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Metabolic syndrome - diagnostics, pathophysiology and treatment

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Abstract

Metabolic syndrome, though it is not a disease included in ICD-10, is a serious epidemiological problem as much as a challenge for medicine and prevention of developed countries. The aim of this work is to discuss, based on literature, the basics of pathophysiology, diagnostic criteria and principles of treatment of the metabolic syndrome. The diagnosis of the metabolic syndrome is based on simple criteria, which include: abdominal circumference, blood pressure and triglycerides, HDL cholesterol and glucose levels. This allows the diagnosis of the metabolic syndrome at the level of primary care. The basis for treatment of the metabolic syndrome is behavioural therapy, sometimes, at non-advanced stage of the disease, it is sufficient. Due to the significant progress in pathophysiology of the metabolic syndrome, it is possible to determine its primary causes and risk factors - obesity and insulin resistance. Both of them belong to the reversible states, which is motivation to detect and treat these conditions before irreversible complications develop.

Keywords: Metabolic syndrome

Introduction

Metabolic syndrome (MS) is a group of risk factors for atherosclerosis, type 2 diabetes and their cardiovascular complications, which include: obesity, hyperglycaemia, hypertension and lipid disorders. Metabolic syndrome is not a separate disease entity and is not included in ICD 10. The individual components of the metabolic syndrome are used for clinical diagnosis. [1] [2] The incidence of metabolic syndrome in Europe is estimated at 36% of women and 38% of men, the percentage rises with age. [1] In Poland, as part of the POLKARD program in 2003-2005, a Multi-Center Nationwide Health Survey of the population – WOBASZ (*Wieloośrodkowe Ogólnopolskie Badanie Stanu Zdrowia*) - was carried out. In this study, using the NCEP-ATP III diagnostic criteria from 2005 (Table 1), the prevalence of metabolic syndrome was estimated at 20% of women and 23% of men. [2] [3] It was also found that the incidence of metabolic syndrome increases with age and this relationship is particularly noticeable in the female population (in the 20-39 age range, the MS criteria met 4%, while in the 60-74 age range 46% of the subjects). It was noticed that among 5 elements of MS, both in women and in men, the most common were hypertension (men 69%, women 50%). [2] After considering the demographic data of that time, the WOBASZ study estimated that the problem of the metabolic syndrome affects 5.8 million Polish population aged 20-74. [2] Considering the prevalence and consequences for health, it is a significant problem and a big challenge for medicine and prevention. The aim of this work is to discuss, based on literature, the basics of pathophysiology, diagnostic criteria and principles of treatment of the metabolic syndrome.

Criteria for the diagnosis of metabolic syndrome

Among the components of the MS, the most frequently mentioned in the literature are: visceral (abdominal) obesity, insulin resistance, atherogenic dyslipidaemia (hypertriglyceridemia and reduced HDL cholesterol fraction), hypertension, proinflammatory state, prothrombotic state. [1] [4] [5] Diagnostic procedure requires tests to identify individual components of MS: measurement of the waist circumference (as an indicator of the amount of visceral fat), determination of glucose, triglycerides, total cholesterol and HDL cholesterol in the serum and measurement of blood pressure. [1]

The first criteria for the diagnosis of the MS were established in 1999 by the World Health Organization (WHO). [1] [4] They emphasize insulin resistance, which plays an important role in the pathogenesis of the MS. The necessity of performing specialized diagnostic tests limited the availability and usefulness of these criteria in everyday clinical practice. [4] In 2001, the criteria for the National Cholesterol Education Program on the Detection, Evaluation, and

Treatment of High Blood Cholesterol in Adults (NCEP-ATP III) were presented. They were created to identify people at risk of cardiovascular disease caused by atherosclerosis. This definition does not indicate the main diagnostic factor, all components are equivalent – the diagnosis of the MS is based on the presence of three of the five factors. In 2005, the criteria were modified and refined based on the recommendations of the American Diabetes Association. The modified NCEP-ATP III criteria are shown in Table 1. [2] [4]

Table 1. Modified NCEP-ATP III criteria of the MS (2005) [2]

For a diagnosis of MS is required presence of any three of the following five factors	
Elevated abdominal circumference	≥102 cm in males [1] ≥88 cm in females [2]
Hypertriglyceridemia	≥150 mg/dl (1,7 mmol/l) or hypertriglyceridemia therapy
Low HDL cholesterol	<40 mg/dl (0,9 mmol/l) in males <50 mg/dl (1,3 mmol/l) in females or therapy
Elevated blood pressure	systolic ≥130 mmHg or diastolic ≥85 mmHg or antihypertensive therapy
Impaired fasting glucose	≥100 mg/dl (5,6 mmol/l) or hypoglycaemic therapy

