioned types of obesity), but is the result of polymorphisms - in the molecular sense and occurs in over 2% of the population differences in the DNA, which translate into a significant change in protein function [1]. Obesity is therefore determined by multiple genes.

In 1962, Neel introduced the hypothesis that explained the environmental non-specificity of obesity. He introduced the theory of the so-called "thrifty genotype" which helped man survive in times of famine, and thus natural selection favored individuals who stockpile energy in the form of fat. And although times have changed, genotypes with such properties have survived to modern times, as the human genome is not able to adapt to the modern diet [12].

Environmental variability.

The progress of civilization and economic lifestyle change appear to be responsible for the increasing prevalence of obesity epidemic in the last 25 years. The occurrence of two phenomena seems to be crucial. The first is the availability of high-caloric and processed foods (i.e. junk food high in fats and simple carbohydrates) and the second is a limitation of daily physical activity. In the last hundred years, the fat content (40-45% vs. 15-20%) has significantly increased in foods, and intake of complex carbohydrates, fiber and minerals [11] has decreased. In recent years, more and more attention is paid to the problem of diet-induced obesity which inhibits basic metabolism [1].

EPIDEMIOLOGY OF OBESITY AND METABOLIC SYNDROME

Obesity is a growing social problem of the last half of the century, especially in developed countries. If a BMI is over 40 kg/m², diseases caused by it also become a problem. Unfortunately, the problem of obesity also occurs in Poland, which now takes the 7th place in Europe in this respect [13]. Results of NATPOL PLUS (Hypertension in Poland. Plus lipid disorders and diabetes), conducted in 2002, showed that overweight was diagnosed in 34% of patients and obesity in 19%. Equally negative results were provided by WOBASZ study (Multicenter National Health Survey) conducted in 2003-2005. It was found that obesity in Poland occurs with similar frequency in both sexes: 20.6% men and 20.2% in women [14]. Overweight or obesity is rare as a single disorder. Usually it occurs with other problems such as type 2 diabetes, dyslipidemia, hypertension, which leads to the formation of metabolic syndrome (MS), the treatment of which absorbs 3-6% of the intended medical treatment country's costs [13]. The size of the problem is evidenced by the fact that according to Sturm and Fontaine et al. obesity above 40 kg / m² shortens life by an average of 20 years, and the consequences of obesity are more serious than the consequences of smoking tobacco or drinking alcohol [13]. BMI is a good indicator of the risk of coronary heart disease and heart attack: it increases in women with a BMI above 25.00 and in men over 26.5 [3,15]. If the BMI exceeds 26, the risk of disease is doubled compared to women with a BMI of 21; in women it is 1.5 times higher than in men [3,16]. The study of NATPOL PLUS to determine the prevalence of MS criteria used NCEP-ATP III (National Cholesterol Education Program, Adult Treatment Panel III). It was found that 5.8 million Poles (20.3%) are affected by metabolic syndrome and it more frequently affects women than men (22.6% and 18%, respectively). In both sexes the incidence increased with age (7.5% between 18-39 years of age, 23.9% between 40 and 59 years of age, and 39.5% aged 60 years and above. In women the growth trend was more rapid [17] (Table 3).

In patients with metabolic syndrome cardio - vascular deaths are 3.5 - 5.5 times more frequent than in the general population and the overall mortality is increased two - fold [18].

Based on the results obtained during the five-year follow-up study in the Scottish project WOSCOPS (according to the criteria of NCEP - ATP III, instead of waist circumference BMI was used) it was found that the presence of the metabolic syndrome increased two-fold risk of coronary heart disease and diabetes - more than 3 times. If a man meets 4 or 5 indicators of metabolic syndrome, there arises a risk of cardio - vascular disease and diabetes which is 3.7 times higher and up to 24.5 times higher compared with healthy controls [18].

The last decade has brought an increase in the percentage of obese people, especially men (5%) and people suffering from diabetes (20%) and an increase of 2% of people with hypertension, while there was a positive decline by approx. 9% of the proportion of people with elevated cholesterol levels. Forecasts test of NATPOL 2011 conducted in Poland for factors of the
metabolic syndrome (obesity, dyslipidemia and hypertension) are not optimistic, namely, they provide an increase in the incidence of diabetes (from 6% to 12%), an increased incidence of obesity (from 22% to 33%), and greater prevalence of hypertension (from 32% to 50%) [17].

