Metabolički sindrom – mit ili stvarnost u endokrinološkoj ordinaciji

Metabolic Syndrome – Myth or Reality in the Endocrinology Clinic

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SAŽETAK: Metabolički je sindrom čest klinički problem koji podrazumijeva skup međusobno povezanih stanja: arterijsku hipertenziju, dislipidemiju, hiperglikemiju i centralni tip pretilosti. Važan je zato što su u ovakvih pacijenata znatno povećani kardiovaskularni rizik te rizik od razvoja šećerne bolesti tipa 2. Ovi se metabolički poremećaji češće pojavljuju udruženo te zajedno znatno povećavaju rizik u usporedbi sa svakim poremećajem zasebno. U osnovi patogeneze metaboličkog sindroma jesu pretilost i inzulinska rezistencija, no određenu ulogu imaju kronično proinflamatorno stanje, endotelijalna disfunkcija i prokoagulantno stanje. Liječenje je usmjereno na promjenu životnih navika i redovitu tjelesnu aktivnost, čime se postiže poboljšanje svih metaboličkih poremećaja u sklopu ovog sindroma. Farmakoterapija je usmjerena na smanjenje specifičnih čimbenika rizika za kardiovaskularne bolesti kada osnovne mjere zdravog načina života ne dovedu do željenog učinka, a krajnji je cilj izbjeći nastanak sustavnih učinaka metaboličkog sindroma.

SUMMARY: Metabolic syndrome is a common clinical problem that encompasses interconnected conditions: hypertension, dyslipidemia, hyperglycemia, and central obesity. It is important because these patients have significantly increased cardiovascular risk and risk of developing Type 2 diabetes. These metabolic disorders more commonly manifest as a syndrome, and together they significantly increase risk in comparison with a single isolated metabolic disorder. Obesity and insulin resistance seem to play a major role in the pathogenesis of metabolic syndrome. Chronic proinflammatory state, endothelial dysfunction, and procoagulant condition contribute as well. Lifestyle modification is the initial intervention of choice, thereby improving all metabolic disorders that are part of this syndrome. Pharmacological treatment should be considered in order to reduce specific risk factors for cardiovascular disease when lifestyle measures fail. The ultimate goal of treatment is the reduction of the systemic effects of metabolic syndrome.

KLJUČNE RIJEČI: metabolički sindrom, inzulinska rezistencija, kardiovaskularni rizik, šećerna bolest, pretilost.

KEYWORDS: metabolic syndrome, insulin resistance, cardiovascular risk, diabetes mellitus, adiposity.

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Kontroverze vezane za naziv i definiciju

Niz godina postoje kontroverze vezane za postojanje metaboličkog sindroma. Definira se kao skup međusobno povezanih stanja koji uključuje arterijsku hipertenziju, dislipidemiju (podrazumijeva povišene trigliceride i/ili snižen HDL kolesterol), hiperglikemiju i centralni tip pretilosti. Važan je u svakodnevnom kliničkom radu jer se pokazalo da tijekom razdoblja od 5 do 10 godina rizik od razvoja šećerne bolest tipa 2 povećava oko pet puta, a rizik od kardiovaskularne bolesti

Controversies related to the terminology and definition

A number of controversies have existed for years regarding the existence of metabolic syndrome. It is defined as a set of interconnected conditions that include arterial hypertension, dyslipidemia (entailing elevated triglycerides and/or lowered HDL-cholesterol), hyperglycemia, and central obesity. It is important in everyday clinical work because it has been shown that it increases the risk for the development of Type 2 diabetes by approximately five times, and doubles the risk of

dvostruko[1]. Metabolički je sindrom, s obzirom na urbanizaciju, sedentarni stil modernog života i povećanu incidenciju pretilosti, veliki javnozdravstveni i klinički izazov. Sve veći dio svjetske populacije prekomjerne je tjelesne težine, ne pridržava se zdravih životnih navika, unosi hranu velike kalorijske vrijednosti i ne kreće se, što u konačnici uzrokuje stanja i bolesti karakteristične za metabolički sindrom.

