Submitted: 25.07.2023
Accepted: 14.09.2023
Early publication date: 07.11.2023

Endokrynologia Polska
DOI: 10.5603/ep.96679
ISSN 0423–104X, e-ISSN 2299–8306

Obesity in perimenopause — current treatment options based on pathogenetic factors

Dominik Porada*, *Jakub Gołacki*, *Beata Matyjaszek-Matuszek

Chair and Department of Endocrinology, Diabetology, and Metabolic Diseases, Medical University of Lublin, Lublin, Poland

Abstract

The health of post-menopausal women has become of paramount concern due to the aging of the world's population. Concurrently, the prevalence of obesity among postmenopausal women is expected to increase, presenting a significant public health challenge. Although weight gain during menopause is a well-observed phenomenon, its underlying causes and mechanisms remain incompletely understood. This manuscript reviews the literature to explore potential hormonal factors and pathomechanisms contributing to obesity during perimenopause, aiming to identify pathogenic factors that can guide treatment selection. Menopause-induced hormonal changes, including hypoestrogenaemia, hypergonadotropinaemia, relative hyperandrogenaemia, growth hormone deficiency, leptin resistance, and chronic stress affecting the hypothalamic-pituitary-adrenal axis, have been implicated in the onset of obesity in perimenopausal women. These hormonal fluctuations, alongside lowered daily energy expenditure, lead to metabolic alterations that elevate the risk of developing metabolic disorders and cardiovascular diseases. Weight gain in perimenopausal women is associated with higher total and abdominal adipose tissue and lower lean body mass. Addressing this issue requires individualized behavioural management, supported by effective pharmacological therapy, and, when warranted, complemented by bariatric surgery. Modern obesity treatment therapies have demonstrated safety and efficacy in clinical trials, offering the potential to reduce excess body fat, improve metabolic profiles, lower cardiovascular risk, and enhance the quality and longevity of women's lives. In addition to standard obesity therapies, the article examines different treatment strategies based on obesity's pathogenic factors, which may offer promising options for treating obesity with or without complications in perimenopausal women. One such potential approach is menopausal hormone therapy (MHT), which hypothetically targets visceral obesity by reducing visceral adipose tissue accumulation, preserving metabolically active lean body mass, and improving lipid profiles. However, despite these reported benefits, gynaecological and endocrinological societies currently do not recommend the use of MHT for obesity prevention or treatment, necessitating further research for validation. Emerging evidence suggests that visceral obesity could result from hypoestrogenaemia during perimenopause, potentially justifying the use of MHT as a causal treatment. This highlights the importance of advancing research efforts to unravel the intricate hormonal and metabolic changes that occur during perimenopause and their role in obesity development.

Key words: *menopause; perimenopause; obesity; pharmacotherapy; menopausal hormone therapy*

Introduction

Obesity has been a growing global health concern worldwide for several decades. It is a well-known cause of many medical complications, such as type 2 diabetes, hyperlipidaemia, arterial hypertension, cardiovascular diseases, osteoarthritis, depression, and several cancers, to name a few [1]. Cardiovascular diseases are more common in obesity, and mortality from them is higher compared to patients without obesity, regardless of other risk factors [2]. Even though a lot of research on the pathophysiology of obesity should be conducted, several scientific societies (e.g. the Polish Society for the Treatment of Obesity, PTLO) have already changed the nosology of obesity from a state to a disease [3]. Therefore, clinical practice guidelines for adult obesity management call for a paradigm shift in obesity treatment that will focus on patient-centred care moving away from the paternalistic "eat less, move more" approach [4].

Obesity prevalence rises with age: from 39.7% in women aged 20–39 years to 43.3% in women aged 40–59 years as well as 60 years and over in the US, and from 6% in women aged 35–44 years to 23–24% in women aged 45–64 years in Poland [5–8]. This finding was corroborated in the United States and 28 European Union countries, Poland included, and it indicates a fourfold increase in prevalence in perimenopausal women (Tab. 1). With the aging of the world's population, the health of post-menopausal women is of unprecedented concern. We can expect a further increase in the prevalence of obesity in postmenopausal women, which is likely to be an important public health challenge.

Menopause is a physiological period in a woman's life associated with many hormonal changes resulting

Jakub Gołacki, MD, Chair and Department of Endocrinology, Diabetology, and Metabolic Diseases, Medical University of Lublin, Jaczewskiego 8, 20–954 Lublin, Poland, tel/fax: 81 7244668/69, e-mail: jakub.golacki@gmail.com

Table 1. *Prevalence of obesity in different age groups in the United States (USA) and Poland*

Country	Age group [years]	Percentage of women with obesity (%)
USA	20–39	39.7
	40–59	43.3
	60 and over	43.3
Poland	24–34	8
	35–44	6
	45–54	23
	55–64	24
	65 and over	26

Table 2. *Potential hormonal causes and pathomechanisms of obesity during perimenopause*

Hypoestrogenaemia and hypergonadotropinaemia (menopause)
Relative hyperandrogenaemia
GH deficiency (somatopause)
Leptin resistance
Chronic stress, dysfunction of the hypothalamic-pituitary-adrenal axis

GH — growth hormone

from complete inhibition of ovarian function, which ultimately leads to the absence of menstruation and the loss of reproductive function. According to the definition proposed by the North American Menopause Society, menopause is diagnosed when menstruation stops for a period of 12 consecutive months with the exclusion of other causes of secondary amenorrhoea. It usually happens at the age of 51.4 years, but the time varies based on socioeconomic status and tobacco use [9, 10]. Because the current life expectancy for a woman is 80 years, the average woman lives about 30% of her total lifespan after menopause.

The presence of increased weight gain during menopause has been observed, but the causes and mechanisms are not fully understood. In this manuscript, we review the literature of possible mechanisms of this pathology to select the treatment most based on pathogenic factors.

Hormonal changes during perimenopause

The female reproductive system matures in a continuous natural process from menarche to menopause as the finite number of oocytes produced during foetal development is gradually lost both through ovulation and aging. The main and characteristic hormonal changes that occur during menopause are as follows: a significant decrease in oestrogen production by the female gonads, replacement of the ovaries by the adrenal glands as the main source of oestrogen precursors, a decrease in progesterone concentrations resulting from anovulation, and a significant increase in the production of gonadotropic hormones and androgens (Tab. 2). As a consequence of the above changes, an increase in the ratio of androgens to oestrogens is observed [11]. Another important issue is the impact of non-sex hormones, such as leptin or growth hormone (GH), on the energy homeostasis of the body and a heightened risk of developing visceral obesity. Changes in the concentrations and mode of action of these hormones in the body are one of the vital factors causing a rise in the total amount of adipose tissue, including visceral adipose tissue, which in turn may lead to abdominal obesity and related metabolic disorders (Fig. 1).

Oestrogens

Among the above-mentioned changes, the most significant clinical effect is associated with hypoestrogenaemia because oestrogen receptors are present throughout the human body and play an extremely important role in the energy metabolism of the body.

Oestrogens suppress appetite and food intake in central mechanisms, which results in stabilization of body weight with promotion of femoral-gluteal adipose tissue distribution [12]. The direct and indirect influence of oestrogens on the control of appetite and food intake underlie this mechanism, which results from the modulation of both anorexic and orexigenic signals in the hypothalamus [13]. Oestrogens can also affect peptide hormones involved in the regulation of eating behaviours such as ghrelin, neuropeptide Y (NPY), and melanocyte-stimulating hormone (MSH). Oestrogens inhibit the orexigenic activity of NPY and MSH, and this effect is most likely due to reduced mRNA expression of both peptides and changes in the activity of their receptors [14, 15]. The direct impact of oestrogens on the orexigenic activity of NPY also has an indirect effect on the action of ghrelin, which in turn has an antagonistic effect on leptin through the neuropeptide Y/Y1 receptor pathway [16]. The role of oestrogens in the regulation of energy homeostasis is confirmed in experimental studies on rats after ovariectomy in which an increase in the amount of food intake and a tendency to develop obesity were observed. In addition, studies conducted both on animals and humans consistently indicate that menopausal hormone therapy (MHT) helps to reduce the excessive amount of food intake resulting from hypoestrogenaemia [17, 18].