**METABOLIC SYNDROME - ETIOLOGY AND DIAGNOSTIC CRITERIA**

Studies to explain the cause of multi-symptomatic forms of MS, pay attention, on the one hand to a genetic predisposition, and on the other hand, to environmental factors, which include, among others, caloric and atherogenic diet and low physical activity [8]. For the genetic background of this disease family history of the features of metabolic syndrome is provided. Symptoms of metabolic syndrome are the result of the interaction of genetic abnormalities, disorders of individual development during fetal and early childhood and the influence of civilization, which all favor the formation of visceral obesity and insulin resistance [7].

Expression of polymorphic genes in which mutation has occurred may also lead to obesity, glucose metabolism in the insulin resistance and hypertension [20].

Among the causes and pathomechanisms of MS three factors are considered: obesity and metabolism of body fat, insulin resistance and compensatory hyperinsulinemia, and the third set of independent risk factors such as physical inactivity, aging, conditions of ethnic or hormonal disorders [8,9].

Shaping the definition and recognition criteria for MS is quite laborious and has been modified many times over the years. However, abdominal obesity has always been considered and treated as the main "culprit" of the disease (Table 4).

Central obesity contributes to the development of other components of the MS, i.e. hyperglycemia, lipid metabolism and hypertension and other factors accelerating the development of cardiovascular disease, atherosclerosis and Type 2 diabetes. Strong relationship between visceral obesity and other predisposing factors for MS made experts of NCEP - ATP III team define this syndrome as the metabolic complications of obesity. NCEP-ATP III (Third Report of the National Cholesterol Education Program - NCEP, Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults Adult Treatment Panel III - ATP III) regarded the obesity epidemic as the main cause of the increase in the prevalence of metabolic syndrome in the world [8, 18].

**THE ROLE OF ABDOMINAL OBESITY IN THE PATHOGENESIS OF THE METABOLIC SYNDROME**

Increasing the amount of fat in the abdominal region coexisting with an increase in abdominal circumference (waist) - in males (Europe) over 94 cm and females over 80 cm, or height in cm divided by 2 - causes many important metabolic changes leading to the MS [23] .

Adverse impact of visceral tissue is mainly due to the release of FFA, glycerol and adipokines directly into the portal circulation. This tissue is denser and has greater expression of G3 – adrenergic receptors, - and releases a lot of biologically active compounds, among others, adiponectin, visfatin and IK - 6 or resistin [24]. Increasing the concentration of free fatty acids in the visceral adipocytes (as a result of increased lipolysis) leads to accumulation of acetyl-CoA reductase inhibitor, pyruvic acid dehydrogenase (glycolysis), and the accumulation of citrate inhibitory phosphofructokinase (glycolysis). This leads to the inhibition of glycolysis.

The visceral obesity has both increased concentration of free fatty acids and their severe oxidation (Radley’s Cycle) [23].

**Hyperleptinemia.** In the development of insulin resistance leptin may play a role by its inhibition of gluconeogenesis [23]. Its absence and resistance to leptin intensify lipogenesis by enhancing PPAR-α factor. Dysfunction of adipokines leads to ectopic accumulation of triglycerides in the tissues of peripheral organs (liver M.I.) and develops insulin resistance (lipotoxicity) [9, 24]. Leptin can induce insulin and post-receptor resistance, resulting in de- phosphorylation of IRS-1. In the obese, this is indicated by increased levels of leptin in the blood [23] and the same concentration is a good marker of vascular complications in obese subjects. Leptin also affects the process of angiogenesis by affecting the expression of metalloproteinases and tissue inhibitor of metalloproteinases, which has been demonstrated in vitro on human aortic muscle cells [9].

**Adipose tissue** secretes pro-inflammatory cytokinines [22] and in the obese there are chronically elevated levels of tumor necrosis factor alpha (TNF-α) [21]. High concentrations of TNF-α contribute to the arterial development. This factor promotes lipolysis and release of FFA [24]. This cytokine inhibitory effect on the function of insulin receptors also impacts directly the metabolism of glucose, reducing the expression of GLUT-4 in muscle cells. Indirectly, by inhibiting the expression of the receptor peroxisome proliferator-activated gamma (PPAR-γ) in myocytes and adipocytes, it reduces the synthesis of triglycerides, while increasing the concentration of fatty acids.