In 2009, a unified definition of the MS was established, consistent with the joint statement of the International Diabetes Federation (IDF) Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute (NHLBI); American Heart Association (AHA); World Heart Federation (WHF); International Atherosclerosis Society (ISA); and International Association for the Study of Obesity (IASO). The criteria for this definition are presented in Table 2. [6]

[1] ≥90 cm for individuals of Asian origin
[2] ≥80 cm for individuals of Asian origin

Table 2. Criteria of MS according to the joint statement of the IDF, NHLI, AHA, WHF, IAS (2009) [6]

For a diagnosis of MS is required presence of any three of the following five factors	
Elevated waist circumference	≥94 cm in males [3] ≥80cm in females [4]
Elevated triglycerides	≥150 mg/dl (1,7 mmol/l) or drug treatment for elevated triglycerides
Reduced HDL-C	<40 mg/dl (1,0 mmol/l) in males <50 mg/dl (1,3 mmol/l) in females or drug treatment for reduced HDL-C
Elevated blood pressure	systolic ≥130 mmHg or diastolic ≥85 mmHg or antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dl (5,6 mmol/l) or drug treatment of elevated glucose

Pathophysiology of the metabolic syndrome

It is believed that environmental and genetic factors are responsible for the development of MS. The first group includes primarily factors of development of obesity: high-calorie diet, high intake of saturated fatty acids and cholesterol, high sodium intake, low physical activity. [1] The second group includes genes whose mutations increase the risk of individual components of the metabolic syndrome. Polymorphic gene variants, the expression of which leads to the development of obesity, insulin resistance and disorders of carbohydrate metabolism and hypertension, are being described. [7] There are also studies confirming the family history of MS components such as: obesity, insulin resistance, dyslipidaemia and hypertension. [5]

Available literature mentions visceral obesity and insulin resistance as the most important aetiological factors of the MS. [8] Numerous attempts are made to demonstrate and describe the mutual influence of the above etiological factors and the relationships between them and other disorders included in the criteria for MS. Research suggests that obesity precedes the development of insulin resistance. The current state of knowledge allows us to assume that the

[3] for Europeans
[4] for Europeans

remaining elements of the MS are a consequence of excess visceral fat tissue and its pro-inflammatory activity. [9] The most frequent is the relationship between the occurrence of MS and visceral fat, however, the literature proves that MS may also be the result of excess subcutaneous fat in the upper body, as well as in people with normal body mass and abnormal distribution of fat tissue. [5] [10] As mechanisms linking obesity and insulin resistance, increased lipolytic activity of visceral fat tissue, oxidative stress associated with the presence of reactive oxygen species (ROS) and adipokines produced by adipose tissue are mentioned. [5] [8] [9] [10] Oxidative stress is the result of a positive energy balance - an excess of substrates in cells leads to increased production of acetyl-CoA and nicotinamide adenine dinucleotide phosphate (NADP), which contributes to the formation of an increased amount of ROS (Figure 1). The cell's defence mechanism consists in the weakening of signals within the insulin-dependent receptors within the cell via free fatty acids (FFA). This results in an increase in insulin resistance and a reduction in the availability of energy substrates inside the cell. It is an adaptive mechanism that protects the cell against glucose and free fatty acid uptake and further production of ROS. Simultaneously by increasing insulin resistance and decreasing glucose uptake by the cells, its concentration in the blood is being increased [5] Excessive visceral adipose tissue (VAT) results in increased lipolytic activity. Insulin resistance of adipocytes strengthens the lipolysis effect (insulin has an anti-lipolytic effect and increases lipoprotein lipase activity). Free fatty acids are released and then stored in hepatocytes and skeletal muscle cells, which is also associated with the development of adaptive insulin resistance. Insulin resistance reduces the transport of glucose to the cells and increases glycogenolysis in the liver, which increases blood glucose levels and may lead to hyperglycaemia. Hyperglycaemia stimulates pancreatic β-cells to increase insulin production and to compensate for hyperinsulinemia. It allows normalization of blood glucose in the short term, while in the long term it can lead to damage to β cells (the phenomenon of glucotoxicity) and increase of hyperglycaemia. [11] In addition, pancreatic β cells are particularly susceptible to oxidative stress due to the low content of ROS-removing enzymes and the inability to adapt by insulin resistance. [5]