Sam je naziv u širokoj primjeni od 2001. godine, no tijekom prošlosti bilo je dosta kontroverzi vezanih za naziv i definiciju. Prvi put ga 1988. godine spominje *Gerald Reaven*, koji je tada skovao termin „sindrom X" kako bi opisao povezanost između inzulinske rezistencije i pretilosti, dislipidemije, intolerancije glukoze i arterijske hipertenzije[2]. Međutim, još davne, 1923. godine švedski liječnik *Kylin* prvi je primijetio povezanost hipertenzije, hiperglikemije i uloga (gihta)[3].

Različite su organizacije tijekom prošlosti pokušavale, u odsutnosti jasnih dijagnostičkih testova, na temelju određenih kriterija definirati metabolički sindrom. Godine 1999. Svjetska zdravstvena organizacija (SZO) predložila je definiciju prema kojoj je za postavljanje dijagnoze metaboličkog sindroma nužna prisutnost intolerancije glukoze ili inzulinske rezistencije, uz najmanje dva poremećaja kao što su arterijska hipertenzija, centralni tip pretilosti i dislipidemija[4]. Uslijedila je revizija definicije dvije godine poslije, a proveo ju je *National Cholesterol Education Program* (NCEP) na temelju istih kriterija, ali bez nužnosti postojanja intolerancije glukoze[5]. U međuvremenu su *National Cholesterol Education Programme Adult Treatment Panel III* (NCEP ATP III) i *American Association of Clinical Endocrinologists* (AACE) dali svoje komentare o metaboličkom sindromu te se usmjerili na potencijalno povećan kardiovaskularni rizik. Međunarodna dijabetološka federacija (IDF) konačno je zadnja dala definiciju metaboličkog sindroma 2005. godine, prema kojoj je centralni tip debljine (mjeren opsegom struka), uz druge kriterije, prijeko potreban uvjet za postavljanje dijagnoze metaboličkog sindroma[6]. Upravo je IDF, uzevši u obzir opseg struka za specifične populacije, uvažila etničke i rasne osobitosti i razlike kod metaboličkog sindroma te u konačnici i razlike u kardiovaskularnom riziku i riziku od razvoja šećerne bolesti.

Iako neki stručnjaci poriču postojanje metaboličkog sindroma, evidentno je da se spomenuti metabolički poremećaji češće pojavljuju udruženo te zajedno znatno povećavaju kardiovaskularni rizik u usporedbi s rizikom koji nosi svaki poremećaj zasebno. Također, rizik se dodatno povećava kako raste broj poremećaja u metaboličkom sindromu.

Epidemiologija metaboličkog sindroma

Prevalencija metaboličkog sindroma varira od < 10 % do čak > 84 %, ovisno o ispitivanoj populaciji, životnoj sredini (urbana ili ruralna), dobi, spolu te etničkoj pripadnosti ispitivane skupine, ali, naravno, i o samoj definiciji[7]. IDF procjenjuje da četvrtina svjetske populacije ima metabolički sindrom. Češći je u osoba većeg indeksa tjelesne mase (ITM) i starijih osoba, no pokazalo se da je češći i u žena u postmenopauzi, u kojih incidencija iznosi od 32,6 % do 41,5 %[8].

Patofiziologija metaboličkog sindroma

Osnovni poremećaji u metaboličkom sindromu jesu inzulinska rezistencija i kompenzatorna hiperinzulinemija, no važnu ulogu imaju i kronično proinflamatorno stanje, endotelijalna disfunkcija i prokoagulantno stanje.

cardiovascular disease over a period of 5-10 years[1]. Metabolic syndrome represents a significant public health and clinical challenge due to urbanization, the sedentary modern lifestyle, and increased incidence of obesity. An increasing number of people in the global population are overweight, do not adhere to healthy lifestyle habits, consume high-calorie foods, and lead sedentary lifestyles, which ultimately leads to conditions and diseases characteristic of metabolic syndrome.

The term itself has been in widespread use since 2001, but there have been some controversies regarding the term and its definition in the past. It was mentioned for the first time in 1988 by Gerald Reaven, who coined the term "syndrome X" to describe the association between insulin resistance and obesity, dyslipidemia, glucose intolerance, and arterial hypertension[2]. However, the Swedish physician Kylin was the first to notice the association between hypertension, hyperglycemia, and gout as early as 1923[3].