**Reducing the concentration of adiponectin.** Adiponectin (ADPN) is a glycoprotein synthesized by mature adipocytes of basic fat tissue and scarcely by muscle cells, cardiomyocytes and osteoblasts. Visceral adipose tissue is its scarce source and contributes to the development of insulin resistance and increases the risk of cardio - vascular disease [22]. Protective effect of adiponectin on the development of insulin resistance and Type 2 diabetes has been demonstrated [23]. ADPN plasma concentration is inversely proportional to the BMI, insulin and triglycerides, and inversely proportional to the concentration of the HDL cholesterol fractions. In women, ADPN concentration is higher than in men and can even vary depending on ethnicity. ADPN increases after weight reduction after the application of a reduced calorie diet [22].

**Reducing the number and the impairment of glucose transporters.** Disorders of the above described nature can be a substrate of the post-receptor insulin resistance. This applies especially to inhibition phenomena of GLUT-4 glucotransporter, which was found in muscle and fat
cells (i.e. tissues, which under the influence of insulin present a rapid increase in glucose transport) [23].

Obesity is attributed to the state of chronic low-grade (LGI, low grade inflammation). Inflammation linking obesity and the cardiovascular disease is atherosclerosis and type 2 diabetes mellitus (due to infiltration of macrophages to the adipose tissue). Between the cells there is a close relationship - macrophages can influence gene expression in adipocytes and adipocyte gene expression in macrophages, primarily the PPAR-γ, TNF, IL-6. It seems that adipocytes initiate inflammation and macrophages worsen it and cause changes in the expression of cytokines. The results showed that macrophages are more likely to pass into the subcutaneous tissue than into the visceral one. The presence of macrophages in adipocytes is much greater in the tissue of "heavier" individuals than the lean ones and the number decreases with decreasing body weight and body fat [9].

**Dysfunction of the nuclear transcription receptors (Peroxisome proliferator Activated Receptors - PPARs)** involved in the regulation of expression of genes whose products are involved in the process of transport and metabolism of fatty acids, glucose and inflammation [20]. Transcription receptors play an important role in the development of obesity and impaired insulin sensitivity. PPAR-γ receptors are one of the three types of receptors which are significantly involved in the regulation of insulin sensitivity [23], and are assigned the largest share in the development of obesity, thereby MS [9]. They increase and intensify the expression of GLUT-4 transporters. Activation of PPAR-γ in adipose tissue is reduced TNF-α, PAI-1 and leptin expression [23]. PPAR-γ receptors are expressed in hepatocytes, cardiomyocytes, skeletal and kidney muscles, where they stimulate the process of beta-oxidation of fatty acids [20].

**Disorders of signaling by β3 adrenergic receptors**, which leads to disruption of lipolysis and thermogenesis and affects the development of insulin resistance. It has been shown that mutation of β3 receptor (Trp64Arg) is more common in people with obesity and insulin resistance and is associated with the risk of developing type 2 diabetes [23].

**OBESITY AND AHEROGENIC DYSLIPIDEMIA**

Excessive fat accumulation in the abdominal results in problems as an increase in triglycerides and decrease of HDL (high density lipoproteins - HDL) cholesterol increased "non-HDL" (total cholesterol - HDL cholesterol) above 130 mg / dl and elevated levels of VLDL (very low density lipoproteins - VLDL) and LDL (low density lipoproteins - LDL) and the formation of qualitative changes in the structure of LDL in the form of small "dense" particles containing more cholesterol [19]. These disorders are referred to the concept of atherogenic dyslipidemia and are a factor in the development of atherosclerosis risk.

Small dense LDL lipoproteins with a high susceptibility to oxidation and a greater ability to infiltrate the blood vessel wall [7] are recognized and captured by the scavenger receptors of macrophages. Lemieux et al. proposed the concept of "hypertriglyceridemic waist" to determine the coexistence of obesity and elevated levels of triglycerides in the blood plasma. Studies have shown that men with so-called atherogenic metabolic triad, consisting of hyperinsulinemia, elevated apolipoprotein B, and small dense LDL cholesterol particles, are also characterised by having a waist circumference ≥90 cm and triglycerides ≥2 mmol / l (≥176 mg / dl). Relatively recently described feature of the insulin resistance in humans is an increased biosynthesis of lipoproteins containing apolipoprotein B-48 in the digestive tract that accompanies the post-prandial hyperlipidemia. It was found that in insulin resistance concentration of LDLs lipoproteins is at the regular level (men) or moderately elevated (for women) while the composition of LDL lipoproteins that have a low content of cholesterol esters and smaller size changes [7, 20].

