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REVIEW

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Metabolic syndrome, adipokines and sex hormone concentrations in middle-aged women

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ABSTRACT

The incidence of metabolic syndrome (MetS) increases with age, something which is more noticeable in women, particularly perimenopausal women. Weight gain and the development of abdominal obesity are considered to be the main cause of increased risk of MetS and cardiometabolic factors in perimenopausal women. Increased visceral adipose tissue correlates with elevated insulin resistance, inflammation, hypertension and hyperlipidaemia in middle-aged women.

In recent years, particular attention has been drawn to the endocrine role of adipose tissue, mainly visceral adipose tissue, and the concentrations of adipokines and inflammation markers such as: leptin, adiponectin, free fatty acids, adipocyte fatty acid binding protein, C-reactive protein (CRP), and inflammatory cytokines. The development of abdominal obesity is mostly associated with a loss of the protective role of oestrogens and a relative increase of circulating androgens. After menopause, the adipose tissue serves as the primary source of oestrogen production via aromatisation that converts androstenedione and testosterone to oestrone and 17β-oestradiol (E2), respectively. Studies looking at the relation between menopause and MetS conducted over the past years have mostly focused on the analysis of such hormone balance parameters as: E2, free oestradiol, oestrone and androgenic indicators: total testosterone, free testosterone, sex hormone binding globulin or dehydroepiandrosterone sulfate. In most cases, the results of the research indicate a greater importance of androgenic markers in the assessment of MetS and cardiometabolic risk factors occurrence in perimenopausal and postmenopausal women.

Key words: menopause, adipokines, inflammation markers, sex hormones

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Introduction

Metabolic Syndrome (MetS) is a co-occurrence of risk factors of metabolic origin, favouring the development of cardiovascular diseases of atherosclerotic and type 2 diabetes origins. In recent years, various organisations have been introducing criteria for MetS diagnosis. Currently, metabolic syndrome is defined on the basis of occurrence of the following: abdominal obesity, hypertension, low HDL-cholesterol levels, elevated levels of triglycerides (TG) and hyperglycaemia. According to the International Diabetes Federation (IDF), abdominal obesity and two additional criteria are essential for a MetS diagnosis [1]. In 2009, IDF criteria were updated and harmonised with the recommendations of other associations and organisations such as: the National Heart, Lung and Blood Institute, the American Heart Association, the World Health Federation, the International Atherosclerosis Society and the International Association for the Study of Obesity. However, the most important change was the introduction of a choice of three out of five criteria, excluding a need for abdominal obesity occurrence when diagnosing MetS (Tab. 1) [2].

In recent years, a notion of 'cardiometabolic risk' has arisen. Cardiometabolic risk is defined as the co-occurrence of risk factors that increase the risk of cardiac diseases and type 2 diabetes. Cardiometabolic risk is not a disease but rather a group of disorders, which, occurring individually or together, can increase cardiac disease and type 2 diabetes risks. The following can be listed as cardiometabolic risk factors: abdominal obesity, low HDL-C levels, high levels of triglycerides, total cholesterol, LDL cholesterol, glucose, increased

Table 1. Chosen definitions of MetS

NCEPT: ATPIII[1] (2001)
Any three out of the following: – waist circumference in men > 102 cm, in women > 88 cm – plasma TG concentration ≥ 150 mg/dL or HDL-C < 40 mg/dL in men and < 50 mg/dL in women – arterial pressure ≥ 130/85 mm Hg – fasting glucose ≥ 110 mg/dL
IDF[2] (2005)
Improper waist circumference (depending on population) in European men ≥ 94 cm, in women ≥ 80 cm Plus two of the following: – plasma TG concentration ≥ 150 mg/dL or HDL-C < 40 mg/dL in men and < 50 mg/dL in women or hypoglycaemia treatment – arterial pressure ≥ 130/85 mm Hg or antihypertensive treatment – fasting glucose ≥ 100 mg/dL or hypoglycaemia treatment
Consensus definition IDF and AHA/NHLBI[3] (2009)
Any three of the following: – improper waist circumference (depending on population) in European men ≥ 94 cm, in women ≥ 80 cm – plasma TG concentration ≥ 150 mg/dL or HDL-C<40 mg/dL in men and < 50 mg/dL in women or hypoglycaemia treatment – arterial pressure ≥ 130/85 mm Hg or antihypertensive treatment – fasting glucose ≥ 100 mg/dL or hypoglycaemia treatment

