REVIEW ARTICLE

CONTENTS

Cortisol and testosterone: Which is more important in metabolic syndrome men

Mariia Cherska[1], Olena Pavlenko[1], Khrystyna Kukharchuk[1], Olena V. Maidanuik[2]

[1]STATE INSTITUTION «V.P. KOMISARENKO INSTITUTE OF ENDOCRINOLOGY AND METABOLISM OF THE NATIONAL ACADEMY OF MEDICAL SCIENCES OF UKRAINE», KYIV, UKRAINE

[2]STATE RESEARCH INSTITUTE OF PHYSICAL CULTURE AND SPORTS, KYIV, UKRAINE

ABSTRACT

Aim: To review information resources on this problem for the provision of modern knowledge in the pathogenesis of this pathology.

Materials and Methods: An analysis of data from literary sources and medical articles in Pub Med was carried out in order to clarify the influence of cortisol and testosterone on the development of metabolic syndrome. The search was conducted over the last 5 years, but there is material from 2001, 2018, and 2019. Total volume of the number of sources: 17.

Conclusions: The metabolic syndrome (MetS) is a collection of abnormalities that predispose individuals to diabetes, atherosclerosis, and cardiovascular disease (CVD). Patients with metabolic syndrome exhibit hyperactivity of the hypothalamic-pituitary-adrenal (HPA) system, resulting in «functional hypercorticism.» Stress is thought to play a significant role in this interaction by increasing the sensitivity of the hypothalamic-pituitary-adrenal axis. The enzyme 11-beta-hydroxysteroid dehydrogenase type 1 (11HSD1), which is involved in glucocorticoid metabolism in peripheral tissues (particularly adipose tissue and liver), has been implicated in metabolic syndrome and central obesity. Overexpression of 11HSD1 in adipocytes is observed in metabolic syndrome and central obesity, leading to increased conversion of cortisone to cortisol and excessive tissue-specific glucocorticoid activity

KEY WORDS: metabolic syndrome, cortisol,testosterone,obesity,diabetes

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INTRODUCTION

The concept of metabolic syndrome was first described in 1923 by Kylin, a Swedish physician, who observed a clinical association between hypertension and gout. In 1947, the definition was expanded to include upper body adiposity [1]. However, it was Reaven, in 1988, who emphasized the significance of metabolic syndrome [2]. He referred to it as *Syndrome X*, characterized by insulin resistance, hyperglycemia, hypertension, low levels of high-density lipoprotein cholesterol (HDL-C), and elevated levels of very-low-density lipoprotein (VLDL) and triglycerides (TG). Since then, metabolic syndrome has been recognized as a major risk factor for coronary artery disease, drawing considerable attention in the field of cardiovascular medicine.

AIM

The aim is to review information resources on this problem for the provision of modern knowledge in the pathogenesis of this pathology.

MATERIALS AND METHODS

An analysis of data from literary sources and medical articles in Pub Med was carried out in order to clarify the influence of cortisol and testosterone on the development of metabolic syndrome.

The search was conducted over the last 5 years, but there is material from 2001, 2018, and 2019.

Key words for search were: metabolic syndrome, insulin resistance syndrome, obesity, atherogenic dyslipidemia, diabetes mellitus, estrogen, gut microbiota, testosterone, human glucocorticoid receptor, adipose tissue dysfunction, adrenal and gonadal steroid hormone, angiogenesis, arterial hypertension, cardiovascular diseases, gender, heart failure, hypercholesterolaemia.

Total volume of the number of sources: 17.

INCLUSION CRITERIA

Recency, empirical research, articles in English, the object of the study is a male patient with metabolic

syndrome, peer-reviewed articles from scientometric databases.

EXCLUSION CRITERIA
Duplication, incomplete data, insufficient quality.

ETHICS
All sources used in this literature review are publicly available.