**OBESITY AND HYPERTENSION**

Obesity is one of the most important risk factors for developing hypertension [4]. The prevalence of hypertension increases progressively with increasing BMI regardless of gender and is 15% with a BMI<25 kg / m², while among those with a BMI≥30 kg / m², hypertension is observed in 40% of them [20]. NHAES II study results indicate that the risk of hypertension is 3 times higher than in people without obesity [11]. The close correlation between blood pressure and the amount of fat is not limited to the so-called morbid obesity, but it is continuous. Waist circumference is an independent and most important predictor for the development of hypertension [20]. The Framingham study showed that weight gain for every 5 kg causes an increase in pressure of 4.5 mmHg [11]. Among the causes of hypertension in the metabolic syndrome are: hemodynamic abnormalities associated with obesity associated with endothelial dysfunction, insulin resistance, and influence of the adipokines released from adipose tissue [20]. With the increase in body weight cardiac output and intravascular volume increase at a lower peripheral resistance in comparison with normal body weight [31]. Finally, a great scientific interest rose around the role of the renin-angiotensin system (renin-angiotensin system - RAS) in regulating physiological processes in the fat tissue and how this leads to the pathogenesis of hypertension in the course of obesity [20]. Adipose tissue contains all the elements of this system [31]. Studies have shown that the expression of angiotensinogen increases in the course of obesity and is correlated with a waist-to-hip ratio. Positive correlation was also shown between the concentration of angiotensinogen and ACE enzyme activity in plasma and BMI [20]. In addition to the aforementioned system control of blood pressure, it is also affected by lectin, which increases the activity of the sympathetic nervous system and its concentration in the blood is higher in patients with hypertension and obesity [31]. It has been shown that people with hypertension have a lower level of adiponectin in blood plasma compared to its concentration in normotensive people. Results of studies in knock-out mice lacking the adiponectin gene (adiponectin-KO mouse) and of people with hypertension were also presented, which show that adiponectin positively correlated with vascular reactivity. From these results it can be concluded that the low
concentration of adiponectin contributes to the development of hypertension, the measurement of adiponectin levels can be a useful indicator of impaired endothelial metabolic syndrome [20].

**OBESITY AND INSULIN RESISTANCE**

Central obesity precedes the development of insulin resistance and the support to its creation is probably the visceral fat and the accompanying inflammatory process [20]. Other researchers believe that in MS, creation subcutaneous adipose tissue can play a role, especially the one located in the upper part of the body [9]. Positive energy balance initiates impaired glucose tolerance and leads to the development of type 2 diabetes. The reason for this is an excess of energy substrates coming into cells in the form of free fatty acids and glucose, which increases the formation of increased amounts of acetyl CoA, and thus of nicotinamide adenine dinucleotide phosphate (NADP) in mitochondria and production of reactive oxygen species (ROS), and the formation of inflammation [9,20]. Cells defend against the damaging effects of ROS trigger on one hand, mechanisms removing free radicals, on the other hand the processes reducing the flow of energy substrates [20]. The risk of developing type 2 diabetes in people with a BMI over 35 kg / m² is 30 - 40 times higher compared to those with a BMI <22 kg / m² [11]. It is believed that the base for atherosclerosis and insulin resistance are adipokines, including leptin, adiponectin and resistin. Resistin increases glycogenolysis resulting in an increased hepatic insulin resistance. It is a factor linking obesity with the incidence of diabetes [5,6]. The appearance of insulin can be considered as an adaptive mechanism that protects cells against further uptake of glucose and free fatty acids to prevent oxidative damage to the cell [20].

