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Review article on the topic: Cognitive impairment in women with type 2 diabetes in the menopausal period.

Begmatova KH.A., Khaidarova F.A., Tojieva I.M.
Republican Specialized Scientific and Practical Medical Center of Endocrinology

Abstract: Climacteric is a physiological period of a woman's life starting from the decline in ovarian activity until the end of ovarian function. This period is commonly accompanied by the development of menopausal metabolic syndrome characterized by the increase in visceral fat mass, insulin resistance, and hyperinsulinemia which result in the disorders of carbohydrate, lipid, and purine metabolism. This paper reviews the factors increasing the risk of metabolic syndrome during menopause. Diagnostic techniques for metabolic syndrome are described. Treatment approaches to menopausal metabolic syndrome, the potentialities, and specifics of menopausal hormone therapy (MHT), its anticipated effects are discussed. The difficulties with MHT are accounted for by the lack of an optimal medication that will maintain the functioning of the cardiovascular system, skeletal system, brain, and optimal weight and also has a minimal risk of side effects and complications. Meanwhile, adequate MHT for climacteric disorders in perimenopausal and early postmenopausal women is an effective and safe treatment for menopausal metabolic syndrome considered as a prerequisite for cardiovascular diseases and type 2 diabetes.

Keywords: menopause, climax, metabolic syndrome, obesity, hypertension, diabetes, menopausal hormone therapy, venous thromboembolism.

Relevance. Menopause is a physiological transitional period in a woman's life when there is a gradual decrease and shutdown of ovarian function. It is during this period that the menopausal metabolic syndrome (MMS) often develops, which is characterized by an increase in the mass of visceral fat, insulin resistance and hyperinsulinemia, causing disturbances in carbohydrate, lipid, and purine metabolism. The article discusses the factors that increase the likelihood of developing MMS and the risks that arise in this case. The methods of diagnostics, approaches to the treatment of MMS, the possibilities and features of prescribing menopausal hormone therapy (MHT), the expected effects from it are described. body and would have minimal risk of side effects and complications. At the same time, properly selected hormonal therapy for menopausal disorders in women in the perimenopausal and early postmenopausal periods is an effective and safe method for the prevention and treatment of MMS, which creates prerequisites for the development of cardiovascular diseases and type 2 diabetes mellitus.

According to the report of the Federal State Statistics Service (2011), every fifth woman is afraid to take drugs based on sex hormones due to the possible development of complications, primarily related to the cardiovascular system [1]. More often these drugs are used in the form of hormonal contraception by young women. Middle-aged and older women are more wary of them. At the same time, with the onset of menopause, a global restructuring occurs in the woman's body, leading to the initiation of many pathological processes. In addition to vasomotor symptoms that appear immediately and significantly reduce the quality of life of

patients, more life-threatening complications such as osteoporosis, sarcopenia, metabolic syndrome, diabetes mellitus (DM) and atherosclerosis of various localization (coronary, cerebral and peripheral arteries) gradually and inconspicuously develop. Complications of these diseases can lead to premature death. At the same time, pathological conditions from the brain also begin to progress: sleep disorders, anxiety, depression, migraine, dementia, etc. [2].

According to the GBD (Global Burden of Disease) study, the main causes of death in economically developed countries are cardiovascular diseases, cancer, chronic obstructive pulmonary disease (COPD), and diabetes [2]. At the same time, the priority of fatal diseases in women differs depending on their age, which is associated with the length of the time period after the onset of menopause.

In 2018, the recommendations of the European Menopause and Andropause Society (EMAS) "Menopause and diabetes mellitus" were published, which summarized the results obtained and, in particular, states [2]:

• MHT has a positive effect on the glycemic profile in women both without and diagnosed with type 2 diabetes;

• timely started MHT can delay the development of type 2 diabetes;

• oral MHT is preferred, as it has the most pronounced effect on carbohydrate metabolism (except in cases of absolute contraindications);

• if there is a high risk of thrombosis, you can try to use transdermal forms of MHT;

• Of the available and studied gestagens in oral MHT, metabolically neutral ones that do not reduce the positive effect of estrogens on carbohydrate metabolism (such as progesterone and dydrogesterone) are preferred.