REVIEW AND DISCUSSION
Metabolic syndrome (MetS) is a cluster of common abnormalities that include elevated blood sugar levels (hyperglycemia), excess abdominal fat (abdominal obesity), reduced levels of HDL-C, and increased levels of triglycerides (TG) and blood pressure (BP). It was initially referred to as "Syndrome X" or "insulin resistance syndrome" by Reaven in 1988. The components of MetS are associated with endothelial dysfunction and the development of atherosclerosis, increasing the risk of type 2 diabetes mellitus (T2DM) as well as vascular morbidity and mortality. It is estimated that approximately one-fourth of the world's adult population has MetS. Despite its growing global prevalence, there is still no universally accepted diagnostic criterion, and the underlying causes of MetS remain a topic of ongoing debate.

MetS is a complex risk factor resulting from insulin resistance combined with abnormal accumulation and dysfunction of adipose tissue [3]. It poses a significant risk for coronary heart disease (CHD), as well as for diabetes, fatty liver disease, and several types of cancer. The clinical features of this syndrome, as mentioned earlier, may include hypertension, hyperglycemia, hypertriglyceridemia, reduced HDL-C levels, and abdominal obesity.

According to the criteria established by the National Cholesterol Education Program (NCEP), MetS is diagnosed when three or more of the following parameters are present:

- Waist circumference exceeding 102 cm in men and 88 cm in women;
- Triglyceride levels of at least 150 mg/dL (1.7 mmol/L);
- HDL cholesterol levels below 40 mg/dL (1.04 mmol/L) in men and below 50 mg/dL (1.29 mmol/L) in women;
- Blood pressure of at least 130/85 mm Hg;
- Fasting glucose levels of at least 110 mg/dL (6.1 mmol/L).

OBESITY
Obesity has become a global epidemic, affecting over 1 billion adults, with at least 300 million classified as clinically obese [4]. This widespread issue adversely impacts blood pressure (BP), lipid profiles, and glucose metabolism due to insulin resistance, leading to a constellation of cardiovascular risk factors collectively referred to as metabolic syndrome (MetS). MetS is strongly associated with a significant increase in cardiovascular morbidity and mortality, making it a leading cause of death in the Western world. Interestingly, men are at higher risk of developing coronary artery disease at an earlier age compared to women, although the underlying reasons for this gender difference remain unclear. Adipose tissue is metabolically active and produces cytokines known as adipocytokines, which play a critical role in linking the various components of MetS to their cardiovascular effects. In particular, central adiposity—as measured by waist circumference or waist-to-hip ratio—is strongly and independently associated with insulin resistance and increased cardiovascular disease (CVD) risk. Visceral adipocytes located in the abdominal cavity are more metabolically active than subcutaneous adipocytes located beneath the skin. Visceral fat is a major source of free fatty acids and adipocytokines, which directly affect the liver. These substances stimulate gluconeogenesis and inhibit insulin binding in the liver, thereby contributing to insulin resistance. Waist circumference is a clinically practical method for assessing abdominal obesity; however, it does not effectively distinguish between visceral and subcutaneous fat. Imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and dual-energy X-ray absorptiometry (DEXA) provide greater accuracy in differentiating fat compartments.

Central obesity is a key component of MetS (Fig. 1). Cortisol plays a role in the pathophysiology of obesity in the context of MetS. One study found an increased urinary cortisone/cortisol ratio in women with elevated abdominal fat compared to those with peripheral fat distribution, suggesting enhanced peripheral cortisol metabolism [5].

GENETIC FACTORS
The glucocorticoid receptor (GR) belongs to the nuclear receptor superfamily and functions as a transcription factor that regulates gene expression. Upon binding with cortisol, the GR undergoes conformational changes that result in dissociation from a protein complex, with heat shock protein 90 being the most notable component. The activated GR-cortisol complex then translocates to the nucleus, where it exerts various genomic effects. Polymorphisms in the GR gene can influence sensitivity to endogenous glucocorticoids.

