JPNU
scientific journal

# PATHOGENESIS AND BIOMARKERS OF METABOLIC SYNDROME

VIKTORIA HURZA, MYROSLAVA VATASHCHUK, MARIA BAYLIAK

**Abstract.** Metabolic syndrome (MetS) is a pathologic multifaceted condition characterized by elevated triacylglycerides, decreased high density lipoproteins, insulin resistance, increased blood pressure and fasting glucose. Together these abnormalities increase a risk of cardiovascular diseases and type 2 diabetes mellitus. Overnutrition and sedentary lifestyle followed by overweight and obesity are the main contributing factors to MetS development. The pathogenesis of MetS is very complex and not fully elucidated. The studies support the concept of oxidant/antioxidant imbalance and low-grade inflammation playing main roles in its manifestations. Diagnosis with MetS and the development of MetS complications can be detected and monitored via specific serum biomarkers. In this paper, we describe classical metabolic, hormonal and pro-/anti-inflammatory markers which are the most frequently used for MetS diagnostic and research. They include serum lipid profile (triacylglycerides, total cholesterol, low and high density lipoproteins), blood pressure, fasting glucose and HOMA-IR index, levels of anti-inflammatory adiponectin, pro-inflammatory C-reactive protein and cytokines (TNF-$\alpha$, IL-1$\beta$, IL-6, *etc*.). We also analyze advantages of additional criteria such as levels of oxidative damages, appetite hormones (leptin, ghrelin), apolipoproteins and oxylipins, the composition of gut microbiota and levels of microbiome-derived metabolites, the ratios between different parameters as helpful biomarkers of MetS and concomitant cardiovascular diseases.

**Keywords**: metabolic syndrome, visceral fat, inflammation, oxidative stress, insulin resistance.

**Abbreviations**: BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; FFA, free fatty acids; HDL, high density lipoproteins; LDL, low-density lipoproteins; MetS, metabolic syndrome; TAG, triacylglycerides; T2DM, type 2 diabetes mellitus; ROS, reactive oxygen species.

## 1. METABOLIC SYNDROME CONCEPT

Metabolic syndrome (MetS) includes a group of metabolic disturbances that occur more frequently together than separately and, in the combination, significantly increase a risk of cardiovascular diseases and type 2 diabetes mellitus. Clinically MetS is characterized by dyslipidemia, elevated glucose levels, increased blood pressure, insulin resistance, a pro-thrombotic state, pro-inflammatory and pro-oxidant states [1, 2]. Metabolic abnormalities related to MetS have been studied for over 100 years, but in the resent 30 years MetS received a special attention. During this period, labels, components and, respectively, definitions of MetS were several times changed. In 2009, the consolidated definition of MetS was accepted by leading health organizations and MetS was defined as a pathologic multifaceted condition characterized obligatory by elevated triacylglycerides (TAG), decreased high density

lipoproteins (HDL), insulin resistance, increased blood pressure and fasting glucose [1]. Despite a tight link between MetS and obesity was established in last years, the presence of abdominal obesity was excluded from obligatory criteria of MetS. This is due to observations that not all obese people develop MetS symptoms and not all patients diagnosed with MetS suffer from obesity. The relationship between obesity and MetS has also ethic specificity. In particular, Asian Americans had higher risks for MetS incidence than Non-Hispanic White adults with the same body mass index [3]. Nevertheless, as the prevalence of obesity increases in population, the number of people with MetS also will increase in parallel.

There is still debate regarding the ethology and pathogenesis of MetS, because a single mechanism underlying this dysmetabolic phenotype is unknown. Overeating of a high-calorie food and physical inactivity due to sedentary lifestyle followed by overweight and obesity are considered as key factors of the MetS development. Aging, emotional stresses, various drugs, gut microbiota composition, genetics, sleep quality and hormonal changes also contribute to MetS onset [4, 5, 6, 7, 8].

## 2. PATHOGENESIS

Mechanisms underlying pathophysiology of MetS are not fully clear. Accumulation of visceral fat is thought to be a major trigger factor in the development of MetS and its complications. In visceral adipose tissue, metabolic responses to caloric excess lead to low-grade chronic inflammation, oxidative stress and increased flux of free fatty acid in blood following insulin resistance [9].

### 2.1. Insulin resistance

Insulin resistance is characterized by elevated blood glucose at normal or even elevated insulin levels due to decrease in sensitivity to this hormone of insulin receptors in glucose-utilizing tissues. Evidence indicates that MetS begins with excess central adiposity or accumulation of visceral fat. When β-cell function of pancreas is responsive, hyperinsulinaemia occurs but fasting and postprandial glycaemia often remains normal for years [10]. When insulin sensitivity impairs, mobilization of free fatty acids (FFA) (lipolysis) from adipose tissue trigacylglyceride stores is accelerated. Under physiological conditions, insulin inhibits adipose tissue lipolysis; however, when insulin resistance is developed, insulin is unable to properly suppress lipolysis, resulting in relatively more circulating FFAs which are releasing from adipose tissue. Not only insulin resistance causes FFA elevation, but elevated FFA levels also provoke insulin resistance [11].

FFA inhibit insulin receptor protein kinase activation in the muscle leading to reduced glucose uptake. They increase protein kinase activation in the liver that promotes gluconeogenesis and lipogenesis. The net effect is the creation of a hyperinsulinemic state to maintain euglycemia. Eventually, the compensation fails and insulin secretion decreases. FFAs are also lipotoxic to β-cells of the pancreas causing decreased insulin secretion. Insulin resistance also contributes to the development of hypertension due to loss of the vasodilator effect of insulin and vasoconstriction caused by FFA [9].

### 2.2. Inflammation

A number of studies suggest that the inflammation associated with obesity and overweight plays an important role in the etiology of the MetS and largely contributes to the related pathological outcomes such as type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD) [12].

Adipose tissue is supposed to play a central role in the induction of inflammation because over-nutrition leads to changes in its cellular composition and production of pro-inflammatory cytokines and chemokines [13]. A local inflammation is also observed in the liver and skeletal muscle. Recent evidence indicates the involvement of inflammasome NLRP3 in the pathogenesis of MetS and T2DM. In pancreas, the activation of NLRP3 inflammasome by high levels of glucose and fatty acids with subsequent release of IL-1β leads to dysfunction and apoptosis of β-cells, insulin deficiency and progression to T2DM. In obese patients with metabolic disorders, NLRP3 inflammasome was shown

also to be activated in macrophages, which infiltrate visceral adipose tissue, and contributes to local inflammation, impairment in adipogenesis and insulin resistance [14].