**ADIPOSE TISSUE AND INFLAMMATION**

Reports from numerous studies indicate inflammation as the main pathological mechanism of metabolic syndrome, and the background to its development are the macrophages infiltrating the adipose tissue [9], which secrete pro-inflammatory proteins, including IL - 6 and TNF - α, contributing to the severity of insulin resistance [6]. Macrophages can also affect gene expression in adipocytes and vice versa. It seems that adipocytes initiate inflammation and macrophages worsen it by their infiltration into adipose tissue and by changing the expression of cytokines [9]. In vitro studies revealed that the adiponectin inhibits the conversion of macrophages into foam cells, reducing the accumulation of lipids in the cells [20]. The best evidence connecting macrophages obesity is the difference between their number in the adipose tissue of obese and lean individuals. In people with overweight the number in adipocytes is much greater than in lean individuals. In addition, more lymphocytes transfer to visceral obesity than to subcutaneous cells [9]. proinflammatory adipokinin should also be mentioned: C-reactive protein (CRP) as a marker of chronic inflammation, but according to the latest knowledge is also a predictor of insulin resistance [5]. We have gathered convincing evidence that the concentration of this protein is elevated in patients with MS and positively correlates with the degree of obesity, increasing proinflammatory character of other adipokinin secreted by adipose tissue [5, 20]. In epidemiological studies a significant correlation has been shown between CRP and body mass index, waist circumference, systolic blood pressure, blood pressure, blood glucose and fasting insulin and insulin sensitivity [5].

**OTHER ISSUES OF OBESITY WITH REGARD TO METABOLIC SYNDROME**

Excess of abdominal fat causes a lot of other disorders as potentiation of the inflammatory activators, eg. cytokines, TNF-α or IL-6 and CRP. Obesity also causes hyperuricemia, and hiperhomocytinemia and hyperleptinaemia [23]. These numerous disorders depend largely on the specific (with the arrangement portal circulation) communications between adipose tissue in the abdominal cavity and liver, which constantly receives higher than physiological amounts of free fatty acids and glycerol (fatty liver) [7, 23].

**ADIPOSE TISSUE AND THE CONCENTRATIONS OF URIC ACID**

There is an ample evidence suggesting that one of the connecting links of obesity to MS and with atherosclerosis may be elevated levels of uric acid. The concentration of serum uric acid (SUA, serum, urine acid) in people with excess body weight is often elevated or close to the upper limits of normal. Compared with those in whom obesity is present as a single disorder in patients diagnosed with MS there still exist higher concentrations of SUA. Concentrations of SUA are affected by leptin - a hormone produced by adipocytes. It is believed that it may be one of the factors determining the presence of hyperuricemia associated with obesity. It was also shown that not every type of obesity is associated with the same predisposition to higher values of SUA. Especially dangerous is the abdominal obesity. This unfavorable correlation is a consequence of the central obesity and insulin resistance, which undoubtedly affects the increase of SUA. Another link between the localized adipose tissue and the ventral hyperuricemia may increase in free fatty acids in the portal vein. They reach the liver, stimulating the production of lipoproteins of very low density (VLDL), thus becoming the cause of hypertriglyceridemia and at the same time, speed of the process for the synthesis of phosphoribosylpyrophosphate (PRPP, 5-phosphoribosyl-1-pyrophosphate) with the accompanying overproduction of uric acid. Abnormal levels of HDL cholesterol also often co-occur with an increase in the concentration of SUA, though the direct cause of this dependence has not yet been revealed. Lipid disorders and hyperuricemia have but one more common causal relationship in the form of adverse effects of hyperinsulinemia. Dyslipidemia and metabolic disorders of uric acid are abnormalities characteristic of insulin resistance syndrome. It is suspected, however, that hypertriglyceridemia can also directly affect the concentration of the SUA, through the so-called toxicity of triglycerides (triglyceride toxicity), part of the triad of disorders known as the "toxicity of obesity" (obesity

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Other elements of the triad are lipotoxicity (lipotoxicity) and the toxicity of free fatty acid (free fatty acid toxicity). Excessive high blood pressure (BP, blond pressure) and elevated levels of SUA also often appear to be associated with metabolic disorders. In rat studies they failed to induce hypertension, hyperuricemia pharmacologically. The key pathogenic role of insulin resistance was both stressed in the definition of group X and the first criteria of the metabolic syndrome in 1999, because this disorder is highly etiologically associated with visceral obesity and can be considered as the cause of each of the other irregularities included in the MS. So you cannot deny that the increase in the concentration of SUA in patients with the syndrome is largely due to the phenomenon of insulin resistance. But this is not for sure the only reason. It seems that each element has certain MS hyperuricemising properties [13].