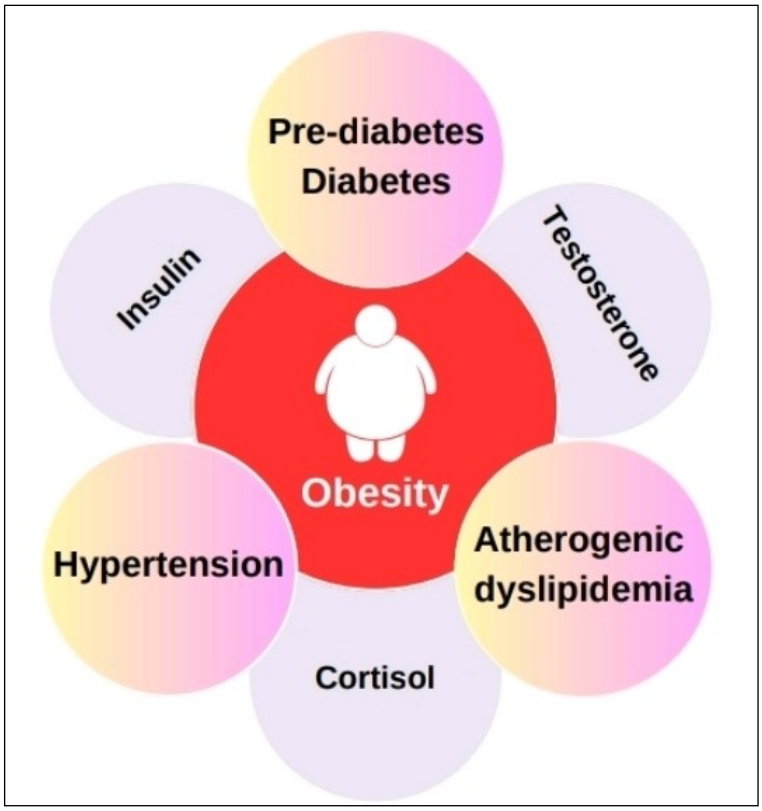

Fig. 1. Components of metabolic syndrome
Source: compiled by the authors based on [5]

Specifically, the N363S and BclI polymorphisms are associated with increased glucocorticoid sensitivity, while the ER22/23EK polymorphism is linked to relative resistance. The N363S variant has been associated with coronary heart disease (CHD), independent of obesity, as well as elevated total cholesterol, triglyceride levels, and the total cholesterol/HDL-C ratio. Both the N363S and BclI polymorphisms may contribute to increased susceptibility to obesity. In contrast, individuals carrying the ER22/23EK variant appear to have a reduced vascular risk [6].

OBESITY AND HORMONAL STATUS

Interestingly, there is an inverse correlation between cortisol clearance and insulin sensitivity, independent of overall body fat levels. It is well-documented that glucocorticoids, such as cortisol, promote the differentiation and expansion of human adipocytes, with glucocorticoid receptors more abundantly expressed in visceral fat compared to subcutaneous fat. Additionally, glucocorticoids facilitate the redistribution of adipose tissue from peripheral to central depots, increase both the size and number of fat cells, and stimulate lipolysis—resulting in elevated circulating free fatty acid levels. A study using MRI to assess central fat distribution found a positive association between excess cortisol and intra-abdominal fat accumulation. In this study, the activity of the hypothalamic-pituitary-adrenal (HPA) axis was evaluated using a single morning cortisol measurement, which supported a link between HPA activity and MetS. Overall, these findings suggest that cortisol plays a significant role in the development of abdominal obesity, a hallmark feature of MetS.

CORTISOL AND WAIST CIRCUMFERENCE: CONFLICTING EVIDENCE

There have been conflicting findings regarding the relationship between cortisol and waist circumference. While some studies report no significant association, others suggest a link between elevated cortisol levels—such as urinary free cortisol and overnight serum cortisol—and insulin resistance, as assessed by the homeostasis model assessment. Higher cortisol concentrations have also been linked to impaired insulin secretion, consistent with previous in vivo and in vitro studies demonstrating the regulatory role of glucocorticoids in insulin dynamics (Fig. 2).