Hypoxia was found to be one of etiologic factors of necrosis and macrophage infiltration into adipose tissue that leads to an overproduction of proinflammatory factors like inflammatory chemokines. This results in a localized inflammation in adipose tissue that propagates an overall systemic inflammation associated with the development of obesity-related comorbidities. Evidence suggests that tumor necrosis factor-alpha (TNF-$\alpha$), a pro-inflammatory cytokine, induces apoptosis of adipocytes and promotes insulin resistance by the inhibition of the insulin receptor substrate 1 signaling pathway. Another proinflammatory cytokine, interleukin-6 (IL-6) was confirmed to be capable of suppressing lipoprotein lipase activity [15].

Obesity progression is connected with changes in production of adiponectin, an adipose-derived plasma protein. Weight loss was shown to increase adiponectin levels; in animal models of obesity and insulin resistance, adiponectin levels are reduced. Adiponectin regulates lipid and glucose metabolism, increases insulin sensibility, regulates food intake and body weight, and protects against chronic inflammation. Human studies show that hypoadiponectinemia is associated with insulin resistance, hyperinsulinemia, and the possibility of developing T2DM, independent of fat mass [16, 17].

Obesity is associated with dysregulation of lipid and carbohydrate metabolism. An increase in either one of these substrates will also increase the demand on the mitochondria and the utilization of the electron transport chain. Intensification of electron transport chain functioning generates increased amounts of reactive oxygen species (ROS) followed oxidative stress development. Oxidative stress activates a number of regulatory proteins including kinases like c-Jun N-terminal kinase (JNK), mitogen-activated protein kinase (p38 MAPK) and inhibitor of nuclear factor-κB (IκB) kinase (IKK) that may directly interfere with insulin signaling or indirectly via induction of nuclear factor-κB (NF- κB) and increased cytokine production [12].

### 2.3. Neurohormonal activation

Activation of the renin-angiotensin system serves as an important neurohumoral pathway contributing to the development of MetS. Angiotensin II (Ang II), formed as a result of angiotensin-converting enzyme activation, is produced by adipose tissue. Obesity and insulin resistance are associated with increased production of Ang II which through activation of the type 1 receptor activates NADPH oxidase leading to the generation of ROS. ROS are responsible for multiple effects including oxidation of low-density lipoproteins (LDL), endothelial injury, platelet aggregation, expression of redox-sensitive transcription factor NF-κB and expression of lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) on the endothelium and vascular smooth muscle cells. Renin-angiotensin system, ROS and LOX-1 form a positive feedback loop that initiates a vicious cycle of inflammation and endothelial damage, that contributes to the development of hypertension, dyslipidemia, T2DM and CVD [9].

### 3. BIOMARKERS OF METABOLIC SYNDROME

The term "marker" is defined as the molecule which serves as an indicator of any defects or alterations in the cells, tissues or whole organism. Biochemical markers help to diagnose or predict the causes and changes in normal conditions and can be represented by different chemical substances such as a specific proteins (antigen, antibody, abnormal enzyme, or hormone), low molecular metabolites or xenobiotics, etc. These substances can be found in blood, urine or any fluid in the body.

The clinical criteria that are the most commonly accepted for diagnostic of MetS include abdominal or central obesity, elevated levels of serum triacylglycerides (TAG) and glucose, increased blood pressure, and low levels of high-density lipoproteins (HDL). When patients have three or more of these signs, they are diagnosed with metabolic syndrome [1, 2, 8].

Adipose tissue consists of adipocytes and many immune cells that produce a variety of biologically active compounds, including adipokines, such as adiponectin and leptin, chemokines, such as monocyte chemoattractant protein (MCP-1), and pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-$\alpha$) and interleukins 1$\beta$ (IL-1$\beta$) and 6 (IL-6). Many of these compounds can serve biochemical markers of MetS [13].

### 3.1. Classical metabolic markers

The total cholesterol and TAG concentrations are commonly significantly higher in patients the MetS than in healthy group. This correlates with the accumulation of lipids in adipose tissue and increase in hepatic synthesis and secretion of lipoproteins [18]. Kamso et al. showed that among Indonesian patients with the MetS more women than men had increased waist circumferences and elevated TAG. In addition, more men than women had impaired fasting glucose and hypertension [19]. Skalicky et al. also confirmed that obese patients had significant elevation of TAG concentration and a significant decrease in HDL cholesterol in comparison with healthy controls [20].

The mechanisms responsible for the alterations in lipid metabolism associated to the MetS involve a high lipolytic activity in visceral adipose tissue resulting in a supply to the liver of large amounts of free fatty acids associated to increased glucose and insulin concentrations. Eventually it results in the increased circulatory concentrations of TAG and cholesterol and their accumulation in muscle and other tissues. This phenomenon of lipotoxicity provokes both the inflammation of pancreatic $\beta$-cells and a decrease of their mass [18, 21].

Lipids and lipoproteins play an important role in the development as well as in consequences of MetS. The dyslipidemia results in increased production of TAG and secretion of very low density lipoproteins along with associated abnormalities like reduction of in HDL cholesterol and increased LDL levels. Hypertriglyceridemia is associated with predominance of small dense LDL particles which is due to relative depletion of unesterified cholesterol, esterified cholesterol and phospholipids with either no change or an increase in LDL triglyceride levels. Small dense LDL is more toxic to endothelium, can transit through endothelial basement membrane easily, adheres well to glycosaminoglycans, is more susceptible to oxidation and is more selectively bound to scavenger receptors on monocytes derived macrophages [22].

Insulin resistance is a core feature of the MetS. Homeostatic model assessment of insulin resistance (HOMA-IR) is a robust clinical and epidemiological marker of MetS. High-molecular weight adiponectin (HMWA) is the multimer responsible for the relationship of adiponectin with insulin sensitivity. HOMA-IR and HMWA are suitable candidates for MetS biomarkers. The ratio of adiponectin to HOMA-IR has been validated as a powerful index of MetS and considered a better marker of its presence [23]. The presence of the MetS is associated with higher values of serum insulin, HOMA-IR, leptin and leptin/adiponectin ratio and lower values of adiponectin and adiponectin/HOMA-IR ratio. In multivariate regression analysis of adiponectin was the only biochemical marker that correlated with MetS. Also, adiponectin correlated with abdominal obesity, low HDL-cholesterol and elevated blood pressure. HOMA-IR correlated with low HDL-cholesterol and raised glycaemia [24].