ADIPOSE TISSUE AND THE THYROID

It is known that people with excess body fat have statistically higher levels of TSH (thyroid stimulating hormone) with normal serum free thyroxine (fT4, free thyroxine). Other studies have shown that patients with increased levels of subcutaneous fat present themselves with statistically higher levels of TSH, fT4 at lower values [25]. Thyroid hormones have a significant impact on glucose metabolism and the development of insulin resistance. Moreover, one should mention their lipolytic effect - increasing the concentration of fatty acids in the blood. Hyperthyroidism impaired glucose tolerance is a consequence of insulin resistance in the liver and an overall worsening of peripheral insulin resistance (explanation for the peripheral insulin resistance can be improved secretion of bioactive mediators (adiponectin), such as IL-6 and TNF-alpha by adipose tissue). There is an increased concentration of adiponectin in women with hyperthyroidism. In the case of hypothyroidism observed, there exists a generalized peripheral insulin resistance associated with an increase in free fatty acids and reduced uptake of glucose. Maratou et al. in their work observed that patients aged 50 years with diagnosed overweight (Wed BMI approx. 26 kg / m²) when compared to patients in the euthyroid have elevated HOMA index and Matsuda index decreased [26]. BMI shows a positive correlation with the values of serum TSH but at a concentration range of 2.5-4.5 mg /dL, an increased risk of obesity and metabolic syndrome compared with TSH levels below 2.5 mg /dL. The results of studies in patients treated with bariatric methods, showed that weight loss leads to a gradual decrease in TSH [25], thereby lowering HOMA on the basis of a negative correlation [26]. This may indicate the influence of TSH to local deposition of subcutaneous fat, or the fat of the action on the pituitary secretion of TSH, although low levels of thyroid hormones fT3 and fT4, seen in obese individuals, seem to contradict such a statement. In the case of significant weight loss, and consequently reduction of the amount of body fat reversibility of the phenomenon, combined with normalization of serum TSH and free triiodothyronine (FT3) was observed. The authors believe that this indicates the impact of adipocytes secretion of TSH and thyroid activity. Recently, the proof on the impact between leptin and activity in serum TSH has appeared in several publications. Certainly, some linkages between thyroid, obesity and MS remain not resolved [25, 26].

SIGNIFICANCE AND DIETARY RECOMMENDATIONS FOR OBESE INDIVIDUALS WITH METABOLIC SYNDROME

The recommended therapeutic procedure in patients with MS is lifestyle modification through gradual reduction in body weight and increasing physical activity. The effectiveness of non-pharmacological treatment of obesity by eliminating environmental factors relevant to the pathogenesis of the metabolic syndrome and type 2 diabetes was confirmed by epidemiological studies [27,29]. Reducing the supply of energy should be based on the initial weight from 500 to 1500 kcal for people with a body mass respectively from 70-90 kg to over 150 kg [28], and gradually reducing body weight by about 7-10% over the baseline in the first 6-12 months of treatment. Weight reduction of 5-10% already leads to a significant clinical benefit of improved metabolic parameters [27]. If body weight is reduced by 10% it will reduce triglycerides by 30% and raise the HDL cholesterol by 8%. In addition, it will decrease blood pressure [28]. The effectiveness of such recommendations of the study was confirmed by the Finnish Diabetes Prevention Study (FDPS) and the American Diabetes Prevention Program (DPP) lasting almost three years. In these studies, obese patients with impaired glucose tolerance were able to reduce the risk of developing diabetes by 58%, and in DFPD study weight reduction was achieved in 43% of the patients. In both studies it was observed that even a modest reduction of overweight or obesity (FDPS study, weight loss was 4.2 ± 5.1 kg in the DPP average weight loss was 5.6 kg) can increase insulin sensitivity, which is beneficial for glucose and lipid metabolism and blood pressure [27,28]. The introduction of a healthy lifestyle is the safest, most effective and recommended way to improve insulin sensitivity of tissues (muscle and liver) and improving glucose uptake by skeletal muscle and the overall economy of glucose in the body [29].

According to the recommendations of the World Health Organization (WHO), the main source of energy should be complex carbohydrates (60%), fat (15-30%), and protein (15%) [29]. The Mediterranean diet is considered to be the most effective diet combating risk factors for MS. The main principles of this type of consumption are to be mono- and polyunsaturated fatty acids with a low omega-6 to omega-3 (5: 1) a need for EPA and DHA is 1-2 g / day (0.2-0.3% of energy) and can be covered by the consumption of marine fish. It is also recommended to eat high-fiber increased amount of fruit, vegetables and nuts (274 g / d.), grains (103 g / d.) and olive oil (8 g/d.), or vegetables, tuberous root, nuts, oatmeal, wholemeal flour, cereal and fruit. In the digestive system there should increase the viscosity of gastric contents causing the release of the arcade mash food. The demand for acid - α, -linolenic is 3 g / day, and its sources are soy, nuts, grains, flaxseed oil, and tofu. Omega-3, after several months of use, reduce systolic blood pressure of 5.5 mm Hg and diastolic blood pressure of 3.5 mm Hg [28,30]. After the loss of body weight in order
to stabilize the achieved results one should observe patients and modify inappropriate behavior habits.

