Review article

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Metabolic Syndrome – A Silent Detonation for the cardiovascular system

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Metabolic syndrome (MetS) represents a major global health concern. It forms a cluster of metabolic dysregulations including insulin resistance, atherogenic dyslipidemia, visceral obesity and hypertension. The pathogenesis of MetS encompases multiple genetic and acquired entities that fall under the umbrella of insulin resistance, chronic low-grade inflammation and oxidative stress. In addition to the increased prevalence of coronary artery disease, the syndrome is associated with more extensive vascular damage. High thrombogenic potential and chronic inflammation jointly contribute to cardiac remodeling, alterations in adhesion and coagulation pathways, ultimately reducing the functional capacity of affected organs. Each component of MetS is known to independently affect cardiac structure and function, but their combination under this syndrome seems to carry additional risk. Thus, cardiac dysfunction can occur in patients with normal coronary artery disease or other etiologies, suggesting the existence of specific cardiomyopathies in patients with MetS.

Metabolic syndrome significantly increases cardiovascular risk through complex pathophysiological mechanisms. Early identification and correction of risk factors are crucial for prevention and effective management of patients with this syndrome.

Keywords: metabolic syndrome, insulin resistance, chronic inflammation, cardiovascular diseases, cardiomyopathy

Pregledni rad

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Metabolički sindrom – tiha detonacija za kardiovaskularni sistem

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Metabolički sindrom (MetS) predstavlja značajan globalni zdravstveni problem. On obuhvata skup metaboličkih poremećaja, uključujući insulinsku rezistenciju, aterogenu dislipidemiju, visceralnu gojaznost i arterijsku hipertenziju. Patogeneza MetS-a uključuje brojne genetske i stečene faktore koji se ujedinuju kroz mehanizme insulinske rezistencije, hronične inflamacije i oksidativnog stresa. Pored povećane prevalencije koronarne arterijske bolesti, ovaj sindrom je povezan i sa značajnim oštećenjem vaskularnog sistema. Visok trombogeni potencijal i hronična inflamacija zajednički doprinose remodelovanju srca, promenama u adhezionim i koagulacionim putevima, što na kraju dovodi do smanjenja funkcionalnog kapaciteta kardiovaskularnog sistema. Poznato je da svaka pojedinačna komponenta MetS-a nezavisno utiče na strukturu i funkciju srca, ali njihova kombinacija u okviru ovog sindroma nosi dodatni kardiovaskularni rizik. Shodno tome, srčana insuficijencija može nastati i kod

pacijenata bez značajne koronarne arterijske bolesti ili drugih prepoznatljivih etioloških faktora, što ukazuje na postojanje specifičnih oblika kardiomiopatije kod bolesnika sa MetS-om.

Metabolički sindrom značajno povećava kardiovaskularni rizik putem složenih patofizioloških mehanizama. Rana identifikacija i korekcija faktora rizika su od ključnog značaja za prevenciju i efikasno lečenje pacijenata sa ovim sindromom.

Ključne reči: metabolički sindrom, insulinska rezistencija, hronična inflamacija, kardiovaskularne bolesti, kardiomiopatija

Metabolic syndrome (MetS) is becoming a global health problem that is increasingly present in today´s population worldwide due to sedentary lifestyle, obesity, and genetic predisposition (1). MetS represents a complex metabolic disorder that includes traditional risk factors for cardiovascular disease (CVD): abdominal obesity, hypertension, elevated triglycerides, low HDL cholesterol, and elevated blood glucose levels (2).

Patients with MetS face a significantly higher long-term risk of cardiovascular morbidity compared with those without this syndrome. According to available data from relevant studies, the risk of CVD in patients with MetS is two to three fold times higher compared with those without it (3). The etiology of CVD in patients with MetS may involve: coronary atherosclerotic disease, arterial hypertension, left ventricular hypertrophy, diastolic dysfunction, endothelial dysfunction, coronary micro-vascular disease and autonomic dysfunction (4).

