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Slanovic-Kuzmanović, Zorana; Kos, Ivan; Domijan, Ana-Marija

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ENDOCRINE, LIFESTYLE, AND GENETIC FACTORS IN THE DEVELOPMENT OF METABOLIC SYNDROME

Zorana SLANOVIC-KUZMANOVIĆ, Ivan KOS, and Ana-Marija DOMIJAN

Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia

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Metabolic syndrome (MetS) is a chronic, multi-component disease characterised by central obesity, hyperglycaemia, dyslipidaemia, and hypertension. Since MetS leads to type 2 diabetes, cardiovascular disease, development of certain cancers, and eventually to premature death, it is not surprising that it draws the attention of scientists around the world. The aetiopathology of MetS is complex and still not fully understood. This review focuses on the role of endocrine factors such as cortisol and insulin in the development of MetS. It also takes a look at some of the contributing lifestyle and genetic factors as well as at the current knowledge about its treatment.

KEY WORDS: *cardiovascular diseases, circadian rhythm, cortisol, hyperglycaemia, hypertension, insulin, MetS, type 2 diabetes*

Metabolic syndrome (MetS) is a modern disease characterised by the clustering of abnormalities such as central obesity, high levels of fasting glucose and triglyceride, low levels of high-density lipoprotein (HDL), and hypertension (1, 2). The prevalence of MetS has been increasing over the past two decades (1), and recent studies (3-5) suggest that it has reached 25 % among the adults worldwide. Reports vary from 21.9 % in men and 16.8 % in women in north-eastern Italy, and 24.6 % in alcohol-dependent male patients in north India to 31.25 % in rural women from Bangladesh. A small study on salt intake with 92 participants in Croatia reports the prevalence of 31.5 % (6). Among obese adolescents and pubertal children, the prevalence of MetS could be around 15 %, judging by the reports of 14 % in Danish obese adolescents (7) and of 9.7 % to 41.2 % in obese pubertal children and 8.3 % to 34.2 % in obese pre-pubertal children in Spain (8). The latter study makes

a point that the prevalence of MetS depends on criteria used. Organisations such as the World Health Organization (WHO) and the American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) differ in diagnostic criteria for MetS (Table 1) (9-12). It is also evident that the prevalence of MetS increases with age; Novalletto et al. (3) reported the prevalence of 29.8 % in a group aged 60 to 69 years vs. 8.0 % in a group aged 30 to 39. The aetiopathology of MetS is still unclear but is believed to be a combination of modern lifestyle, environmental factors, and heredity in some populations (2, 13). More importantly, patients diagnosed with MetS are at high risk of developing type 2 diabetes, cardiovascular disease, certain cancers, and of premature death (14-17).

The subtle interplay between MetS and hormones is well established. Adipose tissue, a hallmark of MetS, is not just inert reserve of fat, but an active endocrine

organ that plays an important role in the secretion of insulin and other hormones which regulate energy metabolism (18). In turn, many hormones and their receptors have important roles in regulating food intake, energy expenditure, and neuro-endocrine output of the pituitary gland and may contribute to the accumulation of fat.

The aim of this article is to give an overview of some of the most important endocrine, lifestyle, and genetic factors that are involved in the development of MetS. It also presents current knowledge on MetS treatment.

Endocrine factors and MetS

Cortisol is a glucocorticoid hormone secreted by the adrenal gland and is regulated by the adrenocorticotropic hormone (ACTH), whose secretion is, in turn, regulated by vasopressin and corticotrophin-releasing hormones, released by the hypothalamus. This complex set of hormone interactions is referred to as hypothalamic-pituitary-adrenal (HPA) axis. Cortisol regulates energy metabolism through gluconeogenesis, but also affects processes such as inflammation (19, 20). Various cortisol-regulated physiological processes depend on glucocorticoid receptor (GR), which is activated upon cortisol binding (20, 21). On the pre-receptor level, cortisol action is additionally regulated by the intracellular enzyme 11 β -hydroxysteroid dehydrogenase (11 β -HSD) (20, 22, 23) that comes in two isoforms: type 1 (11 β -HSD1) and type 2 (11 β -HSD2). Type 1 catalyses the conversion of the inactive form cortisone into active cortisol, while type 2 converts active cortisol into its inactive form cortisone to lower the levels of active glucocorticoid and to inhibit cortisol activity (22, 24). Therefore, the level of cortisol in a particular tissue depends on blood cortisol levels produced by the adrenal gland and on tissue activity of 11 β -HSD1 and density of GR (Figure 1) (20, 21).