[1]National Cholesterol Education Programme Adult Treatment Panel III; [2]International Diabetes Federation; [3]American Heart Association/National Heart Lung and Blood Institute; TG — triglycerides; HDL-C — high-density lipoprotein-cholesterol

rates of insulin resistance and inflammation, hypertension, and smoking.

The results of epidemiological research indicate a high prevalence of MetS in the USA and in Europe, including Poland. It is estimated that 20–25% of the adult population of developed countries meet the MetS diagnostic criteria [3]. The results of the multi-centre Polish Research on Health State of Population programme (WOBASZ — Wielkoośrodkowe Ogólnopolskie Badanie Stanu Zdrowia Ludności) show that in Poland MetS is diagnosed in every fifth person on average (19–23% of men and 19–20% of women) [4]. It is estimated that individuals with MetS have a two-fold increased risk of cardiac disease and a five-fold increased risk of type 2 diabetes.

The incidence of MetS increases with age, something which is more noticeable in women, particularly perimenopausal women. According to various data, the prevalence of MetS during this period increases significantly and is estimated to be 31–41% [5–7]. It has been proven that in postmenopausal women the risk of MetS is increased by up to 60%, not dependent on BMI, age or physical activity [8].

Weight gain and the development of abdominal obesity are considered the main cause of increased risk of MetS and cardiometabolic factors in perimenopausal women. Increased visceral adipose tissue correlates with elevated insulin resistance, inflammation, hypertension and hyperlipidaemia in middle-aged women. In recent years, particular attention has been drawn to the endocrine role of adipose tissue, mainly visceral adipose tissue. It has been shown that adipose tissue can influence the development of MetS by secreting adipokines as well as growth factors and cytokines. These compounds participate in a number of metabolic processes related to carbohydrate and lipid balance, inflammations, coagulation, feelings of hunger and satiety in the central nervous system. While setting criteria for MetS diagnosis, the International Diabetes Federation (IDF) focused on obesity as the main criterion for MetS and supplemented the classification of MetS with additional parameters such as: concentration of leptin, adiponectin, free fatty acids, CRP, inflammatory cytokines (Il-6, TNF-α), and prothrombotic factors (fibrinogen, PAI-1) [9]. These parameters are known as 'platinum standards' due to their significant role in the development of MetS [10].

Relation of CRP, adiponectin, leptin and A-FABP to MetS and cardiometabolic risk factors incidence in women

CRP

Low-intensity inflammation is an important factor in subjects with MetS and can contribute to an increased risk of cardiovascular diseases and the development of diabetes. Among various studied inflammatory biomarkers, CRP is the best documented and most standardised parameter. Numerous studies have confirmed a relation between CRP and MetS and cardiometabolic risk factors [10–12]. A strong correlation between CRP and MetS factors, LDL, insulin and HOMA-1 level has been demonstrated. Ridker et al. in their eight-year prospective study (Women Health

Study) found that CRP above 3 mg/L in MetS women is related to a higher relative risk (RR) of cardiovascular disorders [13]. Studies using recombinant human CRP have demonstrated that CRP can directly interfere with the insulin signalling pathway and stimulate inflammation in the vascular endothelium by increasing the expression of adhesion molecules [14, 15]. Furthermore, it has been observed that leptin correlated positively with CRP in MetS subjects, while the correlation of adiponectin with CRP was negative [16]. It is worth mentioning that CRP is a sensitive but non-specific inflammatory biomarker, which makes its contribution in the assessment of cardiometabolic risk difficult to quantify.