Many authors describe obesity as a chronic inflammation, the effect of which is the expression of proinflammatory cytokines in adipose tissue. [5] [12] [13] This expression is proportional to the amount of adipose tissue. The adipose tissue consists of the following cell types: adipocytes, connective tissue, nervous tissue, vascular endothelial cells and immune cells. Numerous studies have demonstrated the relationship between chronic inflammation in obesity and the development of insulin resistance. It results, among others, from the phenomenon of adaptive insulin resistance, the mechanism of which is presented in Figure 1. [12]

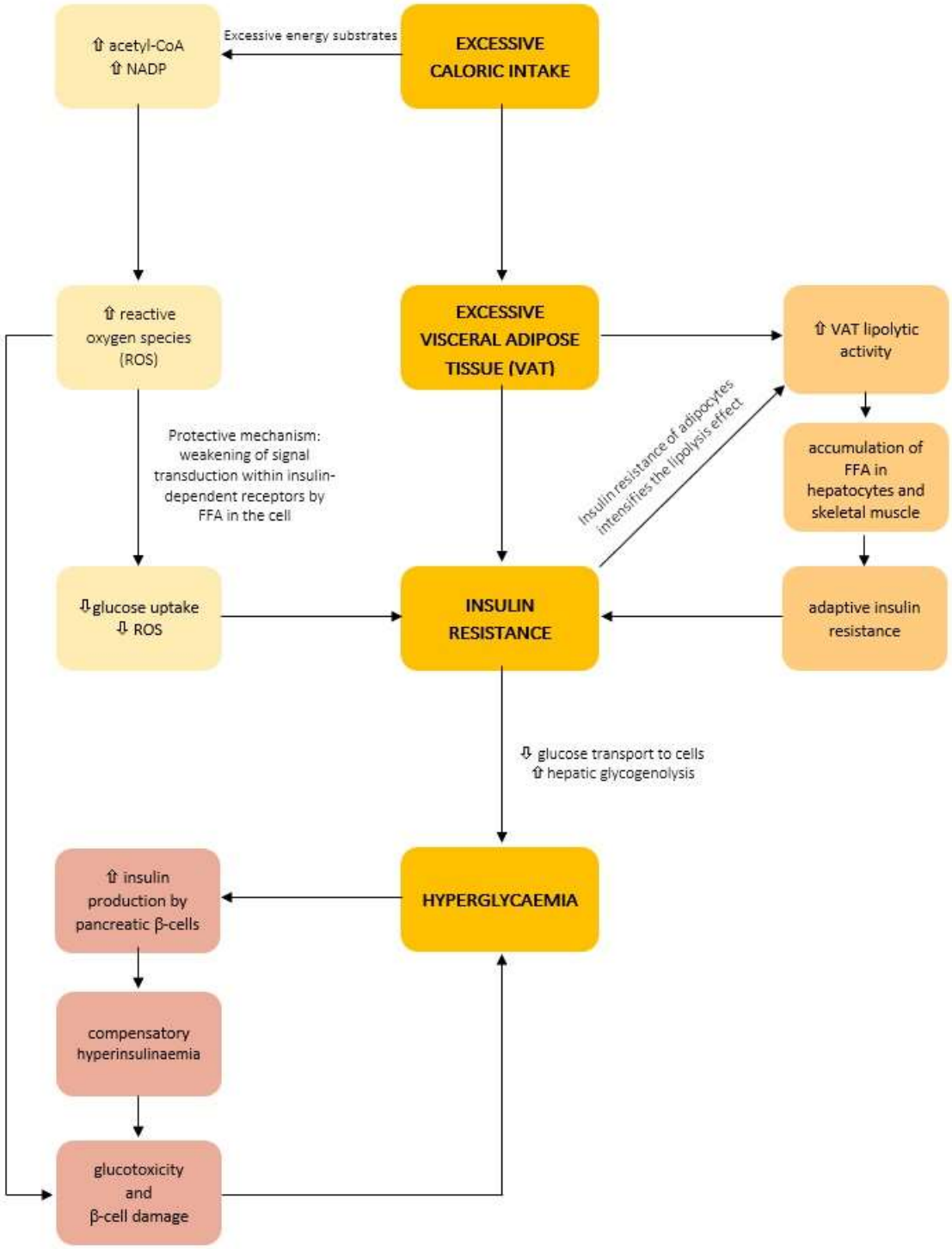

Figure 1. The role of lipolytic VAT activity and oxidative stress in the pathogenesis of carbohydrate metabolism disorders in the MS