Higher cortisol levels in MetS patients suggest that cortisol contributes to the pathogenesis of MetS (22, 25). Studies conducted so far (25, 26) indicate that higher HPA axis activity and cortisol level are associated with central obesity, but the nature of this relationship remains ambiguous. Grossniklaus et al. (26) associated higher body mass index (BMI) and higher morning salivary cortisol levels in middle-aged women with greater waist circumference (WC). Park et al. (25) found that higher cortisol level in Korean men and women was associated with increased risk

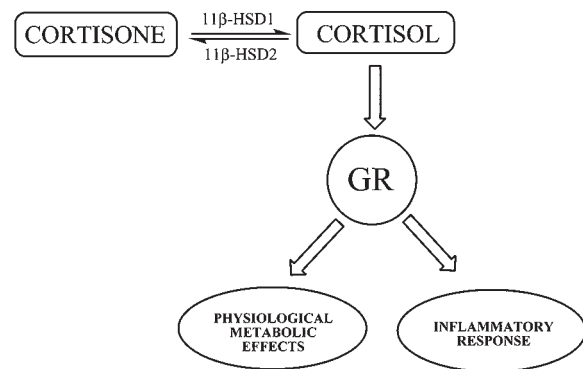


Figure 1 Intracellular action of cortisol depends on the conversion of cortisone to cortisol (and vice versa) by 11 β -hydroxysteroid dehydrogenase (11 β -HSD) and on its binding to glucocorticoid receptor (GR) (adapted from ref. 20). Isoform 11 β -HSD type 1 (11 β -HSD1) converts inert cortisone to receptor-active cortisol. Upon binding of cortisol to GR, GR is activated and can regulate the expression of genes involved in various physiological functions, including energy metabolism and inflammation.

of MetS, but since they found no association between cortisol and BMI or WC, the authors concluded that higher cortisol was associated with MetS regardless of overall adiposity. Mai et al. (27), however, observed a direct association between lipids and cortisol levels. They induced hyperlipidaemia in healthy young women of normal weight by treating them with 20 % lipid/heparin infusion and found higher serum cortisol than in controls (who received saline/heparin infusion). The authors concluded that hyperlipidaemia may increase adrenal sensitivity to ACTH, leading to greater cortisol release, such as in patients with MetS. This effect might contribute to disturbances along the HPA axis found in women with central obesity and impaired lipid metabolism.

It is important to note that cortisol secretion also depends on age and sex. In a study with untreated volunteers, Velhuis et al. (28) observed that cortisol secretion increased with age, especially in men, and that cortisol-ACTH feedback synchrony and ACTH-cortisol feedforward synchrony declined with age and, again, were more pronounced in men. In addition, they observed that pulsatile and basal ACTH secretion and mean ACTH concentrations all increased with BMI and were higher in men than women. In other words, BMI also contributed to cortisol secretion.

We have already mentioned that cortisol action depends on the GR density and the activity of 11 β -HSD1 enzyme. According to a number of reports (19, 22, 25) the visceral adipose tissue stores more GR than other fat depots and shows greater expression of 11 β -

HSD1 in obese subjects (29, 30). Together with excess glucocorticoid secretion by the HPA axis (through increased peripheral glucocorticoidal signalling and cortisol reactivation) this may contribute to higher cortisol level observed in MetS.