Different organizations in the past have tried to define metabolic syndrome on the basis of specific criteria in the absence of clear diagnostic tests. The World Health Organization (WHO) proposed a definition in 1999, according to which the establishment of the diagnosis of metabolic syndrome requires the presence of glucose intolerance or insulin resistance with at least two concurrent disorders such as arterial hypertension, central obesity, and dyslipidemia[4]. The definition was revised two years later by the National Cholesterol Education Program (NCEP) on the basis of the same criteria, but without requiring the existence of glucose intolerance[5]. In the meantime, the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) and American Association of Clinical Endocrinologists (AACE) gave their own comments on metabolic syndrome and focused on the potentially increased cardiovascular risk. The International Diabetes Federation (IDF) finally presented a definition of metabolic syndrome in 2005, according to which the central type of obesity (measured by waist circumference) was, along with other criteria, a requirement for the establishment of the diagnosis of metabolic syndrome[6]. It was IDF that, taking the weight circumferences of specific populations into consideration, addressed the unique characteristics and differences of ethnic and racial groups in metabolic syndrome, which ultimately result in differences in cardiovascular risk and risk of diabetes.

Although some experts deny the existence of metabolic syndrome, it is evident that the abovementioned metabolic disorders more commonly manifest together, significantly increasing cardiovascular risk in comparison with the risk carried by each disorder individually. The risk also increases with the number of disorders present in a case of metabolic syndrome.

Epidemiology of metabolic syndrome

The prevalence of metabolic syndrome varies from <10 % to as much as >84 % depending on the examined population, urban or rural setting, age, sex, and ethnic background of the examined group, and of course on the definition of the syndrome[7]. IDF estimates that one quarter of the global population has metabolic syndrome. It is more common in persons with higher body mass index (BMI) and older persons, but it has also been found to be more common in women in menopause, where the incidence is between 32.6 to 41.5 %[8].

Na inzulinsku rezistenciju, koja se može definirati kao suboptimalan biološki odgovor na normalnu razinu inzulina, utječu genetski čimbenici i način života. Prekomjerna tjelesna težina i tjelesna aktivnost su dvije najvažnije varijable načina života koje u velikom mjeri (50 %) utječu na inzulinsku rezistenciju, dok preostalih 50 % ima podlogu u genskom opterećenju. Mnoga tkiva uključujući mišiće, jetru i masno tkivu mogu biti rezistentna na inzulin. Inzulinska rezistencija ima negativne učinke na metabolizam glukoze, ali i reproduktivni sustav, kožne promjene i muskuloskeletni sustav (prikazano u **Tablici 1**).

Poznato je da je visceralno masno tkivo aktivan organ koji luči brojne proinflamatorne i antiinflamatorne citokine iz adipocita, što je facilitirano infiltracijom masnoga tkiva makrofagima[9]. U metaboličkom je sindromu razina proinflamatornih citokina (leptin, IL-6 i TNF-α) povišena, a antiinflamatornih (adiponektin) smanjena. Ovakva neravnoteža u prilog kroničnoga inflamatornog stanja dovodi do disfunkcije endotelnih stanica, što uzrokuje gubitak njihovih antitrombotskih, vazodilatatornih i antiaterogenih osobina.

U novije vrijeme ima sve više dokaza da natriuretski peptidi (NP) imaju određenu ulogu u patofiziologiji metaboličkog sindroma[10]. Riječ je o „srčanim hormonima" koji se luče u atrijima i ventrikulima srca te u endotelnim stanicama, a važni su za homeostazu i kontrolu vode u tijelu, unosu natrija, transportu kalija, lipolizi u adipocitima te u regulaciji tlaka. Nedavna su istraživanja pokazala insuficijenciju NP-a u pacijenata sa šećernom bolesti tipa 2 i u pretilih. U tijeku su istraživanja koja bi mogla otvoriti prostor za nove terapijske mogućnosti djelovanjem na NP sustav.