In addition, increased adipokine production is observed in obese subjects. These are proteins with pleiotropic effect, affecting directly and indirectly on metabolic processes. Adipokines associated with the pathophysiology of the metabolic syndrome include resistin, leptin, adiponectin, tumor necrosis factor α (TNFα) and interleukin-6 (IL-6). Resistin is a protein associated with the activation of inflammatory processes. It is produced in monocytes and macrophages.

Transcription of the resistin gene (RETN) is induced by proinflammatory cytokines (IL-1, IL-6 and TNF-α). Animal studies have demonstrated the association between resistin and insulin resistance, type 2 diabetes and obesity. It has also been proven that suppression of resistin reduces glycemia and increases insulin sensitivity. Thiazolidinediones (medicines that increase the sensitivity of tissues to insulin) inhibit expression of resistin. [12]

According to available literature the resistin impact on development of the insulin resistance among people have not been confirmed, whereas the connection between resistin and development of inflammation as well as inflammatory diseases has been established in the mentioned clinical studies. [14] The development of the insulin resistance based on obesity may be intensified by leptin - a hormone regulating energy balance in the human body. Leptin is produced mainly by adipose cells, to a lesser degree also by skeletal muscles, liver, stomach fundus cells and placenta. Leptin acts on the hypothalamus receptors or directly on the sensitive tissues. It is responsible for maintaining energy balance by food intake regulation. High leptin concentration inhibits an appetite, whereas low - stimulates it. Among obese patients with co-occur insulin resistance raised leptin concentration in the blood serum and malfunction of this hormone is observed. This indicates occurrence of the leptin resistance, which mechanism remains unknown. [5] [14]

The adipose tissue is also responsible for synthesizing and secreting the anti-inflammatory adipokines, such as adiponectin. The adiponectin secretion is right among normal-weight people. Along with a weight increase and adipocytes structure changes, the adiponectin secretion decreases, which leads to its lower concentration in the blood and adipose tissue. Proinflammatory cytokines, oxidative stress or hypoxia are inhibitors which lead to a reduced hormone synthesis. [14] Thiazolidinediones conduce to adipocytes differentiation and adiponectin secretion increase. Literature shows connection between high adiponectin concentration and low risk of the insulin resistance and diabetes type 2 development. The Japanese study conducted on 590 men demonstrated that the occurring of insulin resistance is preceded by the fall of adiponectin concentration in the blood. [5] This thesis is also confirmed by the insulin resistance and diabetes type 2, independent from body mass, caused by adiponectin gene mutation. [5] Animal tests prove that adiponectin protects against MS spectrum disorders - adiponectin reduces parameters considered as risk factors. Apart from reducing the insulin resistance, adiponectin has the antiatherosclerotic effect. [15]

One of the effective MS diagnostic criteria is a lipid metabolism disorder, especially the atherogenic dyslipidemia characterized by the increased triglycerides concentration and decreased HDL concentration. [1] [6] More detailed studies show presence of abnormal LDL

particles - small dense LDL, which have relatively small affinity to physiological LDL receptors on liver cells and easily permeate to inner arterial membrane. [1] Foregoing disorders pose a significant and autonomous risk factor of arteriosclerosis development. [5] Literature shows connection between the insulin resistance and described above lipid metabolism disorder. As a result of the insulin resistance development the insulin impact on the adipocytes is reduced and insulin anti-lipolytic activity is lost, which leads to a FFA concentration increase. They are transported to the liver, where VLDL synthesis takes place. Diet supply is an extra source of lipids metabolized by the liver. Increased lipid flow leads to post-translational stabilization of apolipoprotein B - a main protein component of VLDL. The insulin resistance also provokes loss of lipoprotein lipase activity. As a result a VLDL synthesis in the liver is intensified and its degradation is decreased, what leads to increase in the concentration of triglycerides in the blood plasma. A decrease in the HDL fraction and occurrence of the small dense LDL are further disturbances of lipid metabolism typical for the MS. This casus is a consequence of changes in the lipoprotein composition and disturbances in their metabolism. Hypertriglyceridemia and increased VLDL concentration results in the exchange of cholesterol esters and triglycerides between VLDL and LDL/HDL - LDL and HDL rich in triglycerides are formed. After hydrolyzing triglycerides by the hepatic lipase small dense HDL and LDL are created. Overloaded with triglycerides HDL are removed from the blood circulation and cannot fulfill their physiological function, which inhibits the cholesterol return transport from the tissues and contributes to the development of atherosclerosis. The small dense LDLs, also known as the LDL type B, show high ability to permeate into the vessel wall and susceptibility to oxidation, which results in significant atherogenicity [5]