Oestrogen deficiency causes changes in adipose tissue distribution towards central predominance (visceral, central, abdominal obesity) compared to periph-

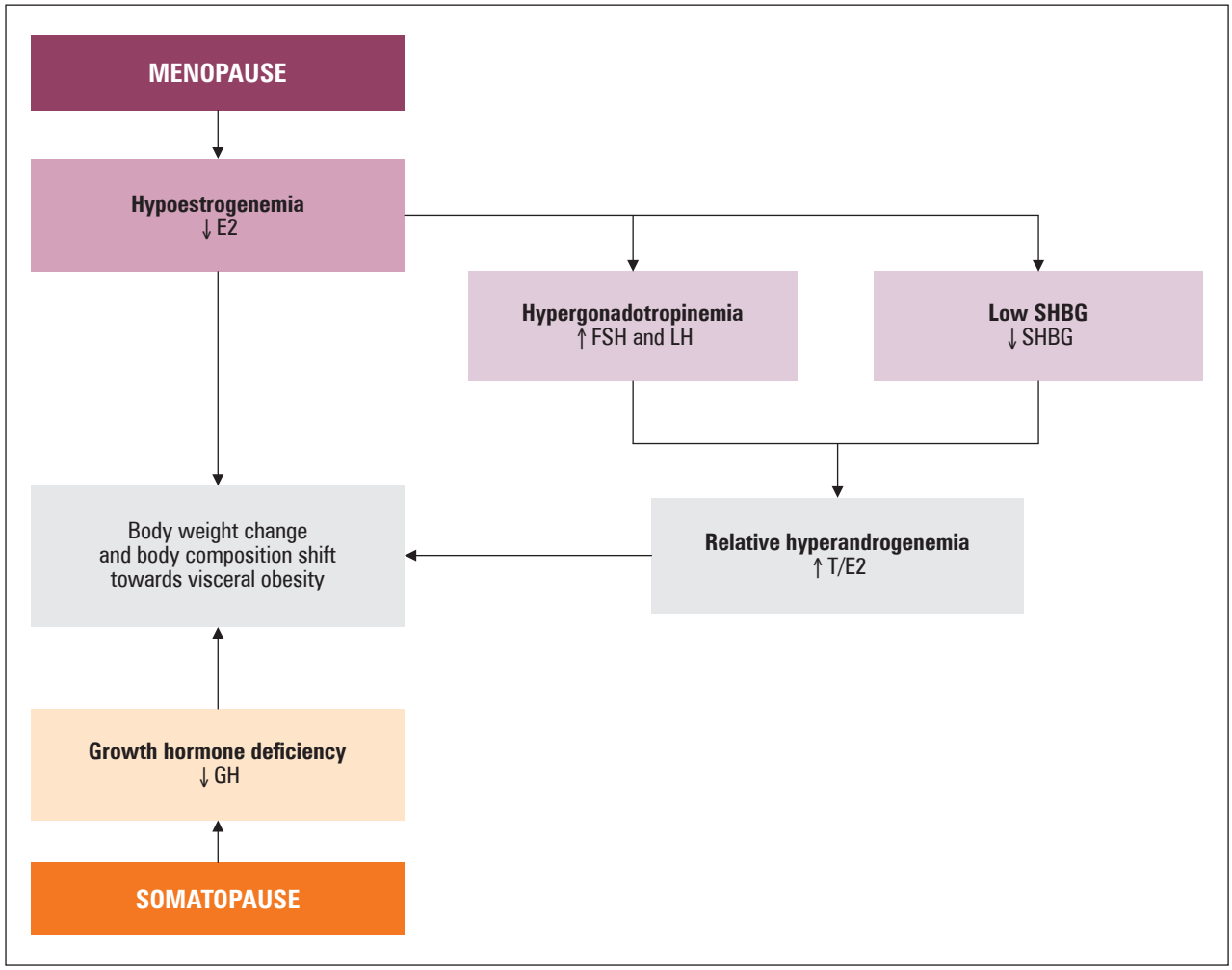

Figure 1. *Pathomechanisms of visceral obesity during perimenopause. E2 — oestradiol; FSH — follicle-stimulating hormone; LH — luteinizing hormone; SHBG — sex hormone-binding globulin; T — testosterone; GH — growth hormone*

eral location (gluteal and femoral). Hypoestrogenaemia interferes with the proper stimulation of lipoprotein lipase (LPL) activity in femoral adipocytes and lipolysis in abdominal adipocytes, thus promoting the accumulation of visceral adipose tissue. The consequence of the loss of lean body mass observed during perimenopause is a reduced resting metabolic rate, which results in a decrease in energy expenditure and fat oxidation at rest, but also during physical activity, which may additionally predispose to weight gain [19]. Importantly, the correlation of menopause with a significant increase in body weight and BMI [20] has not been proven. However, it was found that menopause correlates with an increase in waist circumference and a change of body composition with more adipose tissue, especially in the abdominal area [21–23], where, in fact, this is the parameter that correlates better with metabolic complications typical of obesity [24].

Although the pathomechanism of this phenomenon has not yet been fully elucidated, oestrogens are thought to have a protective effect on glucose metabolism through a number of mechanisms, including increasing insulin levels in response to oestrogen receptor stimulation by oestradiol, regulating insulin release by promoting glucose-dependent stimulation, reducing insulin-mediated glucose uptake, lowering insulin resistance, and inhibiting pancreatic β-cell apoptosis by reducing inflammation as a result of decreasing the concentration of pro-inflammatory cytokines (tumour necrosis factor alpha [TNF-α], interleukin 6 [IL-6], and monocyte chemoattractant protein 1 [MCP-1]). During menopause, this protective effect is significantly weakened due to a high deficiency of sex hormones, including, above all, hypoestrogenaemia [25–30].

Hypergonadotropinaemia observed during perimenopause, and, in particular, elevated FSH concentration, is not only a physiological consequence of hypoestrogenism, but it also plays a direct role in the regulation of body weight and composition. Literature has shown that high FSH concentration promotes adipose tissue accumulation, while blocking the FSH action reduces

this effect, which may explain one of the mechanisms of MHT action on anthropometric indices [31].

Androgens

Another mechanism involved in the induction of obesity, which is also a consequence of hypoestrogenism, is an increase in the ratio of androgens to oestrogens. Testosterone may stimulate appetite in the central mechanism by selectively increasing the number of meals but not their volume. The proposed mechanism of increasing caloric intake is based on the weakening of the expression of anorexigenic signals in the proopiomelanocortin/cocaine- and amphetamine-regulated transcript (POMC/CART) pathway [32]. In addition, testosterone causes higher visceral fat accumulation, but it also affects the increase in lean body mass. Observational studies have found a significant effect of androgens in the development of eating disorders, mainly bulimic behaviour, by stimulating appetite and reducing central impulse control. On the other hand, MHT with the use of oestrogens has an opposite effect that involves reducing bulimic behaviour and counteracting android obesity during perimenopause [12, 32]. An atrophic ovary is stimulated by the increasing FSH levels to produce mainly androstenedione and testosterone, but only about 20% of the circulating androstenedione come from the ovarian pool. These androgens are a substrate for extragonadal aromatization to oestrogens, mainly to oestrone. However, oestrone concentrations are much lower than in women of reproductive age and no longer serve a protective function against the onset of clinical and metabolic symptoms of oestrogen deficiency [33]. Hyperandrogenaemia and a decrease in the pool of circulating sex hormone-binding globulin (SHBG) further increase the bioavailability of androgens, which in turn leads to android distribution of adipose tissue, which indirectly increases insulin resistance. In the Women's Health Study, elevated SHBG levels were associated with a lower risk of type 2 diabetes and circulating SHBG levels negatively correlated with insulin resistance. In turn, low levels of SHBG have been found to be a strong predictor of type 2 diabetes in women, but also in men [34,35].