Studies suggest that individuals with MetS have a greater risk of developing T2DM and CVD [25]. Assessment of CVD risk and MetS in children and adolescents has involved the analysis of serum or plasma biomarkers including total cholesterol, TAG, HDL cholesterol, insulin and C-peptide [22].

### 3.2. Hormonal circulating biomarkers

Adiponectin or adipocyte complement-related protein is the most abundant peptide secreted by adipocytes that negatively correlates with obesity and T2DM because it acts by increasing insulin sensitivity; it is probably the only adipokine whose higher levels corelates with lower body mass index (BMI) and decreased cardiovascular risk because of its anti-inflammatory and antiatherogenic effects. Therefore, adiponectin level was proposed as novel therapeutic target for diabetes and MetS [16].

Human adiponectin is encoded by the Adipo Q gene, which spans 17 kb on chromosome locus 3q27. This chromosome has been identified as carrying a gene susceptible for T2DM and MetS. Adiponectin is also involved in energy homeostasis by action in hypothalamus, therefore the name 'starvation gene' has been proposed [26].

Insulin and adiponectin interact with their receptors, which in activated state trigger a cascade of metabolic actions such as increase in protein synthesis and lipogenesis, glucose uptake and utilization (leading to reduced plasma glucose levels), glycogen synthesis, lipolysis and gluconeogenesis [24]. Sanjari et al. demonstrated that serum adiponectin levels in women with MetS were lower than those in women without MetS [27].

Leptin is a polypeptide hormone produced by adipocytes with increasing their triglyceride content. It is involved in the central control of energy balance since regulates food intake and energy expenditure to maintain body fat stores. The mechanism of action of leptin is due to binding to and activation of the long form of its receptor in the hypothalamus that results in decrease in food intake with simultaneous increase in energy expenditure. Circulating leptin is secreted into the blood and after crossing the brain-blood and cerebrospinal fluid barrier, it acts in the hypothalamus, where leptin inhibits neuropeptide Y (NPY) neurons. The central administration of leptin increases glucose turn-over and glucose uptake in peripheral tissues (heart, skeletal muscle, adipose tissue), stimulates hepatic gluconeogenesis and hepatic insulin sensitivity via the hepatic branch of the vagus nerve [24].

Leptin levels are higher in patients with obesity mainly because of leptin resistance. Moreover, high levels of leptin are associated with increased insulin secretion which further exacerbates obesity and increases leptin levels [27, 28]. Leptin increases insulin resistance and has proinflammatory effects, while adiponectin increases insulin sensitivity and decreases inflammatory response; therefore, the leptin/adiponectin ratio is considered as a good predictor of diabetes risk and MetS [24, 29].

Adiponectin exists in plasma in 3 major oligomeric forms: a low-molecular-weight (LMW) trimer, a middle-molecular-weight (MMW) hexamer, and a high-molecular-weight (HMW) 12- to 18-mer [30, 31]. Frühbeck et al [31] showed that HMW, MMW and LMW adiponectin concentrations were significantly lower in individuals with the MetS. In contrast, leptin levels were significantly higher in subjects with the MetS. The ratio adiponectin/leptin, a marker of dysfunctional adipose tissue, was dramatically decreased in the MetS group. Systemic oxidative stress, confirmed by higher levels of products of lipid oxidation, was significantly increased in patients with the MetS. Markers of inflammation such as serum amyloid A, C-reactive protein and osteopontin were more elevated in subjects with the MetS as compared with individuals without the MetS. Total adiponectin concentrations were negatively correlated with levels of products of lipid oxidation and C-reactive protein concentrations.

Ghrelin is a peptide hormone produced in the gastrointestinal tract, and it has an important role in regulation of the using of energy substrates in human organism. This hormone acts directly on hypothalamus and indirectly by increasing the expression of orexigenic peptides such as neuropeptide Y, agouti-related protein, proopiomelanocortin, and corticotropin-releasing hormone. In addition to its effect on hunger, ghrelin has important effects on glucose homeostasis, energy homeostasis, heart, muscular atrophy and bone metabolism [32]. Ukkola et al. emphasized the correlation of low ghrelin levels in obese patients with MetS incidence. In addition, the positive correlation of ghrelin levels with hypertension, insulin resistance, and obesity was confirmed by numerous studies [33]. McLaughlin et al. concluded that ghrelin correlates with MetS mainly based on obesity as well as they identified lower ghrelin levels in patients with MetS and obesity than in non-obese MetS [34].

### 3.3. Inflammatory markers

Adipose tissue, liver, pancreas and muscles are sites of inflammation in the development of MetS and obesity. An infiltration of macrophages and other immune cells observed in these tissues is associated with a cell population shift from an anti-inflammatory to a pro-inflammatory profile. These

cells produce pro-inflammatory cytokines, which aggravate oxidative stress and affect insulin signaling in peripheral tissues or induce β-cell dysfunction increasing a risk of comorbidities [13, 14].

In numerous studies, MetS and its components are associated with an inflammatory response [35, 36, 37]. C-reactive protein (CRP), an acute phase protein produced primarily by the liver, is considered as one of indicators of inflammatory response as well as a risk factor for MetS [37, 38]. Yoon et al. showed that the risk of MetS was significantly higher (1.5 times) in the group of healthy men with increased CRP levels than that in the group with the decreased or unchanged levels [37]. Additionally, with regards to MetS, Yudkin et al. [35] analyzing 107 nondiabetic patients found a very significant correlation between inflammatory markers and several features of the MetS. CRP levels were shown to be strongly associated with insulin resistance calculated from the homeostatic model assessment (HOMA) model, blood pressure, low HDL, TAG, and to levels of the proinflammatory cytokines, IL-6 and TNF-$\alpha$. Body mass index and insulin resistance were the strongest determinants of the inflammatory state [35]. There is a linear relationship between the number of metabolic features and increasing levels of CRP [35, 36].