The European Congress on Menopause and Andropause, held in Berlin in May 2019, also discussed in detail the effectiveness and safety of various types of MHT. It has been shown that when taken orally, estrogens are absorbed in the intestine and delivered to hepatocytes by the portal circulation, thereby achieving supraphysiological concentration in the liver before dilution within the systemic circulation [3-5]. This allows you to positively influence lipid metabolism in hepatocytes in the form of an increase in HDL synthesis and elimination of LDL from the bloodstream, as well as on carbohydrate metabolism in the form of an increase in insulin sensitivity. With transdermal estrogen therapy, such supraphysiological dosages in the liver that maintain a therapeutic dose cannot be achieved, therefore, transdermal therapy cannot have a beneficial effect on lipid and carbohydrate metabolism. At the same time, it should be noted that, using the example of MHT with dydrogesterone, a statistically significant increase in the concentration of antiatherogenic HDL in blood plasma was shown [6-7].

Following EMAS guidelines on menopause and diabetes mellitus, new guidelines published in 2020

On menopause and dyslipidemia, this noted [7]:

• Systemic estrogens, when taken orally as part of MHT, induce a significant dose-dependent decrease in total cholesterol, LDL and lipoprotein (a), as well as an increase in HDL concentration;

• The preferred gestagens in the combined MHT are metabolically neutral gestagens: dydrogesterone or progesterone;

• Patients with severe triglyceridemia may be recommended transdermal forms of estrogens in combination with metabolically neutral progestogens (dydrogesterone or progesterone);

• MHT should be used in conjunction with the main type of therapy for dyslipidemia, with the correction of nutrition and physical activity.

Separately, one should dwell on dementia, which can be of a vascular nature (be a consequence of atherosclerosis of the cerebral and prevertebral arteries) and have a degenerative nature, manifested by Alzheimer's disease - the third most common cause of death in women over 70 years old. (See Table 1).

The leading causes of death in postmenopausal women [2]

Age	
50-69 years	70 and older
Ischemic heart disease	Ischemic heartdisease
Stroke	Stroke
Breast cancer	Alzheimer’s disease
Lung cancer	Lower respiratory tract infections
Colorectal cancer	Chronic obstructive pulmonary disease
Hepatic cirrhosis	Other cardiovascular disorders
Ovarian cancer	Hypertensive disease
Diabetes mellitus	Lung cancer
Pancreatic cancers	Сахарный диабет / Diabetes mellitus
Gastric cancer	Breast cancer
Cervical cancer	Chronic kidney disease

It has been shown that, along with the classic symptoms, one of the signs of reproductive aging is impaired cognitive abilities: attention, perception, memory, speech, intellect — the ability to cognize the world and interact with it [8]. At the same time, it was found that the turning point in the decline in cognitive abilities falls on the period of perimenopause [9]. One study found a statistically significant relationship between age at early oophorectomy and the onset of dementia (RR = 1.46; 95% CI: 1.13–1.90; p = 0.005) and Parkinsonism (RR = 1 .68, 95% CI: 1.06–2.67, p = 0.003). age when menopause occurs on average), there was no increase in the risk of developing cognitive impairment and dementia [10]. When menopause occurs, a whole complex of pathological imbalance of neurotransmitters occurs in the woman’s brain (Table 2)

Table 2 Changes in concentrations of cerebral neurotransmitters during menopause and menopausal hormone therapy (MHT)

Menopause		MHT	
	Serotonin	↑	Serotonin
	Noradrenaline	↑	Noradrenaline
↓	Dopamine	↑ ↓	Dopamine
	Monoamine oxidase	↓	Monoamine oxidase
	γ-aminobutyric acid	↑	γ-aminobutyric acid
	Opioid peptides	↑	Opioid peptides
	β-adrenergic receptors	↓	β-adrenergic receptors