Growth hormone

However, in addition to ovarian hormones, other hormones also play an important role in the energy homeostasis of the body. Lowering GH concentrations, as a result of aging, the physiological somatopause process, may cause weight gain and changes in adipose tissue distribution (reduction in lean body mass and increase in total adipose tissue, especially visceral) [36]. Significantly lower GH secretion was observed in menopausal women compared to premenopausal women, which suggests a clear relationship between changes in the regulation of adipose tissue volume and weight gain with concomitant somatopause. Of note, obesity and GH concentration are inversely proportional to each other, while obesity itself and the resulting metabolic changes lead to a decrease in GH secretion, which may lead to a vicious circle that exacerbates the problem of obesity. The study by Snel et al. serves as a confirmation of the mechanisms that occur under the influence of GH in the body because it showed an increase in lean body mass and a reduction in total body mass after the use of GH replacement therapy. However, considering the possible adverse events, there is no conclusive evidence that such therapy would be beneficial for menopausal patients. Consequently, safer methods to increase spontaneous GH secretion, such as sleep and exercise, may be considered [36, 37]. In addition, it has been shown that in perimenopausal women, as well as in people with obesity and in elderly people, the growth hormone-releasing hormone (GHRH) is clearly reduced. In turn, the use of MHT in postmenopausal women restores the normal response of GH to GHRH [38].

Leptin

The role of leptin in perimenopausal obesity has not been fully elucidated. Although changes in leptin levels caused by menopause have not been supported by evidence [39], due to the development of leptin resistance, it seems another important element that increases the likelihood of developing obesity after menopause. The central physiological action of leptin is to reduce the feeling of hunger by stimulating the satiety centre in the hypothalamus (arcuate nucleus), while the peripheral action results in lower release of lipids into the bloodstream, decreased triglyceride secretion in target cells, and a reduction in newly formed apolipoprotein B particles, which in turn reduces the production of chylomicrons and low-density lipoproteins (LDL) and increases the synthesis of apoA1, apoA4, and apoE [40]. Leptin secretion rises exponentially with increasing adipose tissue. Under physiological conditions, leptin binds to leptin receptors (LEP-R) in the brain and gives a signal to cease food intake and increase energy expenditure. However, after longer periods of positive energy balance, leptin resistance develops. It is defined as a reduced sensitivity or a failure in response of the brain to leptin, which causes a decrease in the ability of leptin to enhance energy expenditure or suppress appetite [41]. The mechanism and causes of leptin resistance are not yet fully understood. There are several potential mechanisms, namely mutations in the genes encoding leptin and its receptors, mutations in the genes encoding proteins involved in self-regulation of leptin synthesis, and blood-brain barrier permeability [42], as well as

the presence of IgG anti-leptin antibodies [43]. Several studies have shown significantly elevated leptin levels in women with obesity compared to women without obesity, but no significant differences in the levels of this hormone in pre- and postmenopausal periods. The effect of menopause on the increase in leptin synthesis has not been proven either. In the animal model study by Kastin et al., the authors showed a decrease in leptin transport to the central nervous system in mice after ovariectomy compared to mice before gonadectomy. Based on the study cited above, a hypothesis was formulated which indicated that the weight gain resulting from the loss of ovarian function in mice may be associated with decreased leptin transport across the blood-brain barrier, which translates into the development of leptin resistance [39, 44, 45].

Cortisol

Stress is a separate and slightly different issue in the pathogenesis of perimenopausal obesity. In animal studies, chronic stress has been shown to overstimulate food intake and to have an inhibitory effect on the hypothalamic-pituitary-adrenal (HPA) axis, as opposed to the acute stress response, which in turn activates it [46]. Long-term stress stimulation of the HPA axis strongly disturbs the entire homeostasis, and in the long term, chronic hypercortisolism increases the risk of metabolic syndrome, type 2 diabetes, and cardiovascular complications. The body adopts incorrect eating habits by selecting palatable but unhealthy food and adopting a tendency to apply incorrect patters in terms of food quantity, overeating, or undereating. Negative mood associated with the stress reaction also causes an increase in food intake, especially high-calorie foods. The perimenopausal period itself and clinical symptoms negatively perceived by a woman may initially induce a stress reaction, or additionally increase its intensity, which in turn intensifies incorrect eating habits and causes excessive weight gain [47, 48]. In addition, stress has an inhibitory effect on gastric motility, and observational studies on perimenopausal women have reported a reversible reduction in gastric motility, but rather as a result of hypoestrogenaemia [49].

Metabolic consequences of obesity during perimenopause

Numerous metabolic changes observed during menopause, along with lowered daily energy expenditure, significantly increase the risk of developing metabolic disorders and cardiovascular diseases. In perimenopausal women, weight gain is associated with higher total and abdominal adipose tissue and lower lean body mass. Long-term studies have shown that these changes were observed as early as 3–4 years before menopause and remained relatively constant for at least 12–24 months after menopause [7]. In addition, adipose tissue is more often stored ectopically, e.g. in the liver and muscles [50]. The above changes, i.e. alterations in the concentration of ovarian and non-ovarian hormones, increased appetite, followed by increased food intake and stress, lead to higher total adipose tissue, including mainly visceral fat, which in turn leads to many consequences, mainly carbohydrate and lipid metabolism disorders. Glucose metabolism disorders result primarily from increased insulin resistance and decreased insulin sensitivity of peripheral tissues, which directly result in hyperinsulinaemia. Epidemiological studies to date have unquestionably confirmed the correlation between menopause and a higher incidence of insulin resistance and carbohydrate disorders [51–53]. Such disorders can have negative health consequences due to their significant impact on the increased risk of developing diabetes, cardiovascular diseases, and numerous related complications.

In turn, lipid metabolism disorders arise as a result of elevated production of lipids, inhibition of their lipolysis, with simultaneous disturbance of their circulation. On the other hand, studies conducted so far indicate that triglycerides, total cholesterol, LDL, and apolipoprotein B concentrations significantly increase in postmenopausal women. However, the data on the changes in HDL cholesterol concentrations are inconsistent and require further research [54–58]. Additionally, the study by Song et al. reported that a significant increase in the expression of FSH molecules during perimenopause and its interactions with hepatic FSH receptors may be translated into a lower number of LDL cholesterol receptors, which in turn weakens the process of endocytosis of LDL-C particles and leads to their increased serum concentrations. To summarize numerous literature data, it is important to emphasize the vital positive correlation between oestrogens and lipid metabolism through the fact that they can affect hepatic lipid synthesis by stimulating lipolysis and reducing serum lipid concentration and thus exert a protective cardiometabolic effect [59].