Tumor necrosis factor alpha (TNF-$\alpha$) is a well-known proinflammatory cytokine, with important metabolic and/or weight-regulating effects on lipid metabolism. A relationship between serum TNF-$\alpha$, insulin resistance, and obesity was demonstrated in various studies [39, 40, 41]. Moon et al. compared the serum levels of TNF-$\alpha$ and its receptors in obese adolescents. The mean serum TNF-$\alpha$ was significantly higher in the obese than the non-obese group. The mean serum TNF-$\alpha$ receptor 1 and receptor 2 were also significantly higher in the obese than the non-obese group. In the obese group, sex-related differences in the serum TNF-$\alpha$ and its receptor levels were noted, with the males showing higher levels than the females [39].

IL-6 is a pro-inflammatory cytokine that plays important roles in acute and chronic inflammation, immune cell development, and the pathogenesis of autoimmune disease. The increased IL-6 levels were observed in the MetS development and to be associated with an elevated risk of development of diabetes mellitus [32, 42]. In particular, the case-control study of Mohammadi et al. showed that serum IL-6 and TNF-$\alpha$ levels were significantly greater in the MetS patients than in the healthy group [43].

Recently, it has been shown that increased levels of pentraxins are associated with MetS development and progression [32, 44]. Pentraxins are a cluster of serum proteins with similar structures and calcium-dependent ligands that play important roles in inflammatory mediation. Pentraxins are produced by immune cells as a response to bacterial substances, endotoxins, IL-1 and TNF-$\alpha$ [32]. In a study conducted on adolescent subjects with obesity, it was shown that subjects with obesity and MetS had higher values of pentraxin 3 than the subjects without MetS [44].

### 3.4. Oxidative stress markers

The pathogenesis of MetS is very complex and several studies support the concept that oxidant/antioxidant imbalance may play an important role in its manifestations [13, 45, 46]. Oxidative stress is implicated in vascular complications of diabetes and in pancreatic β-cell destruction. Meanwhile, obese people without diabetes also display elevated intensity of oxidative stress. Levels of oxidative stress markers were found to be increased in the adipose tissue of obese rodent models [47, 48, 49]. The increase in oxidizing species formation in MetS is considered as a major underlying mechanism for mitochondrial dysfunction, accumulation of protein and lipid oxidation products, and impairment of the antioxidant systems [46]. The oxidative biomarkers of MetS include increased levels of oxidatively damaged biomolecules (lipid peroxides, malondialdehyde, oxidized low density lipoproteins (LDL), protein carbonyls, 3,5-dinitrotyrosine, 8-hydroxy-2'-deoxyguanosine, *etc.*), and changes antioxidant defense capacity (superoxide dismutase, catalase, glutathione and thioredoxin and associated enzymes [glutathione and thioredoxin reductases and peroxidases, glutathione S-transferase], peroxiredoxins, NAD(P)H:ubiquinone oxidoreductase, paraoxonase, etc.) [13, 47, 48, 49, 50]. Levels of oxidative damages were higher in obese individuals and correlated directly with BMI and the percentage of body fat and TAG levels [51]. At the same time, antioxidant defense capacity was

lower if the amount of body fat and central obesity were higher [52, 53]. Oxidative stress is independently related to TAG concentration, abdominal fat, low HDL cholesterol and low lipid standardized a-tocopherol in obese patients with MetS. High levels of ROS together with the low total antioxidant capacity detected in obese patients indicate elevation of oxidative stress, which is potentiated especially in the case of obese patients with MetS [20].

Paraoxonase-1 (PON-1) is an enzyme produced mostly by the liver that after releasing in circulation protects against lipid oxidation and exogenous toxics. PON-1 extends the lag phase of the oxidation process and reduces aldehyde concentrations, resulting in protective effects on LDL and HDL lipoproteins [32, 54]. A cross-sectional study conducted on 354 Caucasian subjects with MetS has shown that PON-1 activity was significantly lower among patients who had all five MetS criteria [55]. The same study revealed that lower levels of HDL cholesterol and apolipoprotein A1 (ApoA1) decrease the PON-1 activity. Similarly, the study conducted on 2404 subjects with MetS criteria demonstrated that PON-1 activity followed a downward trend with increasing MetS components and increasing lipid peroxides [56]. In conclusion, PON-1 is assumed could have important roles in lowering of the progression of MetS through its antioxidant and anti-inflammatory effects [32, 55, 56].

There are no clear correlations between fat accumulation and antioxidant defense capacity. An increase, decrease or no change in the activity of antioxidant enzymes were found in obese subjects [48, 50, 51, 53]. These controversial data may indicate both tissue-specific responses and time-dependent effects [13].

### 3.5. New potential markers of MetS

Emerging biomarkers such as apolipoproteins apo-AI, a major component of high-density lipoproteins, and apo-B, a major component of low-density and very low-density lipoproteins, have been proposed as precise predictors of atherogenicity and CVD risk [57].

Trimethylamine N-oxide (TMAO), a diet- and microbiome-derived metabolite, has been suggested to be a predictive biomarker and functional mediator in cardiometabolic diseases. Several mechanisms have been proposed to explain the relation of TMAO with CVD including decreased reverse cholesterol transport, increased foam cell formation, increased platelet aggregation, and an upregulation of proinflammatory pathways, all of which are known risk factors for the development and progression of atherosclerosis by favoring vascular plaque build-up and inflammatory responses [57]. Several animal intervention studies and human prospective and cross-sectional studies highlight that TMAO concentrations are associated with unfavorable metabolic and cardiovascular phenotypes, with some inconsistencies identified across studies [58, 59, 60]. Nevertheless, associations between TMAO concentrations and adverse cardiovascular outcomes are stronger in individuals with CVD, compared with healthy populations, and are concentration-dependent [60]. The study of Andraos et al. [60] showed that plasma concentrations of choline, betaine, and dimethylglycine (DMG), but not those of TMAO, are strongly associated with increased MetS scores in adults. Adult plasma choline and DMG concentrations were positively associated with increasing MetS scores. By contrast, betaine was negatively associated with increasing MetS scores. Thus, TMAO precursors, but not TMAO itself, were associated with adverse cardiometabolic and inflammatory phenotypes in children and adults. TMAO precursor concentrations was supposed might better reflect cardiovascular health and inflammatory status within the wider population [60].