Adiponectin

Adiponectin is a polypeptide hormone that is produced and secreted into the blood by mature adipocytes. Adiponectin level in the blood is relatively high compared to other hormones and constitutes 0.01% of all plasma proteins. Furthermore, adiponectin concentration is higher in women than in men and increases with age. Also, higher levels of adiponectin are observed in postmenopausal women compared to premenopausal women. Reduced adiponectin level is related to obesity, MetS, type 2 diabetes and cardio-vascular disorders. Adiponectin influences a number of metabolic processes, particularly glucose and fatty acid metabolism in the liver and muscles. Therefore, it presents anti-inflammatory, antiatherosclerotic and insulin-sensitising activity. A lower adiponectin concentration is also considered to be a link between visceral obesity and insulin resistance [17]. The latest studies suggest that adiponectin improves insulin sensitivity better in postmenopausal than in premenopausal women [18].

Leptin

Leptin is a hormone secreted by adipocytes which is involved in the regulation of food intake and energy balance. After binding leptin to receptors in the hypothalamus, neurons cease to produce neuropeptide Y — an appetite stimulant. By these means, the hormone suppresses the appetite and stimulates the sympathetic system. Leptin concentration correlates positively with the amount of body fat and is higher in women than in men [19]. However, no difference was found among groups of premenopausal and postmenopausal women. In women, leptin is secreted mainly by subcutaneous adipose tissue [20]. Disorders of leptin secretion as well as lack of receptors' sensitivity for this hormone often lead to excess weight or obesity. In the majority of cases, obesity is accompanied by hyperleptinaemia; it seems that obese people become insensitive to the effects of endogenous leptin. Numerous studies have proved the participation of leptin in the development of insulin resistance, hypertension or hyperleptinaemia [21].

Adipocyte fatty acid binding protein (A-FABP) — a new adipokine related to pathophysiology, MetS occurrence and cardiometabolic risk factors

A-FABP belongs to the fatty acid binding proteins. Mostly it is synthesised and released by subcutaneous adipocytes. In adipocytes, it constitutes almost 1% of the total cytosol protein, while, to a smaller extent, it is produced in macrophages and endothelial cells. Cytoplasmic A-FABP binds mainly long chained fatty acids, then directs them to appropriate intracellular disposal [22]. A-FABP participates in the pathophysiology of MetS, particularly by inducing hypertriglyceridaemia and insulin resistance. Studies in animals have demonstrated that A-FABP deletion protected obese mice from insulin resistance, hyperinsulinaemia and increased glucose concentration [23]. Moreover, A-FABP participates in the development of atherosclerotic lesions by promoting the accumulation of triglycerides and cholesterol in macrophages and inducing proinflammatory cytokines in macrophages. A-FABP's influence on endothelial cell proliferation and angiogenesis has also been suggested. In recent years, A-FABP has been recognised as a biomarker of MetS, type 2 diabetes and cardiovascular disorders [24]. It has been also demonstrated that serum A-FABP concentration is higher in women than in men, similarly to the relation of A-FABP and cardiometabolic risk factors. It is suggested that this difference is due to women's greater content of subcutaneous adipose tissue.

Relation of sex hormones to MetS, type 2 diabetes and cardiometabolic risk factors incidence in women

The development of abdominal obesity, and thereby higher incidence of MetS or type 2 diabetes in perimenopausal and postmenopausal women, is mostly associated with a loss of the protective role of oestrogens and a relative increase of circulating androgens. After the menopause, when ovarian production ceases and ovarian feedback is lost, the adipose tissue serves as the primary source of oestrogen production via aromatisation that converts androstenedione and testosterone to oestrone (E1) and E2, respectively. Therefore, obese postmenopausal women have higher concentrations of E2, E1 and oestrone sulfate than non-obese postmenopausal women [25, 26]. Studies looking at the relation

between menopause and MetS conducted over recent years have mostly focused on the analysis of such hormone balance parameters as: 17β-oestradiol, free oestradiol, oestrone and androgenic indicators: total testosterone, free testosterone, sex hormone binding globulin (SHBG) or dehydroepiandrosterone sulfate (DHEA-S). In most cases, the results of the research indicate a greater importance of androgenic markers (especially testosterone and SHBG) in the assessment of MetS and cardiometabolic risk factors occurrence in perimenopausal and postmenopausal women [27, 28].