A study in obese children, with and without insulin resistance, showed that weight loss reduced cortisol levels and improved insulin sensitivity only in the insulin-resistant group, but not in those without insulin resistance. Multiple studies have shown an exaggerated HPA axis response to various stimuli in individuals with abdominal obesity. These stimuli include food intake, low-dose tetracosactide, and CRH-arginine vasopressin. Furthermore, abdominal adiposity has been associated

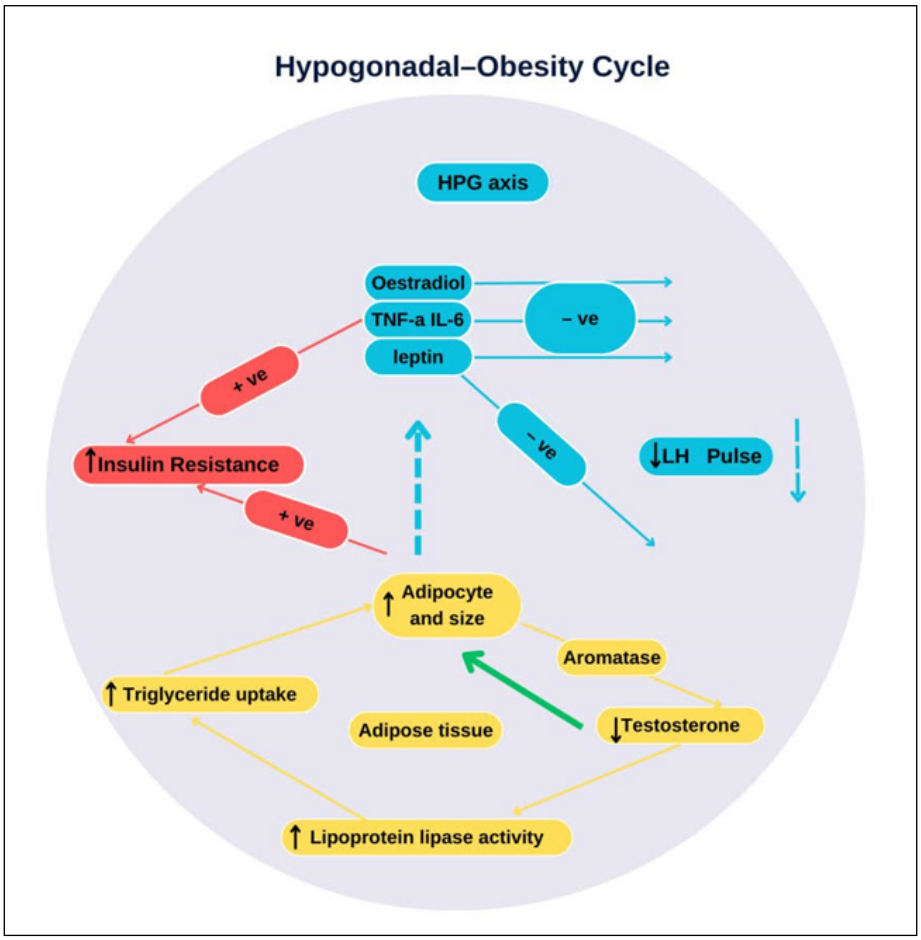

Fig. 2. Hypogonadal-Obesity Cycle
Source: compiled by the authors based on [7]

with impaired negative feedback regulation within the HPA axis and reduced diurnal variation in cortisol levels. Overall, current evidence supports the hypothesis of heightened HPA axis activity in individuals with visceral obesity [7].

Elevated triglyceride levels (hypertriglyceridemia) and low concentrations of HDL-C are commonly observed in metabolic syndrome (MetS). Studies have shown that higher cortisol levels, including urinary free cortisol and overnight serum cortisol, are associated with elevated triglycerides and reduced HDL-C levels. Genetic variations in the glucocorticoid receptor (GR) may also impact the activity of the hypothalamic-pituitary-adrenal (HPA) axis and lipid metabolism.