Individuals who met WHO diagnostic criteria for MetS displayed elevated soluble form plasma angiotensin-converting enzyme-2 (sACE2) levels compared to healthy people; the effect was stronger in men. All of MetS classical biomarkers were positively associated with plasma sACE2. The associations were significantly stronger in men for biomarkers of obesity and adiposity and insulin resistance and hyperglycemia, as well as triglycerides and serum CRP. The strongest association was observed between sACE2 and gamma-glutamyl-transferase, an important indicator of oxidative stress, liver, and bile duct damage [61].

Oxygenated lipid derivatives, cyclo-oxygenase (COX), lipoxygenases (LOX) and cytochrome P450 epoxygenases (CYP) oxylipins, are downstream lipid derivatives from arachidonic acid and play multiple important roles in mediating inflammation. COX oxylipins modulate adipose tissue homeostasis and inflammation making these compounds interesting candidates as potential biomarkers to predict the risk to develop type 2 diabetes [62]. It was found that four oxylipins, PGF2$\alpha$, PGE2, 15-keto-PGE2 and 13,14-dihydro-15-keto-PGE2 showed significant differences between lean, obese controls and T2DM patients, as all oxylipin levels were elevated in T2DM patients compared to either the lean or obese controls. No significant differences in oxylipin levels were observed between the lean and obese control groups [62]. Authors further revealed that the combination of PGF2$\alpha$ and 15-keto-PGE2 had the most predictive value to discriminate type 2 diabetic patients from lean and obese controls.

The study of Sroka-Oleksiak et al. [63] demonstrated that diabetic and obese patients have common core microbiota in their duodenum at the phylum level, consisting of Firmicutes, Actinobacteria, and Proteobacteria. Within the phylum Actinobacteria, the relative abundance of the genus Bifidobacterium was significantly lower in both obese and diabetic groups in relation to the control group. Observing these changes also on higher taxonomic levels may initiate a pathogenic effect that is intensified in later parts of the intestine. Thus, the genus Bifidobacterium should be considered in the future in the context of a potential biomarker in the progress of both T2DM and obesity [63]. The main alterations in the gut microbiota of individuals with MetS consist of an increased Firmicutes/Bacteriodetes ratio and a reduced capacity to degrade carbohydrates to short-chain fatty acids, which in turn is related with the metabolic dysfunction of the host organism rather than with obesity itself [7].

## 4. CONCLUSIONS

Metabolic syndrome is a cluster of related metabolic abnormalities, including visceral obesity, dyslipidemia, hyperglycemia, hypertension, and insulin resistance. These metabolic derangements are significant risk factors for cardiovascular diseases and mortality worldwide. Metabolic syndrome is developed gradually, so early diagnosis is important to prevent a number of undesirable metabolic complications. Diagnosis with MetS and the progression of MetS related complications can be detected and monitored via serum biomarkers. For this, classical metabolic and hormonal biomarkers, and inflammatory biomarkers are the most widely used. In last years, additional MetS markers such as oxidative stress parameters, apolipoproteins, oxylipins, gut composition of microbiota, ratio between different types of markers were proposed and actively introduced in clinical practice.

## REFERENCES

[1]   Samson S.L., Garber A.J. Metabolic syndrome. *Endocrinology and metabolism clinics of North America*, **43** (1) (2014), 1–23. doi: 10.1016/j.ecl.2013.09.009

[2]   Bayliak M. Metabolic syndrome, obesity, and Drosophila. *Journal of Vasyl Stefanyk Precarpathian National University*, **7** (4) (2020), 7–18. doi: 10.15330/jpnu.7.4.7-18

[3]   Zhu L., Yang W.J., Spence C.B., Bhimla A., Ma G.X. Lean yet unhealthy: Asian American adults had higher risks for metabolic syndrome than Non-Hispanic White adults with the same body mass index: evidence from NHANES 2011-2016. *Healthcare*, **9** (11) (2021), 1518. doi:10.3390/healthcare9111518

[4]   Bruce K.D., Hanson M.A. The developmental origins, mechanisms, and implications of metabolic syndrome. *The Journal of nutrition*, **140** (3) (2010), 648–652. doi: 10.3945/jn.109.111179

[5]   Bussler S., Penke M., Flemming G., Elhassan Y.S., Kratzsch J., Sergeyev E., Lipek T., Vogel M., Spielau U., Körner A., de Giorgis T., Kiess W. Novel insights in the metabolic syndrome in childhood and adolescence. *Hormone research in paediatrics*, **88** (3-4) (2017), 181–193. doi: 10.1159/000479510

[6]   Saklayen M.G. The global epidemic of the metabolic syndrome. *Current hypertension reports*, **20** (2) (2018), 12. doi: 10.1007/s11906-018-0812-z

[7]   Santos-Marcos J. A., Perez-Jimenez F., Camargo A. The role of diet and intestinal microbiota in the development of metabolic syndrome. *The Journal of nutritional biochemistry*, **70** (2019), 1–27. doi: 10.1016/j.jnutbio.2019.03.017

[8]   McCracken E., Monaghan M., Sreenivasan S. Pathophysiology of the metabolic syndrome. *Clinics in dermatology*, **36** (1) (2018), 14–20.

[9]   Rochlani Y., Pothineni N.V., Kovelamudi S., Mehta J. L. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. *Therapeutic advances in cardiovascular disease*, **11** (8) (2017), 215-225. doi: 10.1177/1753944717711379

[10]  Eckel R.H., Alberti K.G., Grundy S.M., Zimmet P.Z. The metabolic syndrome. *The lancet*, **375** (9710) (2010), 181-183. doi: 10.1016/S0140-6736(09)61794-3

[11]  Cornier M.A., Dabelea D., Hernandez T.L., Lindstrom R.C., Steig A.J., Stob N.R., Van Pelt R.E., Wang H., Eckel R.H. The metabolic syndrome. *Endocrine reviews*, **29** (7) (2008), 777-822. doi: 10.1210/er.2008-0024

[12]  Monteiro R., Azevedo I. Chronic inflammation in obesity and the metabolic syndrome. *Mediators of inflammation*, (2010), 289645. doi: 10.1155/2010/289645

[13]  Bayliak M.M., Abrat O.B. Role of Nrf2 in oxidative and inflammatory processes in obesity and metabolic diseases. In: Deng H. (Ed.) *Nrf2 and its Modulation in Inflammation. Progress in Inflammation Research*, vol. **85**. Springer, Cham, 2020. doi: 10.1007/978-3-030-44599-7_7