Menopausal hormone therapy as a prevention of metabolic complications and other health consequences during perimenopause

MHT is used in postmenopausal women in particular to reduce the severity of menopausal symptoms, and thus improve the quality of life of patients. According to the guidelines of the Endocrine Society, MHT is offered to women up to the age of 60 years or within 10 years

of menopause in the case of troublesome vasomotor symptoms, regardless of other climacteric symptoms, when there are no contraindications and no increased cardiovascular or breast cancer risk. The standard is oestrogen monotherapy in hysterectomised women, or combined oestrogen and progesterone therapy in women with an intact uterus [60].

The broad-spectrum beneficial effects of MHT on reducing the risk of osteoporosis or pathological fractures have been known for a long time, and the positive effect of this treatment on the cardiovascular system has also been observed. However, the use of this therapy may also entail adverse health consequences. Therefore, the therapeutic intervention in the form of MHT in women with premature ovarian failure and its benefits seem to be more obvious than the implementation of treatment during physiological menopause [9, 61–63].

There are no recommendations regarding the use of MHT for the prevention or treatment of obesity during perimenopause, despite evidence that the use of MHT does not cause weight gain and may promote weight reduction. Body weight was shown to have been reduced by about 2 kg in the period of 3 months after administering MHT. What is more, lower average body weight in women treated with MHT was observed compared to their age-matched controls. It has also been reported that MHT can counteract the accumulation of visceral fat, which is most likely due to increased lipoprotein lipase (LPL) activity in adipocytes in the femoral-gluteal area induced by the use of MHT. Menopause and its related changes lead to carbohydrate metabolism disorders, which confirms the observed significantly higher risk of type 2 diabetes and reduced insulin sensitivity in postmenopausal women compared to the group of premenopausal women. Most researchers agree with the conclusion about the benefits of using oestrogens in MHT, which have been proven to promote glucose-dependent insulin secretion, increase insulin sensitivity, and correct fasting hyperinsulinaemia in postmenopausal women diagnosed with type 2 diabetes. Studies have also shown that MHT in menopausal women significantly delays the onset of type 2 diabetes compared to the control group. Therefore, it seems that women at risk of developing or suffering from type 2 diabetes should not be denied MHT when exhibiting menopausal symptoms. At the same time, it should be emphasized that this therapy has not been approved as an official prevention of type 2 diabetes in women [19, 64, 65].

However, some researchers believe that oestrogens may have an adverse effect on glucose metabolism. Studies have shown that in women using oral contraceptives, high oestrogen levels reduced glucose tolerance, and oestrogens used in supraphysiological doses induced the secretion of glucocorticoids and, consequently, increased blood glucose levels. Therefore, when selecting the dose of drugs, it should be remembered that the level of estrogenaemia in postmenopausal women with obesity using MHT increases significantly more than in women with normal body weight. In addition, the route of administration of oestrogen preparations is also important (transdermal administration seems to be more advantageous than oral). Therefore, the current scientific evidence regarding the effect of MHT on glucose metabolism remains controversial, which may be due to multiple factors, including, but not limited to, the lack of standardization of methods for measuring insulin sensitivity, differences in study groups, and the type and route of administration of hormone therapy [65–67].

Despite the postulated positive effect of MHT also on lipid metabolism, numerous studies conducted so far have not demonstrated a clear effect, also due to the variety of possible treatment regimens and the multitude of metabolic pathways stimulated by them. According to Stevens et al., each of the available therapeutic regimens may lead to the stimulation of separate intracellular processes of molecular signal transduction, which in turn determines a different risk of increasing the incidence of certain diseases, including cardiovascular diseases or cancer when using a given regimen of MHT in perimenopausal women. Also in this case, the choice of a given MHT regimen should be strictly individualized and based on the indications, the spectrum of possible contraindications, the risk of complications, the lipid profile, and other individual factors [52, 68].

Treatment of obesity in perimenopausal women

The basis for the treatment of obesity during perimenopause, as at other stages of life, is not only the choice of appropriate pharmacological therapy, but above all the implementation of appropriate behavioural management, i.e. lifestyle modification, which takes into account not only a permanent change of existing eating habits into metabolically beneficial ones, but also physical activity, which is an important component of a complex therapeutic process. The use of a hypocaloric diet plan is based on both proper quantitative and qualitative selection. In a randomized clinical trial conducted over a period of 12 months by Seimon et al., perimenopausal patients with obesity were divided into groups treated with moderately and severely reduced caloric intake. Decreases in adipose tissue, lean body mass, thigh muscle tissue, and bone mass were observed to

be adequate to caloric restriction; however, a significant, more than 2.5-fold greater loss of total bone mineral density (BMD) was observed in the group of women with strict dietary restrictions compared to the other group. For this reason, it seems extremely important to choose a balanced, non-rigorous diet in menopausal women with obesity in cases of confirmed osteopaenia or osteoporosis [69].

In the absence of satisfactory efficacy of behavioural management, an extremely important place in the treatment of obesity, including obesity in perimenopausal women, is pharmacological management. In the European Union, there are 4 preparations registered for this indication, which differ in their mechanism of action, efficacy, adverse effects, and the cost of therapy, but their use together with lifestyle modification can lead to a significant reduction in body weight. Currently, the following preparations in the treatment of obesity are available in Poland: lipase inhibitors that block the absorption of fat in the gastrointestinal tract (orlistat), naltrexone and bupropion combination, and 2 glucagon-like peptide 1 (GLP-1) analogues (liraglutide and semaglutide). Considering the efficacy and safety of a given therapy, among the available preparations, the drugs with the best action profile are semaglutide, liraglutide, and naltrexone in combination with bupropion.

Liraglutide and semaglutide are analogues of human GLP-1, which, as incretin agents, increase glucose-dependent pancreatic β-cell insulin secretion and inhibit α-cell glucagon secretion in normoglycaemia. Additional mechanisms of action of these drugs are delayed gastric emptying, weight loss, and reduced adipose tissue by suppressing appetite and energy intake. The role of liraglutide and semaglutide in the regulation of appetite is related to the specific activation of the GLP-1 receptor (GLP-1R) in the central nervous system, which increases signalling in the satiety centre and leads to an increase in the feeling of satiety, which translates into decreased feeling of hunger and limited drive of further consumption. GLP-1Rs are also located in other organs and tissues, e.g. in the heart, blood vessels, kidneys, or in the immune system. Liraglutide and semaglutide have a positive effect on lipid and carbohydrate metabolism, and experimental studies have shown that they inhibit the development of atherosclerotic plaque and suppress its inflammation [70–72]. The SCALE Diabetes and SCALE Obesity and Prediabetes trials reported significant weight loss in patients with obesity, both with and without concomitant diabetes, compared to the control group with placebo (weight reduction by 5.9% in patients with obesity and diabetes and 8.0% in patients with overweight or obesity, but without diabetes, compared to approximately a 2% reduction in patients from the placebo group during the 54-week follow-up). In addition, the use of liraglutide in the treatment of obesity reduced the risk of developing overt type 2 diabetes and showed a positive effect on blood pressure and lipid profile [72, 73]. Despite the lack of official registration in the treatment of obesity, other preparations of GLP-1 analogues, due to a similar mechanism of action, have also found clinical application in the treatment of obesity [74, 75].

Another effective drug combination used in the treatment of obesity is naltrexone and bupropion, which, through its central action, has a beneficial effect on weight loss. Naltrexone, as an opioid receptor antagonist, is commonly used in the treatment for alcohol and opioid dependence. Bupropion, in turn, is a selective dopamine and norepinephrine reuptake inhibitor. It has found application as an antidepressant, but it is also used in the treatment for nicotine dependence. The combination of these 2 active substances leads to appetite suppression, but the exact neurochemical mechanisms responsible for this effect have not been explained. The point of action of this preparation is known to be the arcuate nucleus of the hypothalamus and the mesolimbic dopaminergic system known as the reward-related centre [76, 77]. Randomized clinical trials have shown a significant weight loss of approximately 5 kg compared to a placebo group over a one-year treatment period, with one in three patients achieving a weight reduction of 10% or more. Other beneficial effects of the combination of naltrexone and bupropion are also noteworthy. They include reduced waist circumference and lower triglyceride levels with simultaneous higher HDL cholesterol levels and reduced insulin resistance [75, 78].