Sex hormone binding globulin (SHBG)

Sex hormone binding globulin (SHBG) is a protein synthesised in the liver that transports sex hormones into the blood. Since SHBG has a higher affinity to testosterone binding than oestradiol binding, it is considered an efficient androgenisation biomarker [29]. Assessing total testosterone concentration including SHBG allows a calculation of the amount of bioavailable testosterone and free androgen index.

In women, oestrogens stimulate SHBG synthesis, whereas androgens, insulin and excess weight, particularly visceral obesity, influence a decrease of SHBG synthesis. It has been demonstrated that the positive effect of oestrogens on SHBG synthesis is stronger in premenopausal than in postmenopausal women. A number of studies indicate that insulin is a potent inhibitor of SHBG synthesis; therefore, this protein is considered a good indicator of insulin resistance. Reduced SHBG concentration is observed as an effect of severe androgenisation and hyperinsulinaemia in women with polycystic ovary syndrome (PCOS) and in obese postmenopausal women [30, 31]. A relation has also been demonstrated in women between reduced SHBG concentration and MetS incidence, type 2 diabetes and cardiovascular disorders. Low plasma concentration of SHBG is weakly associated with type 2 diabetes in men [32].

Testosterone

Testosterone is a steroid hormone, which is secreted primarily by the testicles of males and the ovaries of females, although small amounts are also secreted by the adrenal glands. In postmenopausal women without diabetes, endogenous total and free testosterone concentration is positively associated with markers of insulin resistance and measures of adiposity [33–35]. On the contrary, testosterone is inversely associated with adiposity in men. Experiments in female rats showed that testosterone impairs insulin-mediated glucose uptake and increases lipogenesis [36]. The results of cross-sectional studies have shown that middle-aged women with type 2 diabetes had significantly higher levels of testosterone compared to controls, whereas men with type 2 diabetes had significantly lower plasma total testosterone. These sex-dependent differences remained significant even after adjusting for study-level differences in age, race and diabetes diagnosis criteria, as well as internal control for BMI and WHR. Several potential explanations exist for the elevations in androgen levels in postmenopausal diabetic women. It is possible that the reduction in SHBG concentration in diabetic women permits more testosterone to circulate in its unbound or active form. Moreover, the ovaries of postmenopausal women remain hormonally active, with an increase in the ratio of androgen to oestrogen production [37].

Dehydroepiandrosterone sulfate

Dehydroepiandrosterone (DHEA) is a steroid hormone produced in the adrenal cortex from cholesterol. It is the primary precursor of natural oestrogens. Dehydroepiandrosterone sulfate (DHEAS) is a more stable circulating form of this hormone. Endogenous DHEAS has been positively associated with both insulin resistance and central adiposity in postmenopausal women [38, 39]. However, other studies have suggested that DHEAS is inversely associated with diabetes and insulin resistance, or is not associated with insulin resistance and other components of metabolic syndrome [40]. Human investigations of exogenous DHEA and glucose metabolism have yielded controversial results [41, 42]. Some authors have found that treatment with DHEA decreased visceral adiposity and improved insulin action, while others did not observe any benefits of DHEA [43, 44].