[14]  Esser N., Legrand-Poels S., Piette J., Scheen A.J., Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes research and clinical practice*, **105** (2) (2014), 141-150. doi: 10.1016/j.diabres.2014.04.006

[15]  Coelho M., Oliveira T., Fernandes R. Biochemistry of adipose tissue: an endocrine organ. *Archives of medical science: AMS*, **9** (2) (2013), 191–200. doi: 10.5114/aoms.2013.33181

[16]  Ntzouvani A., Fragopoulou E., Panagiotakos D., Pitsavos C., Antonopoulou S. Reduced circulating adiponectin levels are associated with the metabolic syndrome independently of obesity, lipid indices and serum insulin levels: a cross-sectional study. *Lipids in health and disease*, **15** (1) (2016), 140. doi: 10.1186/s12944-016-0311-7

[17]  Emanuela F., Grazia M., Marco D.R., Maria Paola L., Giorgio F., Marco B. Inflammation as a link between obesity and metabolic syndrome. *Journal of nutrition and metabolism*, (2012), 476380. doi: 10.1155/2012/476380

[18]  Belhayara M.I., Mellouk Z., Hamdaoui M.S., Bachaoui M., Kheroua O., Malaisse W.J. Relationship between the insulin resistance and circulating predictive biochemical markers in metabolic syndrome among young adults in western Algeria. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, **13** (1) (2019), 504-509. doi:10.1016/j.dsx.2018.11.019

[19]   Kamso S. Body mass index, total cholesterol, and ratio total to HDL cholesterol were determinants of metabolic syndrome in the Indonesian elderly. *Medical Journal of Indonesia*, **16** (3) (2007), 195-200. doi: 10.13181/mji.v16i3.276

[20]  Skalicky J., Muzakova V., Kandar R., Meloun M., Rousar T., Palicka V. Evaluation of oxidative stress and inflammation in obese adults with metabolic syndrome. *Clinical Chemistry and Laboratory Medicine*, **46** (4) (2008), 499-505. doi: 10.1515/CCLM.2008.096

[21]  Singh R.G., Yoon H.D., Wu L.M., Lu J., Plank L.D., Petrov M.S. Ectopic fat accumulation in the pancreas and its clinical relevance: a systematic review, meta-analysis, and meta-regression. *Metabolism*, 69 (2017), 1-13. doi: 10.1016/j.metabol.2016.12.012

[22]  Aggoun Y. Obesity, metabolic syndrome, and cardiovascular disease. *Pediatric research*, **61** (6) 2007, 653-659. doi: 10.1203/pdr.0b013e31805d8a8c

[23]  de Abreu V.G., Martins C.J.M., de Oliveira P.A.C., Francischetti E.A. High-molecular weight adiponectin/HOMA-IR ratio as a biomarker of metabolic syndrome in urban multiethnic Brazilian subjects. *PLoS One*, **12** (7) (2017), e0180947. doi: 10.1371/journal.pone.0180947

[24]  Zaha D.C., Vesa C., Uivarosan D., Bratu O., Fratila O., Tit D.M., Pantis C., Diaconu C.C., Bungau S. Influence of inflammation and adipocyte biochemical markers on the components of metabolic syndrome. *Experimental and therapeutic medicine*, **20** (1) (2020), 121-128. doi: 10.3892/etm.2020.8663

[25] Tune J.D., Goodwill A.G., Sassoon D.J., Mather K.J. Cardiovascular consequences of metabolic syndrome. *Translational research: the journal of laboratory and clinical medicine*, **183** (2017), 57–70. doi: 10.1016/j.trsl.2017.01.001

[26] Siitonen N., Pulkkinen L., Lindström J., Kolehmainen M., Eriksson J.G., Venojärvi M., Ilanne-Parikka P., Keinänen-Kiukaanniemi S., Tuomilehto J., Uusitupa M. Association of ADIPOQ gene variants with body weight, type 2 diabetes and serum adiponectin concentrations: the Finnish Diabetes Prevention Study. *BMC medical genetics*, **12** (2011), 5. doi: 10.1186/1471-2350-12-5

[27] Sanjari M., Khodashahi M., Gholamhoseinian A., Shokoohi M. Association of adiponectin and metabolic syndrome in women. *Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences*, **16** (12) (2011), 1532–1540.

[28] Yun J.E., Kimm H., Jo J., Jee S.H. Serum leptin is associated with metabolic syndrome in obese and nonobese Korean populations. *Metabolism*, **59** (3) (2010), 424–429. doi: 10.1016/j.metabol.2009.08.012

[29] López-Jaramillo P., Gómez-Arbeláez D., López-López J., López-López C., Martínez-Ortega J., Gómez-Rodríguez A., Triana-Cubillos S. The role of leptin/adiponectin ratio in metabolic syndrome and diabetes. *Hormone molecular biology and clinical investigation*, **18** (1) (2014), 37–45. doi: 10.1515/hmbci-2013-0053

[30] Achari A.E., Jain S.K. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. *International journal of molecular sciences*, **18** (6) (2017), 1321. doi: 10.3390/ijms18061321

[31] Frühbeck G., Catalán V., Rodríguez A., Ramírez B., Becerril S., Salvador J., Portincasa P., Colina I., Gómez-Ambrosi J. Involvement of the leptin-adiponectin axis in inflammation and oxidative stress in the metabolic syndrome. *Scientific reports*, **7** (1) (2017), 6619. doi: 10.1038/s41598-017-06997-0

[32] Zlibut A., Agoston-Coldea L., Mocan T., Bocsan I.C., Mocan L. Biomarkers in metabolic syndrome. In: Zaman Z.S. (Ed.) *Ultimate Guide Insulin*, IntechOpen, 2019. doi: 10.5772/intechopen.79427

[33] Ukkola O. (2009). Ghrelin and metabolic disorders. *Current protein and peptide science*, **10** (1) (2009), 2–7. doi: 10.2174/138920309787315220

[34] McLaughlin T., Abbasi F., Lamendola C., Frayo R.S., Cummings D.E. Plasma ghrelin concentrations are decreased in insulin-resistant obese adults relative to equally obese insulin-sensitive controls. *The Journal of clinical endocrinology and metabolism*, **89** (4) (2004), 1630–1635. doi: 10.1210/jc.2003-031572