Centrally distributed fat or central obesity is characteristic of MetS, and adipose tissue not only stores fat but works as an endocrine organ, as it produces pro-inflammatory cytokines (adipokines) such as tumour necrosis factor α (TNF α) and interleukin-6 (IL-6) (1, 23). In other terms, MetS is a state of chronic, low-grade inflammation (23). How does this explain the involvement of cortisol? Cortisol is released to stop tissue destruction and autoimmune processes. Classen (31) has reported that iatrogenic inflammation activates immunosuppressive cortisol response, which protects against type 1 diabetes and other autoimmune diseases, but causes type 2 diabetes, MetS, and obesity. Persistently high cortisol levels cause a number of adverse reactions, as they disrupt normal physiological functions. On the one hand, cortisol induces excessive glucose release from the liver, insulin resistance, free fatty acid release from adipocytes, and hypertension. On the other, it may

chronically suppress immune reactions and anabolic processes in muscles. These changes increase the risk of MetS and other diseases such as morbid obesity, type 2 diabetes, infections, or endocrine disorders.

Fasting hyperglycaemia and/or insulin resistance and compensatory hyperinsulinaemia are the most important symptoms of MetS. Insulin resistance is the inability of insulin to act even though its secretion from β -cells is normal (18). In addition to its important role in energy metabolism, insulin affects cell growth and differentiation, as well as endothelial function. It is probably because of this variety of insulin action that MetS is able to affect it. For one, cortisol can interfere with insulin action by stimulating excessive hepatic gluconeogenesis, by inhibiting glycogen synthase in the muscles, and by promoting lipolysis in the adipose tissue (19, 22, 32). For two, central obesity can affect insulin action, as adipose tissue releases TNF- α , IL-6, and free fatty acids, which block normal insulin signalling pathway (2, 18). In addition, adiposity is characterised by low levels of adiponectin (a tissue-specific circulating adipokine with insulin-sensitising and anti-atherogenic properties), which contributes to systematic insulin resistance (18, 15,

Table 1 Criteria for diagnosing the metabolic syndrome proposed by different organisations

PARAMETER	WHO ^a	AHA/NHLBI ^b	IDF ^c	EGIR ^d
Obesity (as WHR ^e , WC ^f or BMI ^g)	WHR>0.9 (m); WHR>0.85 (w); or BMI>30 kg m ⁻²	WC≥102 cm (m); WC≥88 cm (w) (ethnic values for WC recommended)	WC≥94 cm (m); WC≥80 cm (w); or BMI>30 kg m ⁻²	WC≥94 cm (m); WC≥80 cm (w)
Fasting glucose	≥6.1 mmol L ⁻¹ and/or impaired glucose tolerance	≥5.6 mmol L ⁻¹ or on therapy	≥5.6 mmol L ⁻¹ or DM	≥6.1 mmol L ⁻¹ without DM
Blood pressure	≥140/90 mm Hg	≥130/85 mm Hg or on therapy	>130/85 mm Hg or on therapy	≥140/90 mm Hg or on therapy
HDL cholesterol	<0.9 mmol L ⁻¹ (m); <1 mmol L ⁻¹ (w)	<1.03 mmol L ⁻¹ (m); <1.3 mmol L ⁻¹ (w); or on therapy	<1.03 mmol L ⁻¹ (m); <1.29 mmol L ⁻¹ (w); or on therapy	<1 mmol L ⁻¹ or on therapy
Triglycerides	≥1.7 mmol L ⁻¹	≥1.7 mmol L ⁻¹ or on therapy	≥1.7 mmol L ⁻¹ or on therapy	>2 mmol L ⁻¹ or on therapy
Microalbuminuria	urinary albumin excretion rate ≥20 μ g min ⁻¹	/	/	/
Requirements for diagnosing MetS	≥2 of any + insulin resistance and/or DM	≥3 of any criteria	≥2 of any + obesity (with ethnicity specific values)	≥2 of any + insulin resistance

^aWHO - World Health Organization; ^bAHA/NHLBI - American Heart Association/National Heart, Lung, and Blood Institute; ^cIDF - International Diabetes Federation; ^dEGIR - European Group for the Study of Insulin Resistance; ^eWHR - waist to hip ratio; ^fWC - waist circumference; ^gBMI - body mass index; (m)-men; (w)- women; DM-diabetes mellitus

23). Long-term elevation of insulin levels causes desensitisation of insulin receptors, which in turn may lead to hyperglycaemia, smooth muscle hypertrophy, hypertension and many other physiological disorders (33).