The association between MetS and cardiovascular disease is further emphasized by the high prevalence of MetS among patients with established CVD. For example,the prevalence of MetS has been suggested to be 39,2% in patients undergoing percutaneous coronary intervention (5). Furthermore,the incidence of MetS in patients with acute myocardial infarction is 46%, while in those with acute coronary syndrome it is 43.4% (6). These findings clearly demonstrate the strong link between MetS and CVD. Boulon C et al. demonstrated that patients with coronary artery disease, despite optimal medical therapy and active treatment, continue to have an increased long-term risk of recurrent cardiovascular events (7). These findings were further confirmed in a retrospective study by Lii Xiao and colleagues, which included 55 relevant studies and more than 160,000 patients. This study showed that patients with coronary artery disease and MetS have an increased risk of all-cause mortality, cardiovascular death, myocardial infarction, stroke, and repeat revascularization. Notably, dyslipidemia and abnormal glucose metabolism carried the highest risk among all MetS components, while obesity when assessed using body mass index showed a negative correlation with new cardiovascular events (8) .

The exact pathophysiological mechanism underlying MetS remains unidentified but it was suggested that the primary trigger to the syndrome was visceral adiposity, followed by insulin resistance, neurohormonal activation, and chronic inflammation (9). Insulin resistance plays a

central role in the etiopathogenesis of MetS and represents a mediator of external influences such as visceral obesity, stress, and cardiorespiratory fitness. Insulin significantly affects glucose and lipid metabolism, blood pressure regulation, and vascular activity (1). Importantly, insulin resistance alone is insufficient to impair glucose metabolism; dysfunction of pancreatic β-cells is also required. Similarly, the effect of insulin resistance on lipid metabolism, blood pressure levels, and endothelial function arises only when additional disturbances occur within these multifactorial homeostatic systems. Thus, multiple simultaneous abnormalities must be present for MetS to develop (10).

Visceral obesity has been identified as a primary trigger of MetS and is included as a key diagnostic criterion. Visceral adipose tissue produces significantly higher levels of adipocytokines, collectively referred to as adipokines, compared with subcutaneous adipose tissue (11). Circulating adiponectin levels are inversely correlated with body mass index, with a stronger association observed for visceral rather than subcutaneous adiposity. Higher plasma adiponectin concentrations are associated with improved insulin sensitivity (12). In visceral obesity, adiponectin levels decrease as a consequence of macrophage infiltration into adipose tissue and the subsequent release of pro-inflammatory cytokines during chronic low-grade inflammation, leading to the development of insulin resistance (13). Insulin resistance results in impaired peripheral glucose uptake, reduced suppression of hepatic glucose production, and dysregulated lipolysis. Impaired glucose uptake and inadequate suppression of hepatic glucose production contribute to elevated fasting plasma glucose levels, while increased lipolysis leads to elevated circulating free fatty acids (14). Reduced adiponectin levels are also associated with increased blood pressure, elevated triacylglycerol concentrations, and decreased high-density lipoprotein cholesterol levels (15). Hypoadiponectinemia contributes to the development of hypertension by impairing endothelium-dependent vasoreactivity (12). Additionally, increased renal sodium reabsorption represents another proposed mechanism underlying hypertension in visceral obesity. This effect is mediated through activation of the renin–angiotensin–aldosterone system, which may result from mechanical compression of the kidneys by visceral fat and heightened sympathetic nervous system activity (16).

As previously noted, insulin resistance leads to elevated glucose and insulin levels, promoting oxidative stress, chronic inflammation, and endothelial dysfunction (17). Chronic inflammation plays a significant role in patients with MetS. Elevated levels of CRP, TNF-α, fibrinogen and IL-6 are well documented in these individuals, increase inflammation and further insulin resistance (18). Inflammation occupies a central position in the process of atherosclerosis, accelerating the process of atherosclerosis—the leading cause of coronary artery disease (19). Takeno et al. demonstrated that patients with MetS have significantly higher CRP levels than those without MetS, and elevated CRP was associated with higher risk of new cardiovascular events (20). Inflammation not only accelerates but also broadens the extent of atherosclerosis. Patients with MetS were shown to have a significantly greater prevalence of multivessel coronary artery disease and worse prognosis, with increased incidence of recurrent cardiovascular events. A study conducted in our region among patients surviving STEMI showed that the presence of MetS significantly contributes to the appearance of more complex coronary lesions, assessed via the SYNTAX score. Patients with MetS had significantly higher SYNTAX scores and the score itself was an independent predictor of poor prognosis. Although MetS was associated with higher incidence of new adverse events, it did not impact overall mortality (21).