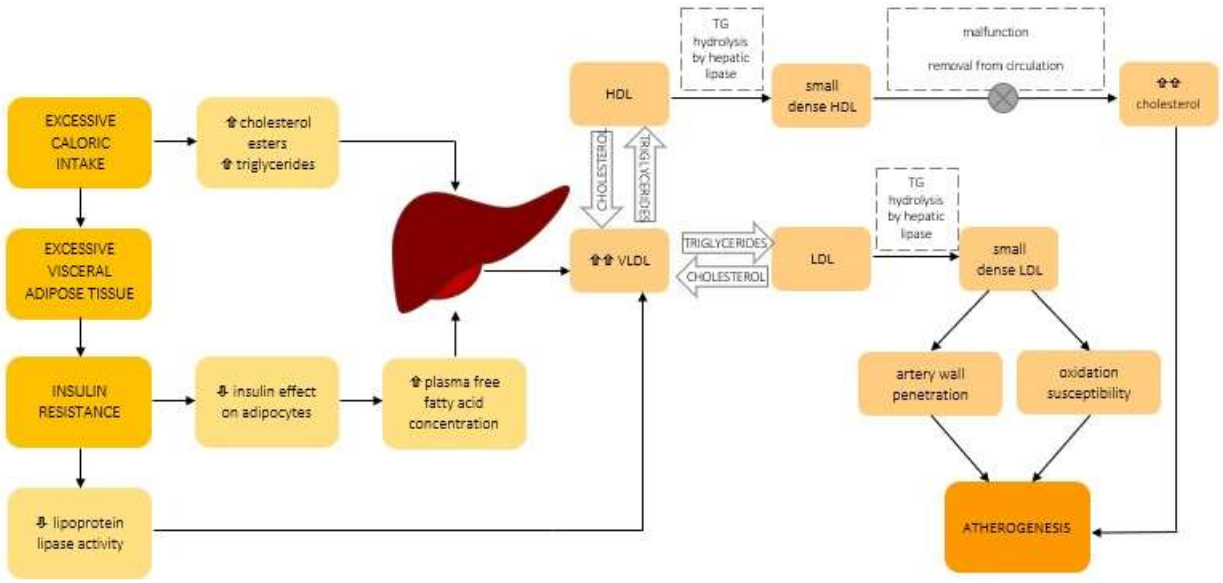

Figure 2 The influence of insulin resistance on the development of lipid metabolism disorders in the MS.

In 2003, within The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, obesity was included among the most important risk factors for the development of hypertension. [16] The risk factors for hypertension in the metabolic syndrome include hemodynamic disorders associated with obesity (increased circulating blood volume and increased cardiac output) and an increase in vascular resistance associated with endothelial dysfunction resulting from previously described conditions.

Available literature describes the likely mechanisms that combine insulin resistance with the development of hypertension. One of the described phenomena is the impairment of insulin-dependent vascular relaxation process - under normal conditions insulin stimulates the biosynthesis of nitric oxide. Insulin resistance leads to a reduction in its biosynthesis. Hyperglycaemia, high concentration of free fatty acids and oxidative stress may also result in disruption of endothelial function and reduction of nitric oxide activity. In addition, hyperglycaemia and compensatory hyperinsulinaemia intensify the biosynthesis of endothelin 1, causing vasoconstriction and the growth of smooth muscle cells. The result is hypertrophy of the vessel wall, narrowing of the vascular lumen and increase in peripheral resistance, which results in increased blood pressure. In addition, studies show that visceral fat may be a source of angiotensin II. Under physiological conditions, it can also produce hormones with the opposite effect, such as the previously described adiponectin, which has vasoconstrictive and cardioprotective effects. The production of adiponectin decreases when there is excess fatty tissue and insulin resistance. [17] [18] [19] Other adipokines are also important in the pathogenesis of hypertension. Literature confirms the role of leptin in regulating blood pressure. It activates the

sympathetic nervous system and stimulates the biosynthesis of endothelin 1 and increases the expression of endothelial nitric oxide synthase, resulting in smooth muscle relaxation. Increased expression of endothelin 1 in endothelial cells after resistin administration has also been demonstrated. [5] It is important to note the significant role of adipose tissue products as an endocrine organ in physiological and pathological processes in the body.

