Chapter

Ovarian Hormonal Change-Related Energy Metabolism and Obesity in Menopausal Women

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Abstract

Obesity and its related severe consequences have been a major public health problem worldwide. A significant weight gain and intra-abdominal adipose tissue accumulation are observed as women begin the menopausal transition. A number of clinical and basic research indicate that ovarian hormone may play a crucial role. However, the underlying mechanisms are largely unknown. In this chapter, we aim to systematically review the literature in the influences of ovarian hormone on the physiology of lipid and glucose metabolism, obesity-related hormone, and the regulation of body weight by the dietary intake, feeding behavior. A variety of research modalities have been used to explore the effects of MHT in perimenopausal women. Hence, we will also summarize the latest progress of MHT use on the effect of body mass, body fat redistribution, and insulin resistance, which lead to protective cardiometabolic effects.

Keywords: menopause, ovarian hormone, estrogen, metabolism, obesity, menopausal hormone therapy, adipose distribution, insulin resistance, leptin, growth hormone, dietary intake

1. Introduction

Menopause is a special period for women, which is the end of menstrual cycle and fertility and also the start of a series of changes, such as hot flashes and mood changes. Energy metabolism also changes during menopausal transition, which is important and yet does not receive enough attention. Clinical surveys observed a trend of weight gain, increased food intake, intra-abdominal fat accumulation, increased low-density lipoprotein cholesterol and triglycerides, insulin resistance, and reduced energy expedition [1, 2]. All of these changes in energy metabolism add to the risk of diabetes and cardiovascular diseases (CVDs).

The characteristic and fundamental differences in postmenopausal women are the changes in ovarian hormones. Estrogen and progesterone decreased while androgen, follicular stimulating hormone (FSH), and luteinizing hormone (LH) increased [3]. Among them, the effect of the declination of estrogen level is most studied. Estrogen receptors are expressed in various tissues, such as brain, adipose tissue, liver, and intestinal mucosa, of which all regulate energy expenditure [4]. Apart from ovarian hormones, leptin, growth hormone, and others also affect energy homeostasis and will be discussed in the text.

In this chapter, we summarize the evidence from clinical and animal studies and target to explain how hormonal changes in menopause lead to alterations in lipid

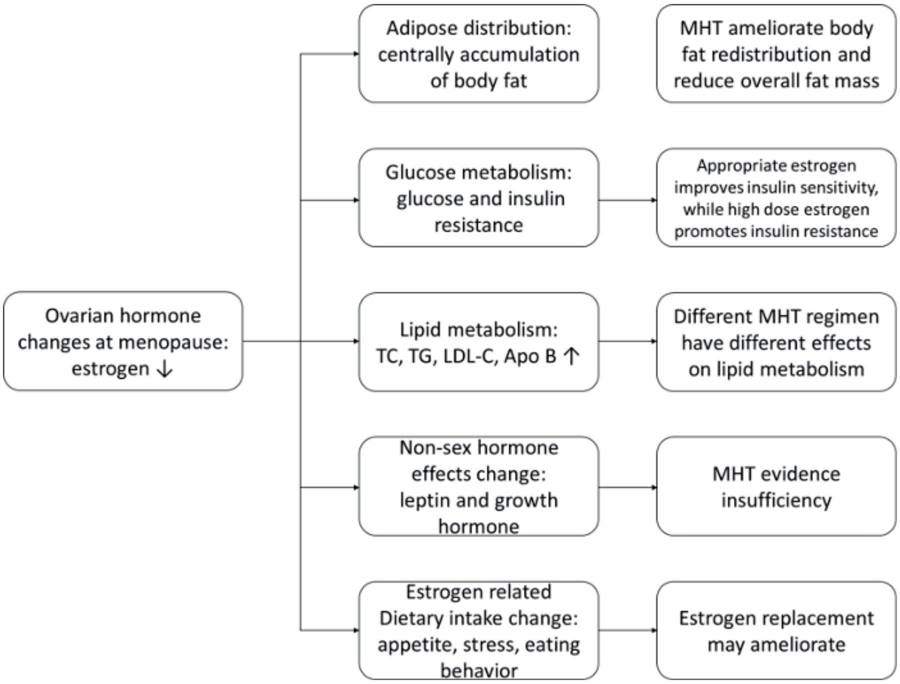

Figure 1.
Graphical overview on the contents of this chapter.