Leading to the formation of a depressive state [11]. Oral estrogen administration can restore normal levels and reduce depression. Studies have been repeatedly conducted aimed at finding out the cause of the development of cognitive impairment in women after menopause. Thus, in a Swedish prospective population-based study, which lasted 20 years and included 6103 women aged 57.5 ± 5.9 years, the association of atherosclerosis with various subtypes of dementia and related diseases was studied. The authors concluded that dementia that developed in 462 people was associated with a higher intima-media index of the carotid artery, i.e., was largely associated with atherosclerosis [12]. Another study showed that estrogen deficiency in perimenopause leads to a decrease in the cognitive functions of the CNS and is a premorbid background for the formation of anxiety-depressive disorders, while estrogens have an antidepressant effect. Timely MHT, affecting, among other things, hippocampal stem cells, prevents the development of neurodegenerative diseases and, according to a meta-analysis, reduces the risk of developing Alzheimer's disease [14]. Thus, in general, estrogens have a whole range of beneficial effects on the brain: they improve the metabolism of neurotransmitters, increase the integration of neurons, have neurotrophic and neuroprotective properties, increase the utilization of glucose by brain cells, have antihypoxant effects, and increase cerebral blood flow [16]. In addition, estrogens reduce pathological deposits of amyloid, a key link in the pathogenesis of Alzheimer's disease, and suppress the activity of microglial cells [16]. proper estrogen levels. Several studies have been carried out to confirm this hypothesis. One of them, a prospective cohort study of cognition and aging (USA), which lasted 12 years and included 2114 white women over 65 years old, evaluated the effect of estrogens on cognitive status. The authors concluded that both a longer reproductive period and the use of MHT are associated with the prevention of cognitive impairment. At the same time, earlier administration of MHT (within 5 years after the last menstruation) is associated with an improvement in cognitive function compared with a later start [13]. Another study, a 20-year Finnish prospective cohort study from 1989 to 2009, examined the association between MHT and Alzheimer's disease. According to the data obtained, the use of estrogen in postmenopausal women is not associated with the risk of developing Alzheimer's disease and, on the contrary, long-term use of MHT is statistically significantly

associated with a decrease in this risk [18]. The following general conclusion can be drawn: the early period after menopause is associated with cognitive decline, which highlights the potential importance of estrogens; Starting MHT soon after menopause and continuing it long-term reduces the risk of developing Alzheimer's disease and other cognitive impairments.

Along with the unequivocal effectiveness of MHT in terms of preventing atherosclerosis, diabetes, vascular and degenerative dementia, increasing immunity, reducing chronic inflammation, etc., there is another side of the coin - the possibility of venous thromboembolic complications (VTEC), which causes women and doctors to be afraid of this therapy. However, the risk of such complications in the use of MHT largely depends on the type of estrogen and its concentration: as a rule, synthetic estrogen is much more dangerous than natural, and an increase in the dosage of estrogen is associated with an increased risk of developing VTEC [18]. This is largely due to the vasodilating properties of estrogens, which slow down blood flow in the veins, as well as to an increase in the blood levels of some coagulation factors [19]. It should be noted that after a year of MHT, the risk of VTEC is significantly reduced, since latent thrombophilic conditions are usually realized during this time [18]

With regard to the possible development of venous thrombosis, gestagens are also of great importance. One recent UK study analyzed the QResearch and Clinical Practice Research Datalink databases from 1997–2017. by the case-control method. The study covered a significant number of women (n = 80,396) [20]. The results of the work carried out showed that:

• MHT with estradiol in combination with dydrogesterone is characterized by a minimal, non-statistically significant increase in the risk of VTEC, unlike other combined MHT;

• Neither a cyclic nor a continuous regimen of estradiol with dydrogesterone is associated with a statistically significant increase in the risk of VTEC;

• The use of MHT with various dosages of estradiol is associated with a low risk of VTEC, provided that dydrogesterone is used;

• with MHT with dydrogesterone in patients aged 65–79 years, the chance of developing VTEC is less than with therapy with other gestagens;

• The most preferred combination of MHT in overweight patients is the combination of estradiol with dydrogesterone;

• Combination therapy with medroxyprogesterone is associated with a higher risk of VTEC.

A statistically significant increase in the risk of VTEC in the described study was observed with MHT with all progestogens, except for dydrogesterone, including drospirenone and norgestrel. However, due to the small number of participants in the study who took norgestrel / levonorgestrel or drospirenone, the authors analyzed these drugs as one type, which could potentially distort the results [20]. It can be assumed that the lack of information in the databases on the use of these progestogens (less than 1%) speaks of their rather rare use in a cohort of women in the UK.

Conclusion

Menopausal hormone therapy (MHT) not only eliminates various menopausal manifestations, but also has the most powerful preventive properties in relation to the development of atherosclerosis, diabetes mellitus, and abdominal obesity, vascular and degenerative dementia. The oral form of MHT is 4–5 times more effective than transdermal ones, however, for treatment, it is necessary to use a therapeutic window of no more than 5-10 years after the onset of menopause. To reduce the risk of developing venous thromboembolic complications, it is preferable to use natural estrogen in the lowest possible dosage, and of the gestagens, dydrogesterone is the safest and most neutral.

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