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REFERENCES


31. Esposito K, Nicoletti G, Guigliiano D.: Obesity, cytokines and endothelial dysfunction: a link for the

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| TAB. 1. OBESITY CLASSIFICATION DEPENDING ON BMI AND WAIST CIRCUMFERENCE. |
|-----------------------------|-----------------------------|-----------------------------|
| Obesity degree (WHO classification) | BMI (kg/m²) | The risk of metabolic diseases risk |
| Norm | 18.5-4.97 | average |
| Overweight | 25.0-29.9 | above average |
| Obesity I° | 30.0-34.9 | elevated |
| Obesity II° | 35.0-34.9 | serious |
| Obesity III°(extreme) | >40 | very serious |

| TAB. 2. CRITERIA OF ABDOMINAL OBESITY |
|-----------------------------|-----------------------------|-----------------------------|
| WHO | WHR > 0.85 | Men | WHR > 1 |
| The degree of obesity | Woman's waist (cm) | Man's waist (cm) | Risk of metabolic complications |
| Norm | < 80 | < 94 | negligible |
| Overweight | 80-88 | 94-102 | slightly elevated |
| Abdominal obesity | | | |
| ATP III 2001 | Waist circumference >88 | Waist circumference >102 | elevated |
| IDF 2005 | Waist circumference >80 | Waist circumference >94 |

| TAB. 3. EPIDEMIOLOGY OF OVERWEIGHT, OBESITY AND THE METABOLIC SYNDROME |
|-----------------------------|-----------------------------|-----------------------------|
| The study | Overweight (BMI>25 kg/m²) | Obesity (BMI>30 kg/m²) | Metabolic syndrome (according to ATP III) |
| NATPOL PLUS | 53% | 19% | M - 18%, W - 22% |

| TAB. 4. COMPARISON OF THE DEFINITIONS OF THE METABOLIC SYNDROME [21] |
|-----------------------------|-----------------------------|-----------------------------|
| Condition indispensable for diagnosis | Type 2 diabetes, improper glycemia, impaired tolerance of glucose or insulin resistance | Central obesity: waist circumference for men ≥ 94 cm, for women ≥ 80 cm. If BMI is >30 kg/m² waist circumference measurement is not necessary for declaring central obesity |
| 2 from the following components: Central obesity: WHR>0.9 men, women WHR > 0.85) and/or BMI > 30 kg/m² dyslipidemia | 2 from 4 components: TG concentration in plasma ≥ 150 mg/dl or treatment hyper triglyceremia | Any 3 components: Central obesity: waist circumference for men ≥ 94 cm, for women ≥ 80 cm. If BMI is >30 kg/m² waist circumference measurement is not necessary for declaring central obesity |
| LDL concentration < 40 mg/dl in men and < 50 mg/dl in women or hypolipemising treatment | Arterial hypertension ≥ 130/85 mmHg or the treatment early diagnosed arterial hypertension | TG concentration in plasma ≥ 150 mg/dl or treatment hyper triglyceremia |
| Arterial hypertension ≥ 130/85 mmHg or the treatment early diagnosed arterial hypertension | Fasting glucose ≥ 100 mg% or hypoglycemising treatment. | Arterial hypertension ≥ 130/85 mmHg or hypotensive treatment |
| Any 3 components: improper waist circumference (depending on population) | TG concentration in plasma ≥ 150 mg/dl or LDL<40 mg/dl in men and < 50 mg/dl in women or hypolipemising treatment Arterial hypertension ≥ 130/85 mmHg or the treatment early diagnosed arterial hypertension | Fasting glucose ≥ 100 mg% or hypoglycemising treatment. |

¹World Health Organization, ²National Cholesterol Education Program Adult Treatment Panel III, ³International Diabetes Federation, ⁴American Heart Association/National Heart Lung, and Blood Institute.