One way in which hyperinsulinaemia leads to hypertension is by overstimulating the sympathetic nervous system through increased plasma noradrenaline levels, heart rate, renal sodium re-absorption, cardiac output, and peripheral resistance (34). There are several other mechanisms (such as the renin-angiotensin-aldosterone system, mitogen-activated protein kinase pathway, increased levels of free fatty acids, and pro-inflammatory cytokines through which MetS (via insulin resistance and obesity) increases blood pressure (for review see 33).

Lifestyle factors and MetS

The release of hormones, including cortisol, follows a daily pattern we usually refer to as circadian rhythm. Normally, cortisol peaks in the early morning, keeps falling for the rest of the day, and troughs around midnight, only to rise quickly over the second half of the night (Figure 2). These circadian oscillations are controlled by the suprachiasmatic nucleus (SCN), a cluster of neurons in the hypothalamus, but also by peripheral oscillators that exist in most tissues of the body (35, 36). The internal biological clock is primarily aligned with the light/dark cycle, but is also affected by other factors such as locomotor activity and food intake (35-37). The circadian clock controls nearly all of the physiological and behavioural events in the body (36, 37). Any chronic misalignment between circadian rhythm and sleep or feeding can therefore lead to adverse metabolic and cardiovascular changes (38, 39). Modern lifestyle seems to be an epitome of this misalignment, as it usually implies physical inactivity, smoking, alcohol consumption, untimely feeding, and exposure to bright light over night. All these factors greatly contribute to the development of MetS. Here we shall focus on shift work, sleep deprivation, and stress.

Shift work can greatly disturb the circadian and behavioural rhythm and contribute to the development of obesity, diabetes, and cardiovascular disease. In a 10-year follow-up study, Morikawa et al. (40) established a clear association between shift work and BMI (the highest increase in BMI was found in workers who transferred from daytime work to shift work). In another retrospective longitudinal study (41) covering the period between 1976 and 2007, night

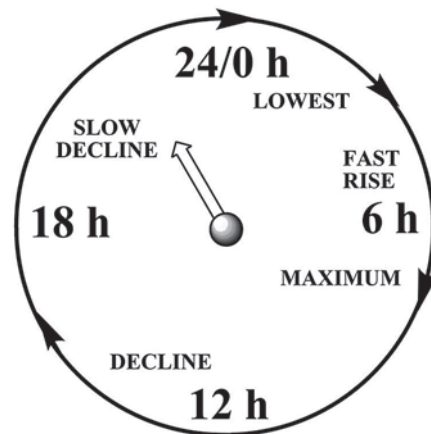


Figure 2 Circadian rhythm of cortisol

workers demonstrated not only significantly higher BMI, but also serum total cholesterol, triglycerides, and incidence of coronary heart disease than day workers. In yet another study, Manenschijn et al. (42) established higher BMI in shift workers and its correlation with higher cortisol levels in scalp hair and cardiovascular risk. Assessing several metabolic and endocrine parameters, Scheer et al. (38) found that experimental short-term circadian misalignment (similar to acute jet lag or chronic shift work) resulted in lower leptin, higher glucose, insulin, and mean arterial pressure, reduced sleep efficiency, and complete inversion of the cortisol behaviour across the circadian cycle. The authors conclude that a change in any of these parameters can trigger underlying mechanisms for MetS and cardiovascular disease. Cases in point, they argue, are the inversion of cortisol behaviour that can lead to insulin resistance and hyperglycaemia and lower leptin that can stimulate appetite and diminish energy expenditure.

Prolonged sleep deprivation is another predisposing factor for obesity, type 2 diabetes, and cardiovascular disease. In an eight-year follow-up study by Gangwisch et al. (43), short sleep (less than five hours a night) was associated with a significantly increased risk of hypertension. Since blood pressure drops 10 % to 20 % in normotensive subjects during sleep, the authors concluded that the reason was the prolonged cycle of higher blood pressure, heart rate, sympathetic nervous system activity, physical and psychosocial stress, and increased salt retention associated with wakefulness. Vgontzas et al. (44) found a strong inverse correlation between sleep deprivation and WC. Several studies have shown that depriving healthy subjects of sleep can raise glucose and cortisol levels,

lower insulin sensitivity and leptin levels, and increase appetite (37). Kumari et al. (45) found that short sleep and sleep disturbances were independently associated with greater cortisol release, especially in the evening, which points to the deregulation of the feedback in the HPA axis. However, the specific mechanisms and the involvement of the sympathetic nervous system and HPA axis remain to be elucidated.