[35] Yudkin J.S., Juhan-Vague I., Hawe E., Humphries S.E., di Minno G., Margaglione M., Tremoli E., Kooistra T., Morange P.E., Lundman P., Mohamed-Ali V., Hamsten A., HIFMECH Study Group. Low-grade inflammation may play a role in the etiology of the metabolic syndrome in patients with coronary heart disease: the HIFMECH study. *Metabolism: clinical and experimental*, **53** (7) (2004), 852–857. doi: 10.1016/j.metabol.2004.02.004

[36] Devaraj S., Singh U., Jialal I. Human C-reactive protein and the metabolic syndrome. *Current opinion in lipidology*, **20** (3) (2009), 182–189. doi: 10.1097/MOL.0b013e32832ac03e

[37] Yoon K., Ryu S., Lee J., Park J.D. Higher and increased concentration of hs-CRP within normal range can predict the incidence of metabolic syndrome in healthy men. *Diabetes & Metabolic Syndrome*, **12** (6) (2018), 977–983. doi: 10.1016/j.dsx.2018.06.008

[38] Szalai A.J., McCrory M.A., Xing D., Hage F.G., Miller A., Oparil S., Chen Y.F., Mazzone M., Early R., Henry S.P., Zanardi T.A., Graham M.J., Crooke R.M. Inhibiting C-reactive protein for the treatment of cardiovascular disease: promising evidence from rodent models. *Mediators of inflammation*, **2014** (2014), 353614. doi: 10.1155/2014/353614

[39] Moon Y.S., Kim D.H., Song D.K. Serum tumor necrosis factor-$\alpha$ levels and components of the metabolic syndrome in obese adolescents. *Metabolism*, **53** (7) (2004), 863–867. doi: 10.1016/j.metabol.2004.02.007

[40] Walsh J.M., McGowan C.A., Byrne J.A., Rath A., McAuliffe F.M. The association between TNF-$\alpha$ and insulin resistance in euglycemic women. *Cytokine*, **64** (1) (2013), 208-212. doi: 10.1016/j.cyto.2013.07.001

[41] Sethi J.K., Hotamisligil G.S. Metabolic messengers: tumor necrosis factor. *Nature metabolism*, **3** (10) (2021), 1302–1312. doi: 10.1038/s42255-021-00470-z

[42] Qu D., Liu J., Lau C.W., Huang Y. IL-6 in diabetes and cardiovascular complications. *British journal of pharmacology*, **171** (15) (2014), 3595–3603. doi: 10.1111/bph.12713

[43] Mohammadi M., Gozashti M.H., Aghadavood M., Mehdizadeh M.R., Hayatbakhsh M.M. Clinical significance of serum IL-6 and TNF-$\alpha$ levels in patients with metabolic syndrome. *Reports of biochemistry & molecular biology*, **6** (1) (2017), 74–79.

[44] Kardas F., Akın L., Kurtoglu S., Kendirci M., Kardas Z. Plasma Pentraxin 3 as a biomarker of metabolic syndrome. *Indian journal of pediatrics*, **82** (1) (2015), 35–38. doi: 10.1007/s12098-014-1542-0

[45] Spahis S., Borys J.M., Levy E. Metabolic syndrome as a multifaceted risk factor for oxidative stress. *Antioxidants & Redox Signaling*, **26** (9) (2017), 445–461. doi: 10.1089/ars.2016.6756

[46] Vona R., Gambardella L., Cittadini C., Straface E., Pietraforte D. (2019). Biomarkers of oxidative stress in metabolic syndrome and associated diseases. *Oxidative medicine and cellular longevity*, (2019), 8267234. doi: 10.1155/2019/8267234

[47] Matsuzawa-Nagata N., Takamura T., Ando H., Nakamura S., Kurita S., Misu H., Ota T., Yokoyama M., Honda M., Miyamoto K., Kaneko S. Increased oxidative stress precedes the onset of high-fat diet-induced insulin resistance and obesity. *Metabolism*, **57** (8) (2008), 1071–1077. doi: 10.1016/j.metabol.2008.03.010

[48] Matsuda M., Shimomura I. Increased oxidative stress in obesity: implications for metabolic syndrome, diabetes, hypertension, dyslipidemia, atherosclerosis, and cancer. *Obesity research & clinical practice*, **7** (5) (2013), e330–341. doi: 10.1016/j.orcp.2013.05.004

[49] Bayliak M.M., Abrat O.B., Storey J.M., Storey K.B., Lushchak V.I. Interplay between diet-induced obesity and oxidative stress: comparison between *Drosophila* and mammals. *Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology*, **228** (2019), 18–28. doi: 10.1016/j.cbpa.2018.09.027

[50] Alcalá M., Calderon-Dominguez M., Bustos E., Ramos P., Casals N., Serra D., Viana M., Herrero L. Increased inflammation, oxidative stress and mitochondrial respiration in brown adipose tissue from obese mice. *Scientific reports*, **7** (1) (2017), 16082. doi: 10.1038/s41598-017-16463-6

[51] Brown L.A., Kerr C.J., Whiting P., Finer N., McEneny J., Ashton T. Oxidant stress in healthy normal-weight, overweight, and obese individuals. *Obesity (Silver Spring)*, **17** (3) (2009), 460–466. doi: 10.1038/oby.2008.590

[52] Chrysohoou C., Panagiotakos D.B., Pitsavos C., Skoumas I., Papademetriou L., Economou M., Stefanadis C. The implication of obesity on total antioxidant capacity in apparently healthy men and women: the ATTICA study. *Nutrition, metabolism, and cardiovascular diseases: NMCD*, **17** (8) (2007), 590–597. doi: 10.1016/j.numecd.2006.05.007

[53] Tinahones F.J., Murri-Pierri M., Garrido-Sánchez L., García-Almeida J.M., García-Serrano S., García-Arnés J., García-Fuentes E. Oxidative stress in severely obese persons is greater in those with insulin resistance. *Obesity (Silver Spring)*, **17** (2) (2009), 240–246. doi: 10.1038/oby.2008.536

[54] Mackness M. I., Arrol S., Abbott C., Durrington P. N. (1993). Protection of low-density lipoprotein against oxidative modification by high-density lipoprotein associated paraoxonase. *Atherosclerosis*, **104** (1-2) (1993), 129–135. doi: 10.1016/0021-9150(93)90183-u

[55] Staňková B., Vávrová L., Rychlíková J., Žák A. Changes in paraoxonase 1 activity and concentration of conjugated dienes in connection with number of metabolic syndrome components. *Klinická biochemie a metabolismus*, **24** (45) (2016), 88–93.