CORTISOL

The underlying cause of MetS and the mechanisms by which its various components manifest are still not fully understood. However, it has been suggested that cortisol, a hormone involved in the stress response, may play a role in the development of MetS. Although MetS is characterized by only mild hypercortisolism compared to Cushing's syndrome (CS)—a condition caused by excess cortisol—both conditions share several diagnostic features. It has been proposed that inhibiting cortisol action could represent a potential therapeutic strategy for MetS. Initial data indicate that individuals with MetS have higher circulating cortisol levels than healthy individuals, both at rest and in response to stress. This difference is more pronounced in MetS patients with hypertension or impaired glucose tolerance. Weight loss has been shown to normalize cortisol levels and improve insulin resistance. Despite having cortisol levels within the normal reference range, individuals with MetS may exhibit increased cortisol activity in peripheral tissues and dysregulation of the HPA axis. Numerous studies have reported an association between cortisol levels and both systolic and diastolic blood pressure. This correlation is likely mediated by the influence of stress, which activates both the HPA axis and the sympathetic nervous system. Individuals with MetS and hypertension have been found to exhibit higher urinary levels of cortisol and catecholamine metabolites compared to healthy controls. Glucocorticoids may contribute to elevated blood pressure through several mechanisms. One potential mechanism involves increased responsiveness to vasoconstrictors, along with decreased production of vasodilators. Some studies have shown that

glucocorticoid-induced hypertension is associated with a reduction in nitric oxide (NO), a key vasodilator. In MetS, it is suggested that hyperinsulinemia and insulin resistance may promote endothelin-1 (ET-1) release, contributing to renal injury frequently observed in these patients and providing another pathway to hypertension [7].

Obesity, a common feature of MetS, is also associated with hypertension. Several mechanisms contribute to this relationship, including volume expansion, increased cardiac output and systemic vascular resistance, enhanced sodium reabsorption, heightened sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) activity, elevated leptin levels with concurrent leptin resistance, and increased ET-1 along with decreased NO. In patients with MetS, serum cortisol levels are significantly correlated with fasting glucose concentrations. The association between fasting hyperglycemia and cortisol is attributed to glucocorticoid effects on hepatic gluconeogenesis and insulin secretion [8].

TESTOSTERONE AND METABOLIC SYNDROME

Testosterone plays a significant role in MetS, and compelling evidence indicates that low testosterone levels are an independent risk factor for the development of MetS and type 2 diabetes in men. Moreover, emerging research suggests that testosterone deficiency is also associated with an increased risk of cardiovascular disease (CVD). Numerous recent reviews have emphasized the critical link between hypogonadism (testosterone deficiency), MetS, diabetes, and CVD.

In men, there is a strong inverse correlation between body fat and testosterone levels. Abdominal obesity is consistently associated with low testosterone in both cross-sectional and longitudinal studies. Waist circumference and waist-to-hip ratio also show an inverse relationship with sex hormone-binding globulin (SHBG) levels. Imaging studies using CT or MRI to quantify abdominal fat have confirmed that low testosterone concentrations are linked to increased visceral fat accumulation. Central fat depots, in particular, exhibit high aromatase activity, which leads to the conversion of testosterone to estrogen—further exacerbating the hormonal imbalance and metabolic dysfunction.

Central fat depots' elevated aromatase activity results in increased local conversion of testosterone to estrogen, which helps explain why obese men often exhibit higher estrogen levels. Testosterone promotes the development of myocytes (muscle cells) and inhibits the differentiation of adipocytes (fat cells) from pluripotent stem cells, contributing to increased lean mass. In contrast, testosterone deficiency favors fat accumulation. Testosterone also increases beta-adrenergic receptor density, promoting lipolysis and reducing fatty acid synthesis. Studies using androgen receptor (AR) knockout mouse models have shown that androgen deficiency impairs lipolysis and significantly contributes to obesity development.