Stress disorders such as depression and post-traumatic stress disorder (PTSD) have also been associated with metabolic abnormalities, including obesity, dyslipidaemia, high blood pressure, and insulin resistance. Paslakis et al. (46) found that 42.1 % of patients with major depression met the criteria for MetS diagnosis. Vogelzangs et al. (47) showed that depression led to increased visceral fat, independent of overall obesity. The same group of authors observed a synergistic relationship between depression, cortisol, and MetS and concluded that depression and high cortisol increase the odds for MetS (48). However, the association between depression and MetS could be a two-way street, that is, it could be MetS that leads to depression and not the other way around (49). Capuron et al. (50) claim that chronic low-grade inflammation pertinent to MetS can contribute to mood alterations. These findings raise the question whether the treatment of depression would positively reflect on MetS and *vice versa*, whether the treatment of MetS would relieve depression. Preliminary evidence suggests that antidepressant therapy (a four-week treatment with reboxetine) can have beneficial effects on several metabolic parameters, independent of treatment outcome, that can be attributed to the pharmacological profile of the drug (46). Vogelzangs et al. (51) showed that antidepressants act differently on inflammation. Tricyclic antidepressants, tetracyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors stimulated inflammation level, whereas selective serotonin reuptake inhibitors inhibited it. Rege (52) demonstrated that first (chlorpromazine, zuclopenthixol, haloperidol, and trifluoperazine) and second-generation antipsychotics (clozapine, olanzapine, risperidone, paliperidone, and quetiapine) stimulated gain weight. Weight gain can be a result of reduced resting energy expenditure. Blocking the histamine H1 receptor increases appetite, while serotonin 2C (2-HT_{2C}) interaction with antipsychotics stimulates food intake despite satiety (53-55). A recent study (56) confirmed that users of tricyclic antidepressants were prone to obesity and dyslipidaemia and it associated low-grade

inflammation with more severe anxiety disorders and depression.

Genetic factors and MetS

The central rhythm generator in mammals, SCN, receives light information from the retinal photoreceptor cells and transmits them as neuronal and/or humoral signals through the body (36). To keep this rhythm regular, the SCN needs *Clock* genes, which make up an auto-regulatory feedback loop by interacting with each other and generate circadian rhythms at the molecular level (36, 37, 57). *Clock* genes are expressed not only in the SCN and other locations in the brain, but also in the liver, heart, skeletal muscle, adipose tissue, and adrenal glands (35, 58). Peripheral *Clock* genes have their own intrinsic oscillatory systems that are regulated by the SCN (36, 59). However, peripheral clocks are capable of sustaining circadian rhythms even in the absence of SCN input and may therefore play an important role in regulating peripheral circadian rhythms of physiological processes (36, 37). Valenzuela et al. (59) found oscillatory expressions of *Clock* genes *Per2* and *Bmal1* in adrenal explants of an adult capuchin monkey, demonstrating that the primate adrenal gland has intrinsic capacity to maintain *Clock* gene oscillation. Also in that study, adrenal *Clock* gene expression was directly affected by the neurohormone melatonin, further confirming the independence of peripheral clocks. Gomez-Abellan et al. (60) demonstrated *Clock* genes in human adipose tissue and their association with MetS. In the next study (61), the same authors confirmed that peripheral *Clock* genes (*hPer2*, *hBmal1*, and *hCry1*) in explants of adipose tissue in morbidly obese women oscillated accurately and independently of the SCN. They also observed that peripheral *Clock* genes controlled the timing of GR and 11 β -HSD1 genes, and that this intracellular circadian clock could independently regulate peripheral cell functions.