Oestradiol

The results examining an association between oestradiol (E2) concentration and the parameters of metabolic syndrome and type 2 diabetes are divergent. Although some studies have shown a positive correlation between oestradiol and insulin resistance or type 2 diabetes in postmenopausal women, even after controlling for BMI [45, 46], other studies have shown no such relationship [47]. The relationship between elevated oestradiol concentration and metabolic syndrome parameters is mainly explained by the fact that E2 concentration is a marker of increased aromatase conversion of androgens in adipocytes of postmenopausal women. The free E2 is a better marker of metabolic disturbances because this fraction is more biologically active and is associated with a lower

level of SHBG in women. E2 may be associated with diabetes risk through its relation to insulin resistance, adiposity, and/or inflammatory markers. High endogenous E2 in physiological states such as puberty, the luteal phase of the menstrual cycle, and late pregnancy, are associated with insulin resistance and may involve reduced glucose transporter 4 (GLUT4) muscle expression [48]. Although studies of low-dose exogenous E2 in the form of hormone replacement therapy have been associated with a lower risk of diabetes in postmenopausal women, other studies have found exogenous oral E2 administration at higher doses to be associated with greater insulin resistance [46]. Endogenous E2 is also associated with the development of adiposity [35, 49], although endogenous E2, itself, results from aromatisation of androgens in adipocytes; thus, the relationship between E2 and adiposity is likely to be bidirectional. One animal study suggested that E2 may have direct effects on adipocyte enlargement, and in consequence, weight gain [50], although other studies show the opposite effect [51, 52]. E2 may also have effects on diabetes incidence through its association with inflammatory markers. Elevated inflammatory factors such as CRP have been found in women on oral oestrogen treatment [53], and inflammatory markers have also been positively associated with endogenous oestrone levels [54]. Because inflammatory markers have been linked to the development of diabetes [55], this might provide another mechanism by which E2 could lead to diabetes. E2 is also associated with lipid abnormalities and lower physical activity [56].

Follicle-stimulating hormone

Follicle-stimulating hormone (FSH) is a glycoprotein secreted by the anterior pituitary gland. In men, FSH stimulates the seminiferous epithelium and synthesis of testosterone, while in the follicular phase in premenopausal women it stimulates follicular development and initiates oestrogen synthesis; in the luteal phase, it stimulates the production of progesterone. Secretion of FSH is regulated by oestradiol and testosterone affecting hypothalamus by a negative feedback. In the early stage of the postmenopausal period, FSH level is changeable; however, in the late stage it increases (above 25 IU/L). The highest FSH concentration can be observed 2–3 years after menopause when oestrogen production is reduced and hormone balance is set at a new level with low oestrogen concentration and high gonadotropin concentration. According to the latest recommendations [Stages of Reproductive Ageing Workshop (STRAW) + 10], the level of FSH and oestradiol (E2) is stabilised about two years after the last menstruation [57, 58]. FSH measurement is used mostly in infertility and impotence diagnostics, as well as in menstrual and maturation disorders. The association between FSH and MetS factors is described mostly in premenopausal PCOS women and men with type 2 diabetes. PCOS is related to weight excess and visceral obesity as well as the development of insulin resistance. The probability of type 2 diabetes occurrence is 5-10-fold higher in PCOS women compared to healthy women. In PCOS women, a higher LH concentration and an unchanged/decreased FSH level can be observed. In PCOS diagnostics, LH/FSH evaluation (value up to 2.5) is used [59, 60]. Reduced LH and FSH along with low free testosterone level (hypogonadotropic hypogonadism) can be observed in 25% of men with type 2 diabetes. Hypogonadotropic hypogonadism in men is related to visceral obesity, insulin resistance, MetS and increased CRP [61]. After menopause, a negative correlation between the concentration of FSH and BMI has also been observed [62, 63].

Conclusion

The incidence of MetS or type 2 diabetes increases with age, something which is more noticeable in women, particularly perimenopausal women. Recent studies have clearly shown that the development of metabolic disorders is significantly associated with concentrations in the circulation of adipokines and sex hormones in women during menopausal transition.

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