Pharmacotherapy does not replace changes of eating habits and increased physical activity, but it complements and helps to implement and strengthen non-pharmacological therapy. According to the PTLO recommendations, the indications for the inclusion of anti-obesity drugs are as follows:

— BMI ≥ 30 kg/m^2 (class 1 obesity);
— BMI ≥ 27 kg/m^2 if overweight is accompanied by complications typical of obesity.

Pharmacological therapy of obesity should be personalized and take into account the aetiopathogenetic factors of obesity and comorbidities. In the case of concomitant metabolic disorders associated with excessive body weight, GLP-1 analogues are the drug of first choice. On the other hand, when a strong, irresistible urge to snack (craving), emotional eating, diagnosed eating disorders, concomitant depression, and/or nicotine dependence prevail, the drug of choice is a combined therapy of bupropion and naltrexone [3].

Bariatric (metabolic) surgery is a complementary method of treating obesity in the case of ineffective behavioural treatment and pharmacotherapy. Among the many available surgical methods, such as Roux-en-Y gastric bypass, biliopancreatic diversion with duodenal switch, sleeve gastrectomy, or laparoscopic adjustable gastric banding (LAGB) seem to be associated with high efficacy and a positive result, which largely depends on the experience of the surgeon performing the procedure. On the other hand, maintaining the achieved effect of surgical treatment depends primarily on the patient and the continuation of non-pharmacological and pharmacological methods used by them. According to current guidelines, indications for bariatric surgery include:

— class 3 obesity (BMI ≥ 40 kg/m^2);
— class 2 obesity (BMI 35–39.9 kg/m^2), with ≥ 1 obesity complication, and surgically induced weight loss may bring potential improvement in obesity-related diseases.

Bariatric surgery may also be considered in patients with class 1 obesity (BMI 30–34.9 kg/m^2) and type 2 diabetes, in whom therapeutic goals cannot be achieved after exhaustion of conservative treatment methods; however, such an indication is not publicly funded in Poland [3].

REVIEW

Hormonal targeted therapy during perimenopause

In the pharmacological treatment of obesity with/without complications in perimenopausal women, in addition to the standard therapies described above, other therapeutic strategies are analysed, based on the pathogenetic factors of obesity, which may be an interesting and effective alternative to existing treatments or be one of the components of such therapy in the future.

One such therapeutic option may be therapy with GH, the positive metabolic effects of which have been known for several decades. Despite the lack of long-term observational studies evaluating the effect of such therapy on visceral obesity in menopausal women, there are reports on the efficacy of short-term GH therapy in this group of people. This is confirmed by the 12-month randomized double-blind clinical trial conducted by Franco et al., whose main objective was to assess the effect of GH therapy on the level of insulin sensitivity. The results obtained after 12 months of observation in the group of people who were treated with GH showed a significant reduction in visceral fat, an increase in muscle mass in the femoral-gluteal area, and a reduction in total cholesterol and LDL compared to the placebo control group. In addition, a significant increase in insulin sensitivity in these patients was found, which was most likely due to a significant reduction in hepatic adipose tissue [60]. Despite this, further research and long-term observations are necessary to corroborate the above effects and the possible advantage of the benefits of this therapy over the potential complications. Currently, a significant obstacle to the use of chronic GH therapy is the significant cost of the recombinant GH preparation [36, 79].

Another interesting therapeutic option seems to be the use of dehydroepiandrosterone (DHEA), whose low plasma level in the elderly is positively correlated with the risk of developing metabolic syndrome and elevated cardiovascular risk. There is abundant scientific evidence from experimental studies showing the beneficial effects of DHEA therapy on carbohydrate metabolism, lipid profile, and cardiovascular system in mice. In the review article by Teixeira et al., the authors summarized the available scientific literature on the impact of DHEA therapy on the broadly understood metabolic profile and cardiovascular risk. However, taking into account the available results, which are often inconsistent, the need for further research on a larger group of people is emphasized [80].

MHT and pathogenetic treatment of visceral obesity

MHT may hypothetically be a new strategy for the treatment of visceral obesity in postmenopausal women – it reduces the accumulation of visceral adipose tissue [81], reduces or even eliminates the loss of metabolically active lean body mass [82, 83], and improves lipid profile parameters [84]. Confirmation of these reports, however, requires further research, which is why none of the gynaecological or endocrinological societies currently recommend the use of MHT for the prevention or treatment of obesity. Despite the lack of such recommendations and guidelines, Lambrinoudaki et al. attempted to create a pattern of use of MHT depending on the category of cardiovascular risk:

— very high risk — do not use MHT;
— high and moderate risk — use transdermal E2;
— low risk — the choice of MHT should match lipid profile parameters:
— Lp(a) > 50 mg/dL → oral E2 if there are no contraindications,
— Lp(a) < 50 mg/dL → oral or transdermal E2,
— ↑ TG → transdermal E2.

The above oestrogen preparations should be supplemented with a progestogen if the uterus is present. The time window for MHT initiation was indicated by the authors as the first 6 years from the menopausal transition because then the greatest improvement in many cardiometabolic parameters is obtained: lipid profile, insulin sensitivity, body composition, arterial

stiffness (carotid intima-media thickness), and chronic inflammation [85]. Sorensen et al. proved, however, that oestrogens used as part of MHT not only reverse the metabolically unfavourable visceral location of adipose tissue, but additionally prevent the loss of metabolically active muscle mass, without affecting the total body weight [83].

It seems controversial that one of the MHT contraindications is heightened cardiovascular risk, while obesity itself is considered such a risk factor. However, a new body of evidence has recently found that visceral obesity may be the result of hypoestrogenaemia during perimenopause; therefore, the use of MHT could be considered a causal treatment. Nonetheless, further research is also necessary to reach such conclusions.

Summary

In conclusion, it should be emphasized that obesity, especially during perimenopause, is a grave health problem for modern women. With the aging of the world's population and the increase in life expectancy for women, the issue of post-menopausal health is of unprecedented concern. Several hormonal changes occurring in menopause, affecting the energy metabolism of the body, lead to obesity and the development of various metabolic disorders and consequently, directly or indirectly, to an elevated risk for developing cardiovascular complications. For this reason, it is vital to undertake appropriate therapeutic strategies through individualized behavioural management, supported by effective pharmacological therapy, and in justified cases supplemented by bariatric surgery. Currently, modern obesity treatment therapies are available in Poland, the safety and efficacy of which have been confirmed by many clinical trials. Their use allows not only the reduction of excess body fat and improvement of the metabolic profile, but also the reduction of cardiovascular risk, thus improving the quality of a woman's life and extending it.

Author contributions

D.P. — conceptualization, investigation, writing — original draft; J.G. — conceptualization, investigation, writing — original draft, writing — review and editing, visualization; B.M.M. — conceptualization, supervision, project administration.

Funding

None declared.

Acknowledgments

None declared.

Conflict of interest

None declared.