Treatment of metabolic syndrome

Treatment of the metabolic syndrome consists in the treatment of individual pathologies included in its composition. The intensity of treatment depends on the severity of the disorder. Causative treatment involves the treatment of obesity. The goal of causative treatment is to reduce body mass by $\geq 10\%$, which should result in improvement of other metabolic parameters. [1]

The method of treatment of obesity should be decided individually depending on the state of nutrition, the presence and severity of complications and psychological attitude of the patient. [1] Dietary treatment and change in eating habits is the basic method of treating obesity. The principles of obesity management are set by the Standards of dietary treatment of simple obesity in adults published in 2015 as the position of the Polish Society of Dietetics. They include 25 recommendations regarding the management of simple obesity diet. Patients with diagnosed obesity and additional risk factors should be cared for by a therapeutic team, which includes a doctor, dietitian, nurse, psychologist, physiotherapist and other specialists. In all adult patients, body mass should be assessed on the basis of BMI classification and waist circumference. It is recommended to measure body composition using the bioelectric impedance method (BIA). It is also necessary to conduct a detailed interview and assess the patient's readiness to change their lifestyle. The goals of treatment should be realistic and set individually. The gold standard for determining individual energy needs of adults with excessive body weight is the measurement of resting metabolism by indirect calorimetry. If it is not possible to carry out the examination, it is recommended to calculate the resting metabolism on the basis of the Mifflin-St Jeor equation. In the dietary treatment of obesity, a daily caloric deficit in 500-800 kcal is recommended. The proportions of macronutrients in the low-energy diet should be adjusted to the needs and preferences of the patient, while the supply of minerals and vitamins should be consistent with current dietary standards. An example of the proportion of macronutrients: protein 10-25%, carbohydrates 45-65%, fat 20-35% of the total energy from the diet. Supplementation of a reducing diet with vitamins and minerals is not required, the exception is vitamin D. In addition, people with excessive body mass should be presented with the benefits of physical activity. The strategy of dietary treatment of patients with obesity should include at least 12 visits during the

first 6 months of therapy. The reduction of body mass brings obese patients numerous documented benefits, both physical, metabolic, endocrine and psychological. [20] For patients who are unable to achieve weight reduction through diet and physical activity, pharmacological treatment and surgery should be considered.

Pharmacological treatment should be considered in people with BMI over 27 kg/m^2 with concomitance of complications and in people with BMI above 30 kg/m2, in case of ineffective weight loss using non-pharmacological treatment. [20] [21] [22]. There are several registered drugs for the treatment of obesity. They enable weight reduction by 5-10%. These include orlistat, liraglutide, phentermine and lorcaserin. There are also combined preparations: naltrexone and bupropion and phentermine and topiramate. Not all of them have been accepted by the European Medicines Agency (EMA), and only three are available in Poland (including liraglutide without registration for the treatment of obesity) (Table 3). [23] [24] Drugs registered in Poland are orlistat and a combined drug containing naltrexone and bupropion (Mysimba). Orlistat inhibits gastrointestinal lipase activity, so it requires a low-fat diet to avoid gastrointestinal side effects. The drug should be used orally, 3 times daily before the main meals, at a dose of 120 mg. The dose should be gradually increased over four weeks to a maximum of 32 mg of naltrexone and 360 mg of bupropion per day. [23] In the EU, liraglutide is registered to support the treatment of obesity. It is a GLP-1 analogue, used subcutaneously at a dose of 0.6 - 3 mg/d. Liraglutide reduces food intake, affecting hypothalamic regulation of satiety and hunger. In obese patients with symptoms of depression, fluoxetine should be considered at a dose of 20 mg in the morning. The drug improves mood and lowers appetite. [22] It should be remembered that qualifying the patient for pharmacological treatment does not eliminate the need to continue the appropriate dietary treatment. [20]

Table 3. Availability of drugs in treatment of obesity in the United States, Europe and Poland [23]