TNF-α beside effects on vascular system, can induce myocardial hypertrophy, activate cardiomyocyte apoptosis, and impair myocardial contractility. It also promotes left ventricular dilation via extracellular matrix degradation. These structural and functional changes lead to heart failure (22). IL-6 has similarly been shown to play a significant role in the development of left ventricular hypertrophy and left ventricular dysfunction (23) Accumulating evidence indicates that interleukin-6 (IL-6) plays a critical role in the progression of heart failure through complex interactions with the vascular endothelium and neurohormonal regulatory systems, thereby promoting volume overload and systemic congestion. Furthermore, IL-6 has been shown to downregulate titin phosphorylation, leading to increased cardiomyocyte passive stiffness and contributing to diastolic dysfunction. (22,24).

The presence of some components of MetS can significantly lead to the increase of oxidative stress, which is strongly associated with cardiovascular complications. Under pathological conditions such as obesity, chronic inflammation, and hyperglycemia, excessive generation of

reactive oxygen species (ROS) is induced through the activation of enzymatic pathways within the cytosol, cellular membranes, and mitochondria. A sustained imbalance between increased ROS production and impaired antioxidant defense systems results in oxidative stress. This state of oxidative stress causes intracellular damage and disruption of redox signaling, leading to the irreversible accumulation of oxidatively modified biomolecules. Consequently, oxidative stress promotes endothelial dysfunction and plays a central role in the initiation and progression of atherosclerotic disease (25). According to several studies sustained hyperglycemia is considered the principal trigger of oxidative stress in MetS, accelerating vascular damage and atherosclerosis through multiple mechanisms, including:

a. Non-enzymatic glycation of proteins and lipids, altering their structure and impairing enzymatic function;
b. Interaction of glycated proteins with their receptors, inducing oxidative stress and inflammation;
c. Polyol pathway activation;
d. Hexosamine pathway activation;
e. Protein kinase activation leading to altered growth factor expression (26).

In addition to the previously described mechanisms, chronic activation of the sympathetic nervous system and RAAS represents a key pathophysiological process in MetS (16). Persistent stimulation of these neurohumoral pathways exerts systemic effects that are detrimental to the cardiovascular system. Among the most significant consequences are elevated blood pressure due to sustained peripheral vasoconstriction and an increased heart rate. To maintain adequate tissue perfusion during neurohormonal activation, the heart initially compensates by enhancing myocardial contractility (27). However, the combined increase in contractile force and heart rate results in heightened myocardial energy demand. In MetS, this demand cannot be efficiently met, as energy production is impaired due to a metabolic shift from glucose utilization to fatty acid oxidation secondary to insulin resistance (28). Consequently, the myocardium becomes unable to sustain compensatory mechanisms, leading to cardiomyocyte hypertrophy. With ongoing exposure to these stressors, pathological cardiac remodeling ensues, ultimately progressing toward heart

failure (29). Abnormal renal sodium reabsorption is also suggested as a possible mechanism causing the appearance of hypertension in obese patients with MetS. The increased absorption of sodium via kidneys is directly related to the activation of RAAS. The activation of RAAS system is considered to be triggered by the direct pressure of visceral obesity to the kidneys and the activation of the sympathetic nervous system (1).

Cardiac dysfunction in MetS arises from the combined effects of its individual components, each of which independently influences cardiac structure and function; however, their coexistence within the syndrome confers an additional and synergistic cardiovascular risk (30). Consequently, cardiac dysfunction may develop in patients in the absence of significant coronary artery disease or other conventional etiologies, supporting the concept of distinct cardiomyopathies, including obesity-related cardiomyopathy, diabetic cardiomyopathy, and insulin resistance–related cardiomyopathy. As summarized in Figure 1, obesity, diabetes, and insulin resistance share several common pathophysiological mechanisms that contribute to myocardial dysfunction. Nevertheless, each component of MetS is also characterized by specific and unique molecular and cellular mechanisms that further modulate cardiac structure and function (17).