[56] Sentí M., Tomás M., Fitó M., Weinbrenner T., Covas M.I., Sala J., Masiá R., Marrugat J. Antioxidant paraoxonase 1 activity in the metabolic syndrome. *The Journal of clinical endocrinology and metabolism*, **88** (11) (2003), 5422–5426. doi: 10.1210/jc.2003-030648

[57] Jing F., Mao Y., Guo J., Zhang Z., Li Y., Ye Z., Ding, Y., Wang J., Jin M., Chen, K. The value of apolipoprotein B/apolipoprotein A1 ratio for metabolic syndrome diagnosis in a Chinese population: a cross-sectional study. *Lipids in health and disease*, **13** (2014), 81. doi: 10.1186/1476-511X-13-81

[58] Fu B.C., Hullar M.A.J., Randolph T.W., Franke A.A., Monroe K.R., Cheng I., Wilkens L.R., Shepherd J.A., Madeleine M.M., Le Marchand L., Lim U., Lampe J.W. Associations of plasma trimethylamine N-oxide, choline, carnitine, and betaine with inflammatory and cardiometabolic risk biomarkers and the fecal microbiome in the Multiethnic Cohort Adiposity Phenotype Study. *The American journal of clinical nutrition*, **111** (6) (2020), 1226–1234. doi: 10.1093/ajcn/nqaa015

[59] Yang J.J., Shu X.O., Herrington D.M., Moore S.C., Meyer K.A., Ose J., Menni C., Palmer N.D., Eliassen H., Harada S., Tzoulaki I., Zhu H., Albanes D., Wang T.J., Zheng W., Cai H., Ulrich C.M., Guasch-Ferré M., Karaman I., Fornage M., Cai Q., Matthews C.E., Wagenknecht L.E., Elliott P., Gerszten R.E., Yu D. Circulating trimethylamine N-oxide in association with diet and cardiometabolic biomarkers: an international pooled analysis. *The American journal of clinical nutrition*, **113** (5) (2021), 1145–1156. doi: 10.1093/ajcn/nqaa430

[60] Andraos S., Jones B., Lange K., Clifford S.A., Thorstensen E.B., Kerr J.A., Wake M., Saffery R., Burgner D.P., O'Sullivan J.M. Trimethylamine N-oxide (TMAO) is not associated with cardiometabolic phenotypes and inflammatory markers in children and adults. *Current developments in nutrition*, **5** (1) (2021), nzaa179. doi: 10.1093/cdn/nzaa179

[61] Kornilov S.A., Lucas I., Jade K., Dai C.L., Lovejoy J.C., Magis A.T. Plasma levels of soluble ACE2are associated with sex, metabolic syndrome, and its biomarkers in a large cohort, pointing to a possible mechanism for increased severity in COVID-19. *Critical care*, **24** (1) (2020), 452. doi: 10.1186/s13054-020-03141-9

[62] Tans R., Bande R., van Rooij A., Molloy B.J., Stienstra R., Tack C.J., Wevers R.A., Wessels H.J.C.T., Gloerich J., van Gool A.J. Evaluation of cyclooxygenase oxylipins as potential biomarker for obesity-associated adipose tissue inflammation and type 2 diabetes using targeted multiple reaction monitoring mass spectrometry. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, **160** (2020), 102157. doi: 10.1016/j.plefa.2020.102157

[63] Sroka-Oleksiak A., Młodzińska A., Bulanda M., Salamon D., Major P., Stanek M., Gosiewski T. Metagenomic analysis of duodenal microbiota reveals a potential biomarker of dysbiosis in the course of obesity and type 2 diabetes: a pilot study. *Journal of clinical medicine*, **9** (2) (2020), 369. doi: 10.3390/jcm9020369

**Address**:  Viktoria Hurza, Myroslava Vatashchuk, Maria Bayliak, Vasyl Stefanyk Precarpathian National University, 57 Shevchenko Str., Ivano- Frankivsk, 76018 Ukraine.

**E-mail:** viktoriia.hurza@pnu.edu.ua, myroslava.vataschuk@pnu.edu.ua, maria.bayliak@pnu.edu.ua.

_____

Метаболічний синдром — це патологічний багатокомпонентний стан, що характеризується підвищенням рівня триацилгліцеридів, зниженням рівня ліпопротеїнів високої щільності, інсулінорезистентністю, підвищенням артеріального тиску та глюкози натще. Разом ці відхилення підвищують ризик розвитку серцево-судинних захворювань та цукрового діабету 2 типу. Переїдання та сидячий спосіб життя, що ведуть до надлишкової маси тіла та ожиріння, вважаються основними факторами розвитку метаболічного синдрому. Патогенез метаболічного синдрому дуже складний і не до кінця вивчений. Дослідження підтверджують концепцію про те, що про-/антиоксидантний дисбаланс і низькоінтенсивне запалення можуть відігравати ключові ролі у розвитку метаболічного синдрому. Діагностику метаболічного синдрому та розвиток пов'язаних з ним ускладнень можна виявити та контролювати за допомогою специфічних біомаркерів у сироватці крові. У цій роботі ми описуємо класичні метаболічні, гормональні та про-/протизапальні маркери, які найчастіше використовуються для діагностики та дослідження метаболічного синдрому. Вони включають ліпідний профіль крові (триацилгліцериди, загальний холестерин, ліпопротеїни низької та високої щільності), артеріальний тиск, рівень глюкози натще та індекс HOMA, рівні протизапального адипонектину, прозапальних маркерів – С-реактивного білка та цитокінів (TNF-$\alpha$, IL-1$\beta$, IL-6) та ін.) Ми також аналізуємо переваги додаткових критеріїв таких, як рівень окисних пошкоджень, гормонів

апетиту (лептин та грелін), аполіпопротеїнів та оксиліпінів, склад мікробіоти кишечника та рівні метаболітів мікробіому, а також співвідношення між різними показниками як допоміжних біомаркерів метаболічного синдрому та серцево-судинних захворювань.

**Ключові слова:** метаболічний синдром, вісцеральний жир, запалення, оксидативний стрес.