Drug	US Food and Drug Administration	European Medicines Agency	Poland
Orlistat	+	+	+
Liraglutide	+	+	+*
Phentermine	+	+	-
Lorcaserin	+	-	-
Naltrexone and bupropion	+	+	+
Phentermine and topiramate	+	-	-

* off-label obesity treatment

Qualification for surgical treatment of obesity should include a multidisciplinary assessment of the patient's state of health. According to the European Association for the Study of Obesity (EASO) recommendations, bariatric surgery may be used for people aged 18-60, diagnosed with grade III or grade II obesity, if there are concomitant diseases, in which surgically induced weight loss results in improvement of the patient's condition. [25] Generally available surgical techniques can be divided into operations limiting food intake - restrictive and operations limiting the absorption of food. The laparoscopic technique is the first choice technique in the absence of contraindications. In order to consolidate changes in lifestyle and maintain the resulting weight reduction after bariatric surgery, regular medical check-ups and qualified post-operative care are essential throughout life. According to the available literature, some patients do not achieve a permanent loss of weight. [25]

Treatment of type 2 diabetes is carried out according to the Guidelines on the management of diabetic patients published in 2019 as the position of the Polish Diabetes Association. According to the above recommendations behavioural therapy is an essential part of treatment in all patients with diabetes, regardless of the patient's age and type of diabetes. Therapeutic treatment should include: varied diet, regular physical activity, no smoking and alcohol consumption, enough sleep and avoiding stress. All patients with diabetes should be educated about the general principles of proper nutrition in diabetes by qualified personnel, including a doctor, dietitian, diabetes nurse and diabetes educator. Each patient should receive dietary recommendations tailored to their

needs and capabilities. There is no universal diet for all diabetic patients. The optimal proportions of macronutrients for the patient should be determined individually taking into account age, physical activity, the presence of diabetes complications and additional disorders. Physical effort should be an integral part of comprehensive management of diabetes, it should be systematic, taken at least every 2-3 days. The diet of diabetic patients should include the general principles of healthy nutrition of healthy people, in addition, regular eating, controlling portion sizes, controlling the amount of carbohydrates consumed and restricting food containing easily digestible carbohydrates is particularly important. In type 2 diabetes, the primary goal of therapy is metabolic control of the disease and, in the case of body weight exceeding the norm, reduction of excess body weight. This goal can be achieved by determining the appropriate calorie deficit in the diet. A reduction in body weight by at least 5% compared to the initial weight brings measurable improvement in glycaemic control. According to the recommendations, the following diets are recommended: Mediterranean, DASH (Dietary Approaches to Stop Hypertension), portfolio, vegetarian or vegan, low-fat or low-carbohydrate diet. Fasting is not recommended to reduce weight. The golden standard in the treatment of diabetes in patients with excessive body weight is a low carbohydrate diet. Carbohydrates should be a source of about 45% of the total energy intake, a possible higher carbohydrate contribution is acceptable if they come from products with a low glycaemic index and high fiber content. The fiber content in the diet should be about 25-50 g / day or 15-25 g per 1000 kcal. Fats should provide 30-35% of the total energy intake (saturated fat below 10%, monounsaturated fat 10-15%, polyunsaturated fat 6-10%). The daily cholesterol intake of the diet should not exceed 300 mg. The intake of trans-fatty acids should be reduced. The protein should provide 10-20% of the total energy intake, in patients with type 2 diabetes with excessive body weight, a diet with reduced energy and a protein content of 20-30% of energy is recommended. The amount of sodium chloride in the diet should not exceed 5 g a day, in the case of hypertension coexistence, greater salt restrictions are recommended. With the exception of vitamin D3, there is no indication for supplementation of vitamins and microelements. [26] [27]

The pharmacological treatment of type 2 diabetes has been divided into stages. Stage 1 is metformin monotherapy and lifestyle modification, including weight reduction. If metformin intolerance or contraindications to its use, other antidiabetic drugs may be used. In the case of obesity, metformin is the preferred drug, and if metformin can not be used, DPP-4 inhibitors and SGLT-2 inhibitors should be included (these drugs help reduce weight). Stage 2 is an oral combination therapy. Dual therapy includes lifestyle modification, metformin and one additional

drug: a sulphonylurea, an incretin drug (DPP-4 inhibitor or GLP-1 receptor agonist), an SGLT-2 inhibitor, or a PPAR-γ agonist. Triple therapy includes adding one more of the above or an α-glucosidase inhibitor (acarbose). Stage 3 involves modifying the lifestyle and simple insulin therapy with the possible continuation of metformin, especially with excessive body weight. Stage 4 is lifestyle modification and insulin therapy combined with the possible continuation of metformin or another antidiabetic drug. The choice of drugs at individual stages of the algorithm should be individualized. Individualization includes consideration of effectiveness, side effects, effects on body weight, risk of hypoglycaemia, the price of the drug and patient preferences. [27]