We have mentioned earlier that the expression of the enzyme 11 β -HSD1 is higher in the adipose tissue of obese subjects and that it increases the risk of obesity and MetS (22, 23). Gambineri et al. (62) established a correlation between single nucleotide polymorphisms (SNPs) of *HSD11B1*, the gene encoding for enzyme 11 β -HSD1, and type 2 diabetes, hypertension, and hyperandrogenism in women with the polycystic ovary syndrome (PCOS). They studied two common SNPs (rs846910 and rs12086634) in *HSD11B1* in a population of Southern European Caucasian women with and without PCOS and found

that regardless of PCOS, *HSD11B1* alleles containing rs846910 A and rs12086634 T increased 11 β -HSD1 expression and activity (observed in higher 11 β -HSD1 mRNA levels in the adipose tissue and higher rates of appearance of an active cortisol during cortisol steady-state infusion). To establish tissue-specific cortisol profile in morbidly obese patients, Torrecilla et al. (63) investigated the mRNA expression of genes related to peripheral cortisol activity, including those coding for 11 β -HSD1, hexose-6-phosphate dehydrogenase (H6PDH), GR, and phosphoenolpyruvate carboxykinase (PEPCK) in the liver, visceral, and subcutaneous adipose tissues in morbidly obese patients with and without MetS. In the liver, mRNA expression of the tested genes was higher in patients with MetS and positively correlated with a number of clinical characteristics of MetS. Interestingly, those genes were not differently expressed in the visceral and subcutaneous adipose tissues between the groups. The authors therefore attributed liver-specific up-regulation of genes involved in peripheral cortisol activity and consequent hepatic hypercortisolism to MetS.

Other studies found that the adipose tissue had a higher frequency of genes coding for adipokines than other tissues (13, 64). Moreover, visceral adipose tissue had 30 % of these genes whereas the subcutaneous adipose tissue had 20 % (13, 65).

One adipokine that highly increases the risk of thrombotic diseases is plasminogen activator inhibitor type 1 (PAI-1). Mertens et al. (66) found a strong correlation between its plasma levels and visceral adiposity. Matzusawa (64) found a tenfold increase in PAI-1 mRNA in animal visceral adipose tissue during fat accumulation while its level in subcutaneous adipose tissue remained unchanged. Funahashi et al. (15), in turn, investigated the genetic reasons underlying the lowering of plasma levels of adiponectin, adipokine that protects against insulin resistance and atherosclerosis, in MetS patients. What lowered adiponectin levels was the missense mutation of the adiponectin gene, with the substitution of isoleucine 164 to threonine in the globular domain. Subjects carrying this mutation were frequently hypertensive, hyperlipidemic, diabetic, and had atherosclerotic vascular diseases.

Studies (67, cf. 68) on separated twins and adopted children, designed to compare environmental and genetic influences, showed that obesity was inherited by between 40 % and 70 % of the participants. Ramachandrapa and Farooqi (68) report that by

genotyping between 350,000 and 500,000 SNPs covering more than 75 % of the human genome, genome-wide association studies identified more than 20 genetic loci relevant for body weight regulation.

Other researchers (22, 69) have reported that maternal diet, growth during early foetal development, and low birth weight are independently associated with the increased risk of MetS in adult life. In a study on nonhuman primates (70), exposure of pregnant mothers (regardless of whether they were lean or obese) to a high-fat diet led to a number of changes in liver metabolism in their offspring that increase the risk of metabolic diseases. The reader may ask how this is related to genetic predisposition. According to Sebert et al. (69), changes in maternal diet or in uterine blood supply near the term can result in cellular stress in the offspring and can modify genes that control DNA methylation. In other words, maternal diet can set off the phenotypes prone to the development of metabolic diseases (69). However, we still do not understand how maternal diet affects DNA modifications and how this interaction triggers the development of metabolic diseases.

Treatment of MetS

Current therapy of choice for patients diagnosed with MetS is to change their lifestyle by increasing physical activity and improving dietary habits. De Souza Leao et al. (71) compared 15 studies with different approach to the treatment of MetS. Some investigated normocaloric diet alone, some normocaloric diet combined with exercise, some low-calorie diet combined with exercise, and some low-calorie diet alone. The best results were obtained with the combination of low-calorie diet and exercise.

Pharmacological treatment of MetS seeks to target a number of specific factors that lead to the disease. On the one hand, this diversity of factors provides many options for drug development, but on the other, diversification encourages partial approach that may not address the complex nature of the disease as efficiently as one hopes for.