The hypogonadal–obesity cycle hypothesis [9] proposes that testosterone inhibits the activity of lipoprotein lipase in adipocytes—an enzyme responsible for breaking down triglycerides into absorbable free fatty acids, which are then re-esterified and stored. Low testosterone, due to increased aromatase activity, creates a self-reinforcing cycle that increases fat storage and further decreases testosterone levels. The hypogonadal–obesity–adipocytokine hypothesis further suggests that the body is unable to compensate for low testosterone due to the suppressive effects of estrogen and certain adipocytokines (e.g., TNF-α, IL-6, leptin) on the hypothalamic-pituitary-gonadal axis, resulting in hypogonadotropic hypogonadism.

Additionally, excessive aromatase activity in obese men suppresses gonadotropin-mediated testosterone production. Most of the negative feedback exerted by circulating testosterone on the hypothalamic-pituitary axis is mediated via its conversion to estradiol, either in peripheral adipose tissue or centrally. This supports the known association between type 2 diabetes, MetS, and low gonadotropins. Several studies have reported increased levels of LH, FSH, and testosterone secretion in obese men treated with aromatase inhibitors and selective estrogen receptor modulators [10].

Insulin resistance and hyperglycemia are hallmark features of type 2 diabetes, often linked to obesity. Emerging evidence shows a strong association between low testosterone and diabetes, with testosterone replacement therapy (TRT) showing potential benefits in improving insulin sensitivity and glycemic control.

Multiple studies have demonstrated an inverse relationship between total testosterone and insulin levels, independent of age and obesity, in healthy, non-diabetic men. The San Antonio Heart Study also confirmed this inverse correlation between total and free testosterone and insulin levels. A meta-analysis of 21 clinical studies involving 3,825 men confirmed a high prevalence of low testosterone in individuals with diabetes and/or MetS. Conversely, men with higher testosterone levels had a 42% lower risk of developing type 2 diabetes. Some studies also suggest that low testosterone may precede the onset of diabetes or insulin resistance [11].

Moreover, the third National Health and Nutrition Examination Survey (NHANES III) found that men in

the lowest tertile of free or bioavailable testosterone were significantly more likely to have diabetes than those in the highest tertile—even after adjusting for age and obesity. These findings collectively suggest that low testosterone is closely linked with diabetes and MetS and may play a crucial role in the pathogenesis of insulin resistance.

In a recent cross-sectional study of 355 men with type 2 diabetes, Kapoor and colleagues found that 17% had overt hypogonadism (defined by clinical symptoms and total testosterone <8 nmol/L and/or bioavailable testosterone <2.5 nmol/L), while an additional 25% had borderline hypogonadism. Another study, using equilibrium dialysis to measure free testosterone in 103 men with type 2 diabetes, found that 33% had free testosterone levels below the normal range, indicating biochemical hypogonadism [12].

Longitudinal studies have confirmed that low testosterone is an independent risk factor for the development of diabetes and MetS. Baseline testosterone levels were inversely associated with central fat accumulation (but not with other fat depots) in a cohort of 110 men. The Massachusetts Male Aging Study (MMAS), the Multiple Risk Factor Intervention Trial (MRFIT), and the Rancho Bernardo Study all demonstrated inverse correlations between baseline testosterone and the subsequent development of diabetes. A Finnish study also showed that low baseline testosterone and SHBG levels predicted the onset of MetS and diabetes during an 11-year follow-up period [13].

The precise mechanisms linking testosterone with insulin resistance and type 2 diabetes are not yet fully understood. While testosterone deficiency can lead to increased fat accumulation—thereby contributing to insulin resistance—this alone may not fully explain its overall impact on insulin sensitivity. For example, a study using hyperinsulinemic-euglycemic clamps to assess insulin resistance in 60 men with varying degrees of glucose tolerance (from normal to diabetic) found an inverse relationship between total testosterone and insulin resistance. The researchers also discovered that low testosterone impairs mitochondrial oxidative phosphorylation in muscle biopsies. Since up to 70% of the body's insulin sensitivity is attributed to skeletal muscle, reduced insulin sensitivity in the hypogonadal state may significantly contribute to systemic insulin resistance.