References

1. Haslam DW, James WP. Obesity. Lancet. 2005; 366(9492): 1197–1209, doi: 10.1016/S0140-6736(05)67483-1, indexed in Pubmed: 16198769.
2. Afshin A, Forouzanfar MH, Reitsma MB, et al. GBD 2015 Obesity Collaborators. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med. 2017; 377(1): 13–27, doi: 10.1056/NEJMoa1614362, indexed in Pubmed: 28604169.
3. Zalecenia kliniczne dotyczące postępowania u chorych na otyłość 2022. Stanowisko PTLO - Nadwaga i otyłość - Medycyna Praktyczna dla lekarzy. https://www.mp.pl/nadwaga-i-otylosc/wytyczne/303522,zalecenia-kliniczne-dotyczace-postepowania-u-chorych-na-otylosc-2022 (28.05.2023).
4. Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline. CMAJ. 2020; 192(31): E875–E891, doi: 10.1503/cmaj.191707, indexed in Pubmed: 32753461.
5. Czy Polacy jedzą za dużo? https://www.cbos.pl/PL/szukaj/okienko.php?pub_id=5058 (28.05.2023).
6. Hales CM, Carroll MD, Fryar CD, et al. Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017-2018. NCHS Data Brief. 2020(360): 1–8, indexed in Pubmed: 32487284.
7. Lovejoy JC, Champagne CM, de Jonge L, et al. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes (Lond). 2008; 32(6): 949–958, doi: 10.1038/ijo.2008.25, indexed in Pubmed: 18332882.
8. UpToDate. 28.05.2023 (https://www.uptodate.com/contents/obesity-in-adults-prevalence-screening-and-evaluation).
9. Paciuc J. Hormone Therapy in Menopause. Adv Exp Med Biol. 2020; 1242: 89–120, doi: 10.1007/978-3-030-38474-6_6, indexed in Pubmed: 32406030.
10. Potter B, Schrager S, Dalby J, et al. Menopause. Prim Care. 2018; 45(4): 625–641, doi: 10.1016/j.pop.2018.08.001, indexed in Pubmed: 30401346.
11. Finch CE. The menopause and aging, a comparative perspective. J Steroid Biochem Mol Biol. 2014; 142: 132–141, doi: 10.1016/j.jsbmb.2013.03.010, indexed in Pubmed: 23583565.
12. Eyster KM. The Estrogen Receptors: An Overview from Different Perspectives. Methods Mol Biol. 2016; 1366: 1–10, doi: 10.1007/978-1-4939-3127-9_1, indexed in Pubmed: 26585122.
13. Butera PC. Estradiol and the control of food intake. Physiol Behav. 2010; 99(2): 175–180, doi: 10.1016/j.physbeh.2009.06.010, indexed in Pubmed: 19555704.
14. Nahon JL. The melanocortins and melanin-concentrating hormone in the central regulation of feeding behavior and energy homeostasis. C R Biol. 2006; 329(8): 623–38; discussion 653, doi: 10.1016/j.crvi.2006.03.021, indexed in Pubmed: 16860280.
15. de Souza FSJ, Nasif S, López-Leal R, et al. The estrogen receptor α colocalizes with proopiomelanocortin in hypothalamic neurons and binds to a conserved motif present in the neuron-specific enhancer nPE2. Eur J Pharmacol. 2011; 660(1): 181–187, doi: 10.1016/j.ejphar.2010.10.114, indexed in Pubmed: 21211522.
16. Kojima M, Kangawa K. Ghrelin: structure and function. Physiol Rev. 2005; 85(2): 495–522, doi: 10.1152/physrev.00012.2004, indexed in Pubmed: 15788704.
17. Davis SR, Castelo-Branco C, Chedraui P, et al. Writing Group of the International Menopause Society for World Menopause Day 2012. Understanding weight gain at menopause. Climacteric. 2012; 15(5): 419–429, doi: 10.3109/13697137.2012.707385, indexed in Pubmed: 22978257.
18. Duval K, Prud'homme D, Rabasa-Lhoret R, et al. Effects of the menopausal transition on dietary intake and appetite: a MONET Group Study. Eur J Clin Nutr. 2014; 68(2): 271–276, doi: 10.1038/ejcn.2013.171, indexed in Pubmed: 24065065.
19. Reimer RA, Debert CT, House JL, et al. Dietary and metabolic differences in pre- versus postmenopausal women taking or not taking hormone replacement therapy. Physiol Behav. 2005; 84(2): 303–312, doi: 10.1016/j.physbeh.2004.12.011, indexed in Pubmed: 15708782.
20. Wing RR, Matthews KA, Kuller LH, et al. Weight gain at the time of menopause. Arch Intern Med. 1991; 151(1): 97–102, indexed in Pubmed: 1985614.
21. Janssen I, Powell LH, Crawford S, et al. Menopause and the metabolic syndrome: the Study of Women's Health Across the Nation. Arch Intern Med. 2008; 168(14): 1568–1575, doi: 10.1001/archinte.168.14.1568, indexed in Pubmed: 18663170.
22. Ho SC, Wu S, Chan SG, et al. Menopausal transition and changes of body composition: a prospective study in Chinese perimenopausal women. Int J Obes (Lond). 2010; 34(8): 1265–1274, doi: 10.1038/ijo.2010.33, indexed in Pubmed: 20195288.
23. Abdulnour J, Doucet E, Brochu M, et al. The effect of the menopausal transition on body composition and cardiometabolic risk factors: a Montreal-Ottawa New Emerging Team group study. Menopause. 2012; 19(7): 760–767, doi: 10.1097/gme.0b013e318240f6f3, indexed in Pubmed: 22395454.