Current dietary recommendations in the field of prophylaxis and treatment of cardiovascular complications of MS are specified in the Standards of dietary behaviour in cardiology in adults according to the position of the Polish Society of Dietetics for 2016. The energy value of the diet should correspond to the energy needs of the patient. In the case of excessive body weight, a reduced calorie diet is recommended. In the prevention and treatment of cardiovascular diseases a diet with a controlled content of fatty acids is recommended. It is particularly important to limit the supply of total fat to less than 30% of total energy intake, intake of saturated fatty acids below 7% of energy, possibly lowest intake of trans fatty acids, cholesterol intake below 300 mg/d and substitution of unsaturated saturated fatty acids. A daily intake of 250 - 500 mg of polyunsaturated fatty acids (PUFA) from the n-3 family (EPA and DHA) is recommended. Regular consumption of sea fish allows to lower blood pressure, however, the highest effect is observed in patients receiving higher doses of n-3 PUFA, which can be obtained only through supplementation. It is recommended to eat two portion of fish per week, including a minimum of one portion of oily fish. It is recommended to consume about 2 g of plant sterols or stanols per day (this has been shown to result in a reduction in total cholesterol and LDL cholesterol by 7-10%). Daily intake of dietary fiber should be at least 14 g per 1000 kcal of diet. A daily supply of sodium chloride below 5 g is recommended. Further recommendations include eating nuts (30 g per day), garlic (1-2 cloves of garlic per day) and soy protein (minimum 25 g of soy protein per day). As diets with documented effectiveness in the prevention of cardiovascular diseases, the DASH diet, the Mediterranean diet and the Portfolio diet are mentioned. Systematic activity is also recommended (at least 30-60 minutes of physical activity a day most days a week). [28] [29] In patients with hypertension, the decision to initiate antihypertensive therapy depends on the value of blood pressure and the presence of the risk of cardiovascular disease. In all cases of elevated blood pressure, a lifestyle change is recommended. In patients with grade 3 hypertension (regardless of cardiovascular risk) as well as in patients with grade 1 or 2 hypertension and very

high cardiovascular risk, pharmacotherapy is recommended. [30] The main groups of hypotensive drugs used in monotherapy and combination therapy are: thiazide diuretics, β-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). In the absence of indications and contraindications to the use of a drug in a given group, pharmacological antihypertensive therapy can be started with the use of one drug, any group, low dose or, in the case of significantly elevated blood pressure or high cardiovascular risk, from the use of two drugs in small doses. If treatment with one drug has not led to control of blood pressure, it is possible to add a second drug (the first choice), change the drug to another or increase the dose of the first drug. If the use of two drugs in low doses is ineffective, the next step is to increase the dose of medication or add a third drug at a low dose. Usually 2 or 3 antihypertensives are used. [30]

Non-pharmacological treatment of atherogenic dyslipidaemia includes: weight reduction in overweight and obese people, dietary management in accordance with the above-mentioned principles of cardioprotective diet, supplementation of polyunsaturated fatty acids n-3 at a dose of 2-4 g per day and limitation of alcohol consumption. Pharmacological management includes statin monotherapy or, in the case of high triglycerides (≥ 5.6 mmol/l), with fibrates. If the effect of monotherapy is insufficient, combination therapy is recommended: a combination of a statin and fibrate or a statin, a fibrate and n-3 fatty acids (fish oil). [31] Pharmacological treatment does not eliminate the need to comply with dietary recommendations. [28]

Conclusions

Metabolic syndrome is a significant epidemiologically problem. Diagnosis is based on simple criteria and uses the results of easy-to-do tests. This allows the diagnosis of the metabolic syndrome at the level of primary care. Due to the significant progress in pathophysiology of the metabolic syndrome, it is possible to determine its primary causes and risk factors, which allows to determine the rules of preventive and therapeutic treatment. It should be emphasized that the primary causes - obesity and insulin resistance - belong to the reversible states, which is an additional motivation to detect and treat these conditions before irreversible complications develop.

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