Liječenje

Budući da nije poznat jedinstveni uzrok metaboličkog sindroma, ne može se niti liječiti kao takav, no konačni je cilj smanjenje kardiovaskularnog rizika. Kako su u osnovi metaboličkog sindroma pretilost i inzulinska rezistencija, temelj je liječenja, prije svega, pridržavanje zdravih životnih navika, uravnotežena prehrana i redovita tjelesna aktivnost. Pokazalo se da ove mjere djeluju na poboljšanje svih metaboličkih poremećaja koji su dio metaboličkog sindroma. Farmakoterapija je usmjerena na smanjenje specifičnih čimbenika rizika za kardiovaskularne bolesti kada se spomenutim osnovnim mjerama zdravoga stila života ne postignu željeni učinci, a krajnji je cilj izbjeći nastanak sustavnih učinaka metaboličkog sindroma (**Tablica 1**).

Pathophysiology of metabolic syndrome

The basic disorder in metabolic syndrome is insulin resistance and the compensatory hyperinsulinemia, but chronic proinflammatory condition, endothelial dysfunction, and procoagulatory condition play an important role as well.

Insulin resistance, which can be defined as a suboptimal biological response to a normal level of insulin, is influenced by genetic and lifestyle factors. Excess body weight and physical activity are the two most important lifestyle variables with a large (50 %) influence on insulin resistance, while the other 50 % is based on genetic burden. Many tissues, including the muscles, liver, and fat tissue, can be resistant to insulin. Insulin resistance has negative effects on glucose metabolism but also on the reproductive system, skin changes, and the musculoskeletal system (shown in **Table 1**).

It is known that visceral fat tissue is an active organ secreting numerous proinflammatory and anti-inflammatory cytokines from adipocytes, which is facilitated by the macrophage infiltration of the fat tissue[9]. In metabolic syndrome, the levels of proinflammatory cytokines (leptin, IL-6, and TNF-α) are elevated, while the levels of anti-inflammatory cytokines (adiponectin) are reduced. Such disbalance in favor of chronic inflammatory states leads to dysfunction of endothelial cells, which causes the loss of their antithrombotic, vasodilatory, and antiatherogenic characteristics.

Recently, there has been an increasing amount of evidence indicating that natriuretic peptides (NP) have a certain role in the pathophysiology of metabolic syndrome[10]. These are "heart hormones" that are secreted in the atriums and ventricles of the heart as well as endothelial cells, and are important for homeostasis and controlling water balance, sodium, potassium transport, lipolysis in adipocytes, and blood pressure regulation. Recent studies have found NP insufficiency in obese patients and in patients with Type 2 diabetes. Studies are underway that could create opportunities for new therapeutic possibilities by acting upon the NP system.

Treatment

Since there is no known singular cause of metabolic syndrome, it cannot be treated as such, however the ultimate goal is reducing cardiovascular risk. Because obesity and insulin resistance form the base of metabolic syndrome, treatment is based primarily on adherence to healthy lifestyle habits,

TABLE 1. Systemic effects of metabolic syndrome (adapted from Cardiol Res Pract. 2014;2014:943162.)

Cardiovascular system	Coronary heart disease, myocardial infarction, cerebrovascular accident
Kidney	Microalbuminuria, focal segmental glomerulosclerosis, hyperfiltration, hypofiltration, chronic kidney disease
Liver	NASH, NAFLD, liver fibrosis and cirrhosis
Eyes	Nondiabetic retinopathy, cataract, glaucoma, oculomotor nerve palsy, central retinal artery occlusion
Sleep	OSA
Reproductive system	Hypogonadism, erectile dysfunction, PCOS
Cancers	Breast, pancreas, prostate
Skin	Acantosis nigricans, SLE, lichen planus, androgenetic alopecia, psoriasis

NASH = nonalcoholic steatohepatitis; NAFLD = nonalcoholic fatty liver disease; OSA = obstructive sleep apnea; PCOS = polycystic ovarian syndrome; SLE = systemic lupus erythematosus.