24. Gierach M, Junik R. Metabolic syndrome in women - correlation between BMI and waist circumference. Endokrynol Pol. 2022; 73(1): 163–164, doi: 10.5603/EP.a2021.0108, indexed in Pubmed: 35119095.
25. Bruun JM, Nielsen CB, Pedersen StB, et al. Estrogen reduces pro-inflammatory cytokines in rodent adipose tissue: studies in vivo and in vitro. Horm Metab Res. 2003; 35(3): 142–146, doi: 10.1055/s-2003-39074, indexed in Pubmed: 12734773.
26. Kalish GM, Barrett-Connor E, Laughlin GA, et al. Postmenopausal Estrogen/Progestin Intervention Trial. Association of endogenous sex hormones and insulin resistance among postmenopausal women: results from the Postmenopausal Estrogen/Progestin Intervention Trial. J Clin Endocrinol Metab. 2003; 88(4): 1646–1652, doi: 10.1210/jc.2002-021375, indexed in Pubmed: 12679451.
27. Collins P, Rosano GM, Jiang C, et al. Cardiovascular protection by oestrogen--a calcium antagonist effect? Lancet. 1993; 341(8855): 1264–1265, doi: 10.1016/0140-6736(93)91158-i, indexed in Pubmed: 8098404.
28. Tramunt B, Smati S, Grandgeorge N, et al. Sex differences in metabolic regulation and diabetes susceptibility. Diabetologia. 2020; 63(3): 453–461, doi: 10.1007/s00125-019-05040-3, indexed in Pubmed: 31754750.
29. Wong WPS, Tiano JP, Liu S, et al. Extranuclear estrogen receptor-alpha stimulates NeuroD1 binding to the insulin promoter and favors insulin synthesis. Proc Natl Acad Sci U S A. 2010; 107(29): 13057–13062, doi: 10.1073/pnas.0914501107, indexed in Pubmed: 20616010.
30. Chen ZJ, Yu L, Chang CH. Stimulation of membrane-bound guanylate cyclase activity by 17-beta estradiol. Biochem Biophys Res Commun. 1998; 252(3): 639–642, doi: 10.1006/bbrc.1998.9716, indexed in Pubmed: 9837759.
31. Kohrt WM, Wierman ME. Preventing Fat Gain by Blocking Follicle-Stimulating Hormone. N Engl J Med. 2017; 377(3): 293–295, doi: 10.1056/NEJMcibr1704542, indexed in Pubmed: 28723332.
32. Hirschberg AL. Sex hormones, appetite and eating behaviour in women. Maturitas. 2012; 71(3): 248–256, doi: 10.1016/j.maturitas.2011.12.016, indexed in Pubmed: 22281161.
33. Santoro N, Roeca C, Peters BA, et al. The Menopause Transition: Signs, Symptoms, and Management Options. J Clin Endocrinol Metab. 2021; 106(1): 1–15, doi: 10.1210/clinem/dgaa764, indexed in Pubmed: 33095879.
34. Ding EL, Song Y, Manson JE, et al. Sex hormone-binding globulin and risk of type 2 diabetes in women and men. N Engl J Med. 2009; 361(12): 1152–1163, doi: 10.1056/NEJMoa0804381, indexed in Pubmed: 19657112.
35. Weinberg ME, Manson JE, Buring JE, et al. Low sex hormone-binding globulin is associated with the metabolic syndrome in postmenopausal women. Metabolism. 2006; 55(11): 1473–1480, doi: 10.1016/j.metabol.2006.06.017, indexed in Pubmed: 17046549.
36. Fanciulli G, Delitala A, Delitala G. Growth hormone, menopause and ageing: no definite evidence for 'rejuvenation' with growth hormone. Hum Reprod Update. 2009; 15(3): 341–358, doi: 10.1093/humupd/dmp005, indexed in Pubmed: 19228699.
37. Snel YE, Brummer RJ, Bol E, et al. Direct assessment of extracellular water volume by the bromide-dilution method in growth hormone-deficient adults. Eur J Clin Invest. 1995; 25(9): 708–714, doi: 10.1111/j.1365-2362.1995.tb01990.x, indexed in Pubmed: 7498247.
38. Norman C, Rollene NL, Erickson D, et al. Estradiol regulates GH-releasing peptide's interactions with GH-releasing hormone and somatostatin in postmenopausal women. Eur J Endocrinol. 2014; 170(1): 121–129, doi: 10.1530/EJE-13-0733, indexed in Pubmed: 24114435.
39. Çelik F, Belviranli M, Okudan N. Circulating levels of leptin, nesfatin-1 and kisspeptin in postmenopausal obese women. Arch Physiol Biochem. 2016; 122(4): 195–199, doi: 10.3109/13813455.2016.1171365, indexed in Pubmed: 27011110.
40. Van Doorn C, Macht VA, Grillo CA, et al. Leptin resistance and hippocampal behavioral deficits. Physiol Behav. 2017; 176: 207–213, doi: 10.1016/j.physbeh.2017.03.002, indexed in Pubmed: 28267584.
41. Liu J, Yang X, Yu S, et al. The Leptin Resistance. Adv Exp Med Biol. 2018; 1090: 145–163, doi: 10.1007/978-981-13-1286-1_8, indexed in Pubmed: 30390289.
42. Gruzdeva O, Borodkina D, Uchasova E, et al. Leptin resistance: underlying mechanisms and diagnosis. Diabetes Metab Syndr Obes. 2019; 12: 191–198, doi: 10.2147/DMSO.S182406, indexed in Pubmed: 30774404.
43. Vázquez-Solórzano R, Valdés-Miramontes E, Porchas-Quijada M, et al. Leptin-reactive antibodies are distinctly correlated with body composition parameters and metabolic risk indexes in children and adolescents. Clin Exp Immunol. 2022; 208(2): 233–244, doi: 10.1093/cei/uxab001, indexed in Pubmed: 35020844.
44. Kastin AJ, Akerstrom V, Maness LM. Chronic loss of ovarian function decreases transport of leptin into mouse brain. Neurosci Lett. 2001; 310(1): 69–71, doi: 10.1016/s0304-3940(01)02074-2, indexed in Pubmed: 11524160.
45. Lisko I, Tiainen K, Stenholm S, et al. Are body mass index, waist circumference and waist-to-hip ratio associated with leptin in 90-year-old people? Eur J Clin Nutr. 2013; 67(4): 420–422, doi: 10.1038/ejcn.2013.39, indexed in Pubmed: 23443829.
46. Tryon MS, DeCant R, Laugero KD. Having your cake and eating it too: a habit of comfort food may link chronic social stress exposure and acute stress-induced cortisol hyporesponsiveness. Physiol Behav. 2013; 114-115: 32–37, doi: 10.1016/j.physbeh.2013.02.018, indexed in Pubmed: 23500173.
47. Hackett RA, Steptoe A. Type 2 diabetes mellitus and psychological stress - a modifiable risk factor. Nat Rev Endocrinol. 2017; 13(9): 547–560, doi: 10.1038/nrendo.2017.64, indexed in Pubmed: 28664919.
48. Epel E, Lapidus R, McEwen B, et al. Stress may add bite to appetite in women: a laboratory study of stress-induced cortisol and eating behavior. Psychoneuroendocrinology. 2001; 26(1): 37–49, doi: 10.1016/s0306-4530(00)00035-4, indexed in Pubmed: 11070333.
49. Huerta-Franco MR, Vargas-Luna M, Somoza X, et al. Gastric responses to acute psychological stress in climacteric women: a pilot study. Menopause. 2019; 26(5): 469–475, doi: 10.1097/GME.0000000000001274, indexed in Pubmed: 30586006.
50. Stefanska A, Bergmann K, Sypniewska G. Metabolic Syndrome and Menopause: Pathophysiology, Clinical and Diagnostic Significance. Adv Clin Chem. 2015; 72: 1–75, doi: 10.1016/bs.acc.2015.07.001, indexed in Pubmed: 26471080.
51. Villaverde Gutiérrez C, Ramírez Rodrigo J, Olmedo Alguacil MM, et al. Overweight obesity and cardiovascular risk in menopausal transition. Nutr Hosp. 2015; 32(4): 1603–1608, doi: 10.3305/nh.2015.32.4.9380, indexed in Pubmed: 26545524.
52. Baber RJ, Panay N, Fenton A, et al. IMS Writing Group. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. Climacteric. 2016; 19(2): 109–150, doi: 10.3109/13697137.2015.1129166, indexed in Pubmed: 26872610.
53. Zhu J, Ji M, Xing L. Ovarian Hormonal Change-Related Energy Metabolism and Obesity in Menopausal Women. In: Rangel L, Kirubamani H, Victor Silva I, Cilas Morais Lyra Junior P. ed. Hormone Therapy and Replacement in Cancer and Aging-related Diseases. IntechOpen 2020.
54. Touraine P, Beau I, Gougeon A, et al. New natural inactivating mutations of the follicle-stimulating hormone receptor: correlations between receptor function and phenotype. Mol Endocrinol. 1999; 13(11): 1844–1854, doi: 10.1210/mend.13.11.0370, indexed in Pubmed: 10551778.
55. Murano T, Izumi Si, Kika G, et al. Impact of menopause on lipid and bone metabolism and effect of hormone replacement therapy. Tokai J Exp Clin Med. 2003; 28(3): 109–119, indexed in Pubmed: 15055403.
56. Matthews KA, El Khoudary SR, Brooks MM, et al. Lipid Changes Around the Final Menstrual Period Predict Carotid Subclinical Disease in Postmenopausal Women. Stroke. 2017; 48(1): 70–76, doi: 10.1161/STROKEAHA.116.014743, indexed in Pubmed: 27909203.
57. Ko SH, Jung Y. Energy Metabolism Changes and Dysregulated Lipid Metabolism in Postmenopausal Women. Nutrients. 2021; 13(12), doi: 10.3390/nu13124556, indexed in Pubmed: 34960109.
58. El Khoudary SR. HDL and the menopause. Curr Opin Lipidol. 2017; 28(4): 328–336, doi: 10.1097/MOL.0000000000000432, indexed in Pubmed: 28459707.
59. Song Y, Wang ES, Xing LL, et al. Follicle-Stimulating Hormone Induces Postmenopausal Dyslipidemia Through Inhibiting Hepatic Cholesterol Metabolism. J Clin Endocrinol Metab. 2016; 101(1): 254–263, doi: 10.1210/jc.2015-2724, indexed in Pubmed: 26583582.
60. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015; 100(11): 3975–4011, doi: 10.1210/jc.2015-2236, indexed in Pubmed: 26444994.
61. Suchecka-Rachoń K, Rachoń D. Rola hormonalnej terapii zastępczej (HTZ) u kobiet w okresie pomenopauzalnym. Choroby Serca i Naczyń. 2005; 2(3): 115–124.
62. Lindsay R, Hart DM, Clark DM. The minimum effective dose of estrogen for prevention of postmenopausal bone loss. Obstet Gynecol. 1984; 63(6): 759–763, indexed in Pubmed: 6374537.
63. Nash Z, Al-Wattar BH, Davies M. Bone and heart health in menopause. Best Pract Res Clin Obstet Gynaecol. 2022; 81: 61–68, doi: 10.1016/j.bpobgyn.2022.03.002, indexed in Pubmed: 35400590.
64. Mauvais-Jarvis F, Manson JE, Stevenson JC, et al. Menopausal Hormone Therapy and Type 2 Diabetes Prevention: Evidence, Mechanisms, and Clinical Implications. Endocr Rev. 2017; 38(3): 173–188, doi: 10.1210/er.2016-1146, indexed in Pubmed: 28323934.
65. Paszkowski T, Kłodnicka M. Hormonal replacement therapy and obesity. Menopause Rev. 2007; 2: 106–109.
66. Bitoska I, Krstevska B, Milenkovic T, et al. Effects of Hormone Replacement Therapy on Insulin Resistance in Postmenopausal Diabetic Women. Open Access Maced J Med Sci. 2016; 4(1): 83–88, doi: 10.3889/oamjms.2016.024, indexed in Pubmed: 27275336.
67. Godsland IF, Stevenson JC, Crook D, et al. Hormone replacement therapy and the cardiovascular system. Nonlipid effects. Drugs. 1994; 47 Suppl 2: 35–41, doi: 10.2165/00003495-199400472-00007, indexed in Pubmed: 7517832.