Obesity-related cardiomyopathy is a distinct myocardial disorder that may occur independently or in association with dyslipidemia and represents an important cause of heart failure in humans (31). Chronic obesity results in increased hemodynamic load due to expanded blood volume and cardiac output, leading to cardiac hypertrophy and left ventricular remodeling (17). In addition, excessive lipid accumulation within cardiomyocytes and altered substrate metabolism contribute to myocardial lipotoxicity, mitochondrial dysfunction, and impaired energy utilization. Adipose tissue functions as an active endocrine organ, releasing adipokines that significantly influence myocardial structure and function. Elevated circulating leptin levels are associated with adverse outcomes in heart failure and coronary artery disease, while reduced adiponectin levels correlate with metabolic syndrome, diabetes mellitus, and an increased risk of myocardial infarction and heart failure. Experimental studies demonstrate that reduced adiponectin promotes left ventricular hypertrophy, highlighting its antihypertrophic properties (32). Resistin further contributes to myocardial dysfunction by inducing cardiac hypertrophy and reducing myocardial contractility (33). Additionally, increased levels of fatty-acid binding protein four, a fat-specific factor strongly associated with metabolic syndrome, impair cardiac function through modulation of intracellular

calcium handling (34). These combined metabolic, inflammatory, and structural alterations predominantly lead to diastolic dysfunction, with systolic impairment developing in advanced stages. Ultimately, obesity-related cardiomyopathy significantly increases the risk of heart failure and adverse cardiovascular outcomes.

Diabetic cardiomyopathy is a distinct myocardial disorder associated with diabetes mellitus and occurs independently of hypertension and coronary artery disease. Diabetes mellitus markedly increases the risk of heart failure, with cardiovascular disease occurring 2–3 times more frequently in diabetic patients and being associated with poorer survival (17). According to the molecular theory of diabetic cardiomyopathy, chronic hyperglycemia represents the primary pathogenic stimulus, inducing metabolic and molecular abnormalities at the level of cardiac myocytes (35). Impaired insulin signaling leads to reduced myocardial glucose utilization and a compensatory increase in fatty acid oxidation, resulting in mitochondrial dysfunction and increased oxidative stress. Hyperglycemia promotes inflammatory signaling pathways and the accumulation of advanced glycation end products, contributing to myocardial stiffness and interstitial fibrosis. Enhanced deposition of glycosylated glycogen further exacerbates structural remodeling of the diabetic myocardium. Additionally, abnormalities in intracellular calcium handling, including reduced activity of sarco(endo)plasmic reticulum Ca^{2+}-ATPase, impair myocardial relaxation (17). These molecular and cellular alterations primarily manifest as diastolic dysfunction in the early stages of the disease. With disease progression, systolic dysfunction may develop. Ultimately, these pathological changes predispose diabetic patients to the development of heart failure.

MetS and insulin resistance are linked to abnormalities in left ventricular diastolic function and to structural remodeling of the myocardium, thereby contributing to the development of heart failure independently of other well-established risk factors such as diabetes mellitus and obesity (36). In addition, the isolated impact of insulin resistance on cardiac function, in the absence of the systemic disturbances characteristic of MetS, has been explored using a mouse model with cardiomyocyte-specific deletion of insulin receptors (37). Evidence from this model suggests that insulin resistance–induced cardiac dysfunction is mediated through several mechanisms, including

dysregulated myocardial substrate metabolism, persistent reactivation of the fetal β-myosin heavy chain isoform, impaired angiogenesis, and mitochondrial dysfunction (17).

In summary, MetS represents a cluster of traditional cardiovascular risk factors that identifies individuals at substantially increased cardiovascular risk. This frequently underrecognized and undertreated condition, primarily driven by abdominal obesity and insulin resistance, predisposes affected individuals to the development of cardiovascular disease and type 2 diabetes mellitus. The clinical diagnosis of MetS serves as a valuable tool for identifying patients at heightened cardiovascular risk and provides an opportunity for early intervention through aggressive lifestyle modification and appropriate medical therapy. Furthermore, the diagnosis of MetS may be used as a complementary approach to refine cardiovascular risk assessment derived from established risk prediction models, such as cardiovascular risk scoring systems.

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