Prije svega u liječenju metaboličkog sindroma važno je smanjenje tjelesne težine. Pokazalo se da smanjenje od samo 10 % može znatno smanjiti razinu triglicerida i povećati HDL kolesterol[11] te povoljno utjecati na arterijsku hipertenziju i hiperglikemiju. Postiže se pridržavanjem zdravih životnih navika i vježbanjem, no u obzir dolaze bihevioralna terapija i barijatrijska kirurgija. Zanimljivo je da uklanjanje masnoga tkiva liposukcijom ne poboljšava inzulinsku rezistenciju niti smanjuje kardiovaskularni rizik, što upućuje na to da je negativna energijska ravnoteža uzrokovana upravo prehranom i vježbanjem nužna za postizanje metaboličkih prednosti gubitka tjelesne težine[12]. Osobito je zanimanje zadnjih godina izazvao liraglutid, glukagonu sličan peptid-1 (GLP-1) koji se uspješno upotrebljava za liječenje šećerne bolesti tipa 2, a u dozi od 3,0 mg učinkovit je u smanjenju tjelesne težine. Postoje naznake da djeluje i na snizivanje vrijednosti arterijskoga tlaka te se čini da ima kardioprotektivne učinke[13].

Nema specifičnih istraživanja o liječenju hiperglikemije u pacijenata s metaboličkim sindromom koji nisu dijabetičari. Preporučuje su liječiti intoleranciju glukoze dijetalnim mjerama i pojačanom tjelesnom aktivnošću, sa svrhom gubitka 5–10 % tjelesne težine. Rutinska se primjena farmakoterapije ne preporučuje, međutim, metformin se može razmotriti u određenih pacijenata s intolerancijom glukoze. Nedvojbeno je dokazano da bolesnici sa šećernom bolesti trebaju terapiju. U svrhu smanjenja inzulinske rezistencije, koja je u osnovi metaboličkog sindroma, prije svega se upotrebljuju metformin, ali često i tiazolidindioni koji upravo djeluju tako da povećavaju inzulinsku osjetljivost.

U svrhu smanjenja povećanoga kardiovaskularnog rizika liječe se dislipidemija, arterijska hipertenzija i šećerna bolest te se savjetuje prestanak pušenja. Najučinkovitiji lijekovi za liječenje dislipidemije jesu statini, koji, osim učinka na smanjenje LDL kolesterola i triglicerida te povećanje HDL kolesterola imaju plejotropne učinke, povoljno djeluju na kronično proinflamatorno stanje, disfunkciju endotela i kardiovaskularne događaje te na taj način dodatno pridonose liječenju bolesnika s metaboličkim sindromom[14,15]. Procjenjuje se da smanjenje sistoličkoga tlaka za 5 mmHg u općoj populaciji dovodi do ukupnoga smanjenja smrtnosti od cerebrovaskularnog događaja za 14 %, za 9 % od kardiovaskularnih događaja te 7 %-tno smanjenje ukupnog mortaliteta[16]. Inhibitori angiotenzin konvertirajućeg enzima (ACEi) i blokatori angiotenzinskih receptora prva su terapijska opciju u pacijenata s metaboličkim sindromom, osobito ako imaju šećernu bolest. Dokazano su učinkoviti u smanjenju incidencije albuminurije i progresije dijabetičke nefropatije. Dugoročna učinkovitost i sigurnost beta-blokatora i diuretika dokazana je u velikim istraživanjima, kao što je *Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial* (ALLHAT) koje je uključivao više od 40 000 ispitanika[17]. To je istraživanje pokazalo da je liječenje diureticima tiazidskog tipa superiorno za smanjenje kardiovaskularnih događaja u pacijenata s metaboličkim sindromom u usporedbi s blokatorima kalcijskih kanala, beta-blokatorima i ACEi. Istraživanja ALLHAT i *United Kingdom Prospective Diabetes Study* (UKPDS) pokazala su da lijekovi poput tiazidskih diuretika i beta-blokatora smanjuju rizik od kardiovaskularnih događaja čak i u pacijenata sa šećernom bolesti[18,19]. Kako većina bolesnika s arterijskom hipertenzijom treba više lijekova, fiksne su kombinacije korisna i jednostavna terapijska opcija.

balanced diet, and regular physical activity. It has been found that these measures affect the improvement of all metabolic disorders that metabolic syndrome consists of. Pharmacotherapy is focused on reducing specific risk factors for cardiovascular diseases, if these basic healthy lifestyle measures do not lead to the desired effect, and the ultimate goal is to avoid the manifestation of the systemic effects of metabolic syndrome (**Table 1**).