One promising specific-target approach is the inhibition of the 11 β -HSD1 enzyme in order to normalise cortisol (21, 22). Studies on animals and humans have shown that pharmacological inhibition of 11 β -HSD1 activity has favourable metabolic (reduction of glucose level, insulin resistance, and dyslipidaemia) and anti-inflammatory effects (22, 23, 72). A large number of chemical classes have been identified as potent and selective small-molecule

inhibitors of 11 β -HSD1 (73, 74, cf. 75). This finding is important since 11 β -HSD1 could be a valid therapeutic target not only for obesity and MetS, but also for other comorbidities, such as type 2 diabetes (21, 72).

Currently, MetS is pharmacologically managed by treating its components: obesity, diabetes, hypertension, and hyperlipidaemia. At the moment, the only registered pharmaceutical for the treatment of obesity through removal of fat tissue, a major component of MetS, is orlistat. Orlistat inhibits pancreatic lipase, and by preventing the hydrolysis of triglyceride esters to free fatty acids and triglyceride, prevents their gastrointestinal absorption (76). Registered antidiabetic drugs include derivatives of sulfonylurea, glinides, and acarbose, which all lower blood glucose (77, 78). Metformin, a biguanide-type antidiabetic agent, can induce weight loss, and has recently become the first choice in diabetes type 2 treatment in patients with MetS (79). Hypertension, another component of MetS, is treated with anti-hypertensive drugs. There are several groups of antihypertensives that are successfully used in practice, such as diuretics, sympatholytic drugs, vasodilators, and angiotensin-converting enzyme (ACE) inhibitors (80). Some of them, such as ACE inhibitors, central acting antihypertensives, and antagonists of α 1-adrenoreceptors, have also shown beneficial effects against insulin resistance (81). Atherogenic dyslipidaemia is usually treated with statins, which target hypercholesterolaemia, and with fibrates or derivatives of nicotinic acid, which target hypertriglyceridaemia (82).

CONCLUSION

The prevalence of MetS has reached epidemic proportions and the number of patients rises exponentially. Its aetiology is still unclear, but research has identified a number of aetiological and pathophysiological factors and lifestyle triggers. These predisposing factors can be genetic or environmental and persist throughout our life (from foetal development to adult age). Since MetS is associated with diabetes type 2, cardiovascular disease, and certain cancers and significantly diminishes the quality of life and life expectancy, an early recognition and prevention, where possible, is extremely important. Because of known comorbidities of MetS including Cushing's syndrome, PCOS, and depression, treatment should

focus on the management of these conditions and improvement of MetS symptoms.

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Sažetak

ENDOKRINI I GENETIČKI ČIMBENICI TE ŽIVOTNE NAVIKE KOJI PRIDONOSE NASTANKU METABOLIČKOG SINDROMA

Metabolički sindrom (MetS) kronična je višekomponentna bolest, koju karakteriziraju abdominalna debljina, hiperglikemija, dislipidemija i hipertenzija. Kako MetS dovodi do razvoja šećerne bolesti tipa 2, kardiovaskularnih i nekih malignih bolesti te posljedično do prerane smrti, ne čudi da MetS privlači pozornost znanstvenika diljem svijeta. Etiopatologija MetSa je kompleksna te još nije u potpunosti razjašnjena. Cilj je ovoga rada dati literaturni pregled uloge nekih endokrinih poremećaja, kao što su poremećaj kortizola i inzulina, u razvoju MetSa. Također, razmatrani su i neki faktori načina života/životnog stila te genetički faktori koji pridonose razvoju MetSa. Na kraju su spomenuta trenutačna saznanja u liječenju MetSa i njegovih komponenti.

KLJUČNE RIJEČI: *cirkadijalni ritam, hiperglikemija, hipertenzija, inzulin, kardiovaskularne bolesti, kortizol, MetS, šećerna bolest*

CORRESPONDING AUTHOR:

Ana-Marija Domijan
Faculty of Pharmacy and Biochemistry,
University of Zagreb
A. Kovačića 1, 10 000 Zagreb, Croatia
E-mail: *adomijan@pharma.hr*