68. Stevens VL, Wang Y, Carter BD, et al. Serum metabolomic profiles associated with postmenopausal hormone use. Metabolomics. 2018; 14(7): 97, doi: 10.1007/s11306-018-1393-1, indexed in Pubmed: 30830410.
69. Seimon RV, Wild-Taylor AL, Keating SE, et al. Effect of Weight Loss via Severe *vs* Moderate Energy Restriction on Lean Mass and Body Composition Among Postmenopausal Women With Obesity: The TEMPO Diet Randomized Clinical Trial. JAMA Netw Open. 2019; 2(10): e1913733, doi: 10.1001/jamanetworkopen.2019.13733, indexed in Pubmed: 31664441.
70. Grill HJ. A Role for GLP-1 in Treating Hyperphagia and Obesity. Endocrinology. 2020; 161(8), doi: 10.1210/endocr/bqaa093, indexed in Pubmed: 32516384.
71. Flint A, Raben A, Ersbøll AK, et al. The effect of physiological levels of glucagon-like peptide-1 on appetite, gastric emptying, energy and substrate metabolism in obesity. Int J Obes Relat Metab Disord. 2001; 25(6): 781–792, doi: 10.1038/sj.ijo.0801627, indexed in Pubmed: 11439290.
72. le Roux CW, Astrup A, Fujioka K, et al. SCALE Obesity Prediabetes NN8022-1839 Study Group, SCALE Obesity and Prediabetes NN8022-1839 Study Group. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. N Engl J Med. 2015; 373(1): 11–22, doi: 10.1056/NEJMoa1411892, indexed in Pubmed: 26132939.
73. Davies MJ, Bergenstal R, Bode B, et al. NN8022-1922 Study Group. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial. JAMA. 2015; 314(7): 687–699, doi: 10.1001/jama.2015.9676, indexed in Pubmed: 26284720.
74. Perez-Montes DE Oca A, Pellitero S, Puig-Domingo M. Obesity and GLP-1. Minerva Endocrinol (Torino). 2021; 46(2): 168–176, doi: 10.23736/S2724-6507.20.03369-6, indexed in Pubmed: 33213122.
75. Shi Q, Wang Y, Hao Q, et al. Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. Lancet. 2022; 399(10321): 259–269, doi: 10.1016/S0140-6736(21)01640-8, indexed in Pubmed: 34895470.
76. Gadde KM, Parker CB, Maner LG, et al. Bupropion for weight loss: an investigation of efficacy and tolerability in overweight and obese women. Obes Res. 2001; 9(9): 544–551, doi: 10.1038/oby.2001.71, indexed in Pubmed: 11557835.
77. Greenway FL, Whitehouse MJ, Guttadauria M, et al. Rational design of a combination medication for the treatment of obesity. Obesity (Silver Spring). 2009; 17(1): 30–39, doi: 10.1038/oby.2008.461, indexed in Pubmed: 18997675.
78. Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. Obesity (Silver Spring). 2011; 19(1): 110–120, doi: 10.1038/oby.2010.147, indexed in Pubmed: 20559296.
79. Mekala KC, Tritos NA. Effects of recombinant human growth hormone therapy in obesity in adults: a meta analysis. J Clin Endocrinol Metab. 2009; 94(1): 130–137, doi: 10.1210/jc.2008-1357, indexed in Pubmed: 18940879.
80. Teixeira CJ, Veras K, de Oliveira Carvalho CR. Dehydroepiandrosterone on metabolism and the cardiovascular system in the postmenopausal period. J Mol Med (Berl). 2020; 98(1): 39–57, doi: 10.1007/s00109-019-01842-5, indexed in Pubmed: 31713639.
81. Yüksel H, Odabasi AR, Demircan S, et al. Effects of postmenopausal hormone replacement therapy on body fat composition. Gynecol Endocrinol. 2007; 23(2): 99–104, doi: 10.1080/09513590601152177, indexed in Pubmed: 17454160.
82. Chen Z, Bassford T, Green SB, et al. Postmenopausal hormone therapy and body composition--a substudy of the estrogen plus progestin trial of the Women's Health Initiative. Am J Clin Nutr. 2005; 82(3): 651–656, doi: 10.1093/ajcn.82.3.651, indexed in Pubmed: 16155280.
83. Sørensen MB, Rosenfalck AM, Højgaard L, et al. Obesity and sarcopenia after menopause are reversed by sex hormone replacement therapy. Obes Res. 2001; 9(10): 622–626, doi: 10.1038/oby.2001.81, indexed in Pubmed: 11595778.
84. Davis SR, Walker KZ, Strauss BJ. Effects of estradiol with and without testosterone on body composition and relationships with lipids in postmenopausal women. Menopause. 2000; 7(6): 395–401, doi: 10.1097/00042192-200011000-00005, indexed in Pubmed: 11127762.
85. Lambrinoudaki I, Armeni E. Understanding of and clinical approach to cardiometabolic transition at the menopause. Climacteric. 2023 [Epub ahead of print]: 1–7, doi: 10.1080/13697137.2023.2202809, indexed in Pubmed: 37224871.