The reduction of body weight is paramount in the treatment of metabolic syndrome. It has been shown that a reduction of only 10 % can significantly reduce triglyceride levels and increase HDL-cholesterol[11], positively influence arterial hypertension and hyperglycemia. This can be achieved by adhering to healthy lifestyle habits and exercise, but behavioral therapy and bariatric surgery can be considered as well. It is interesting to note that removing fat tissue using liposuction does not improve insulin resistance or reduce cardiovascular risk, indicating that it is the negative energy balance achieved by diet and exercise that is irreplaceable in achieving the metabolic advantages of weight loss[12]. Liraglutide, a glucagon-like peptide-1 (GLP-1), has garnered special attention in recent years due to its successful use for the treatment of Type 2 diabetes and is effective in reducing body weight at a dose of 3.0 mg. There are indications that it also affects the reduction of arterial pressure and that it might have cardioprotective effects[13].

There are no studies specifically investigating the treatment of hyperglycemia in patients with metabolic syndrome who are not diabetics. It is recommended to treat glucose intolerance using dietary measures and increased physical activity with the goal of losing 5–10 % of body mass. Routine application of pharmacotherapy is not recommended; however, metformin can be considered in some patients with glucose intolerance. It has been indubitably demonstrated that patients with diabetes require therapy. Reducing insulin resistance, which is the base of metabolic syndrome, is primarily achieved using metformin but often also using thiazolidinediones, which increase insulin sensitivity.

Dyslipidemia, arterial hypertension, and diabetes are treated in order to reduce increased cardiovascular risk, and smoking cessation is recommended. The most effective drugs for dyslipidemia are statins, which in addition to reducing LDL-cholesterol and triglycerides as well as increasing HDL-cholesterol also have pleiotropic effects and positively affect chronic proinflammatory states, endothelial dysfunction, and cardiovascular events, thus contributing to the treatment of patients with metabolic syndrome[14,15]. It is estimated that a reduction of systolic pressure of 5 mmHg in the general population leads to a total reduction in mortality from cerebrovascular events of 14 %, a reduction of 9 % for cardiovascular events, and a 7 % reduction of total mortality[16]. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers represent the first line of treatment in patients with metabolic syndrome, especially if they also have diabetes. They have been demonstrated to be effective in the reduction of the incidence of albuminuria and progression of diabetic nephropathy. The long-term effectiveness and safety of beta-blockers and diuretics has been demonstrated in large studies such as the *Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial* (ALLHAT), which included more than 40 000 participants[17]. This study showed that treatment with thiazide diuretics is superior for the reduction of cardiovascular events in patients with metabolic syndrome in com-

Možemo raspravljati o tome je li metabolički sindrom mit, no pojedini su metabolički parametri tog sindroma stvarnost ne samo u endokrinološkoj ordinaciji nego i za svakog liječnika. Važno ih je prepoznati i pravodobno liječiti kako bismo u konačnici mogli djelovati na smanjenje rizika od pojave šećerne i kardiovaskularnih bolesti.

parison with calcium channel blockers, beta-blockers, and ACE inhibitors. ALLHAT and the *United Kingdom Prospective Diabetes Study* (UKPDS) have shown that drugs like thiazide diuretics and beta-blockers reduce the risk of cardiovascular events even in patients with diabetes[18,19]. Since most patients with arterial hypertension require multiple drugs, fixed dose drug combinations represent a useful and simple therapeutic option.

We can debate whether metabolic syndrome is a myth, but the individual metabolic parameters of the syndrome are a reality not only in the endocrinology clinic but for any physician. Timely recognition and treatment are important in order to ultimately reduce the risk of diabetes and cardiovascular diseases.

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