Low testosterone levels are closely associated with the development of metabolic syndrome (MetS). Hypogonadal men tend to have increased body fat mass, as shown in a study of 57 men aged 70–80 years, where testosterone levels were negatively correlated with percentage body fat. Several epidemiological studies have also demonstrated associations between testosterone and MetS. For instance, a Finnish study of 1,896 nondiabetic men found that both free and total testosterone levels were significantly lower in individuals with MetS. The Quebec Family Study reported that higher testosterone levels were associated with a reduced risk of MetS and improved insulin sensitivity. Conversely, another study involving 803 men found that hypogonadism was highly prevalent among individuals with MetS [14].

The Baltimore Longitudinal Study of Aging, which included 618 community-dwelling healthy men with a mean age of 63 years, showed that age alone did not predict the development of MetS. However, both total testosterone and SHBG levels were inversely associated with the development of MetS over a mean follow-up period of 5.8 years, while the free testosterone index and body mass index (BMI) were positively associated with MetS incidence. Similarly, the Massachusetts Male Aging Study analyzed 950 non-obese men without MetS and found that low testosterone levels predicted the subsequent development of MetS [15].

Moreover, follow-up data from the aforementioned Finnish study indicated that men with MetS at baseline were at increased risk of developing hypogonadism over an 11-year period [16]. A recent cross-sectional study from Australia involving 2,502 community-dwelling men aged 70 years without diagnosed diabetes reported that men with hypogonadotropic hypogonadism had a high prevalence of MetS. These findings further support the strong association between low testosterone levels and the development of MetS.

In summary, there is substantial evidence linking low testosterone levels and clinical hypogonadism to a higher prevalence of MetS and type 2 diabetes in men. Hypogonadism negatively influences several components of MetS, especially cardiovascular risk factors. Testosterone deficiency itself is recognized as a significant risk factor for the development of MetS and type 2 diabetes [17].

CONCLUSIONS

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities that predispose individuals to the development of diabetes, atherosclerosis, and cardiovascular disease (CVD). It is important to determine whether MetS is accompanied by diabetes, as many individuals with MetS may already have established diabetes and/or vascular disease. Due to the overlapping characteristics between MetS and Cushing's syndrome (CS), it has been proposed that the pathogenesis of MetS and central obesity may involve chronic exposure to elevated glucocorticoids.

Emerging evidence suggests that patients with MetS exhibit hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in a state referred to as "functional hypercortisolism." Stress is thought to play a key role in this process by increasing the reactivity of the HPA axis. Furthermore, low birth weight has been associated with elevated circulating cortisol levels, indicating a possible long-term dysregulation of the HPA axis due to early-life stress or epigenetic programming.

The enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which regulates glucocorticoid metabolism in peripheral tissues—particularly adipose tissue and the liver—has been implicated in both MetS and central obesity. Overexpression of 11β-HSD1 in adipocytes has been observed in individuals with MetS, leading to enhanced conversion of inactive cortisone into active cortisol, thereby increasing local glucocorticoid activity. Experimental studies using 11β-HSD1 inhibitors support the involvement of this enzyme in the pathogenesis of MetS and suggest that targeting 11β-HSD1 may offer novel therapeutic strategies for managing MetS and obesity.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Mariia Cherska
V.P. Komisarenko Institute of Endocrinology and
Metabolism of the National Academy of Medical Sciences of Ukraine
69 Vyshgorodska St., 04114 Kyiv, Ukraine
e-mail: emariya83@gmail.com

ORCID AND CONTRIBUTIONSHIP
Mariia Cherska: 0000-0002-3689-2683 A B D F
Olena Pavlenko: 0009-0003-8913-6130 D
Khrystyna Kukharchuk: 0000-0002-2495-2693 D
Olena V. Maidanuik: 0000-0003-0451-1847 D E F

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