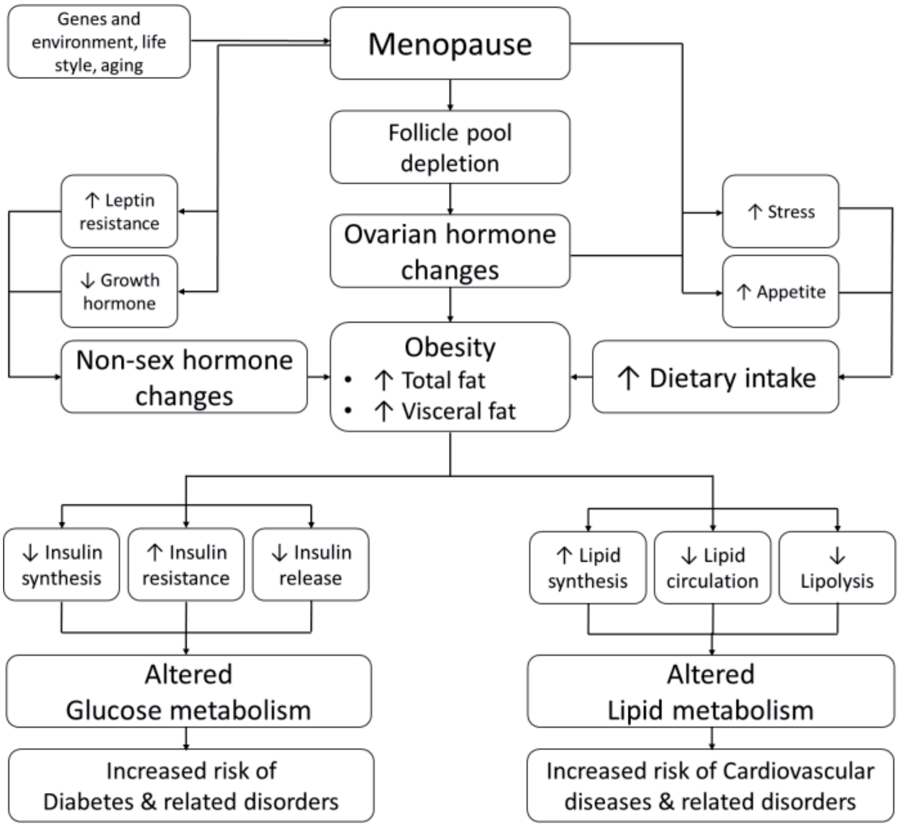

Figure 2.
Schematic illustration of possible pathophysiology underlying the ovarian hormone changes related to energy metabolism and obesity in menopause women.

and glucose metabolism, fat distribution, and food intake (**Figures 1** and **2**). We are also interested in the latest progress of the menopausal hormone therapy (MHT) and how it influences fat redistribution and metabolism (**Figure 1**).

2. Adipose distribution, metabolic consequences at menopause, and menopausal hormone therapy

2.1 The influence of menopause on adipose distribution and menopausal hormone therapy

2.1.1 Adipose distribution at menopause

The body adipose tissue distribution is different between males and females. The figure of men is pear shaped, since the adipose tissue tends to accumulate on the subcutaneous and intra-abdominal part. Whereas women's figure is apple shaped, since women's fat is more likely to accumulate on gluteal and femoral part [5]. However, mounting evidence indicated that postmenopausal women underwent deleterious changes of body adipose tissue distribution, from noncentral adiposity to central adiposity, which leads to an increased risk of CVD [6–8].

A number of factors contribute to the altered body adipose tissue distribution in postmenopausal women, including age, menopause, appetite, physical activity, and emotional changes, while age and menopause are the main reasons. A prospective study carried by Ho et al. concerning Chinese women aged 44–55 showed that the body fat percentage and central adiposity were higher among perimenopausal and postmenopausal women than that in premenopausal women [6]. Another study followed up by Caucasus and black women for 4 years and found that menopause was related to total fat increase and visceral fat increase [7]. A meta-analysis revealed that the decrease in total leg fat percentage and increase in measures of central fat were related to menopause, while increasing age was a predominant contributor [8]. This epidemiological and clinical evidence suggests that ovarian hormone may play a major role in the regulation of adipose tissue distribution.

Since 1990s, accumulating evidence suggests that androgen receptor (AR), estrogen receptor (ER), and progesterone receptor (PR) are present in adipose tissues [5]. Ovarian hormones enter the cell and bind to their specific receptors, and then the complex regulates the transcription of targeted genes. Lipoprotein lipase (LPL) is one of the most important proteins that are involved in lipid deposition. LPL is the key enzyme hydrolyzing the circulating triglycerides into glycerol and free fatty acids, which accumulate in the adipose tissues. The hormonal regulation of LPL in adipose tissues is complicated. Generally, growth hormone and estrogen inhibit lipid accumulation by suppressing the activity of LPL, while cortisol and insulin appear to exert opposite function [5].

Iverius et al. found that fasting plasma LPL activity was inversely correlated with plasma estradiol levels and positively correlated with plasma-free testosterone in obese women [9]. One study observed that when 17β-estradiol patch was placed transdermally in the gluteal region of postmenopausal women, LPL in adipose tissue from beneath was significantly decreased compared to placebo group [10]. It is also found that compared to premenopausal women, postmenopausal women have lower LPL activity in femoral adipose tissue, whereas abdominal LPL activity is comparable [11]. Palin et al. found that estrogen regulates LPL activity in a dose-dependent manner, the highest concentration of estrogen 10^{-7} mol/L significantly reduced LPL expression relative to control, while the lower concentration significantly increased LPL expression relative to control [12]. However, whether estrogen regulates LPL activity directly or indirectly remains unclear. A research from the rat model suggested that ovarian hormones exerted their regulation of LPL activity indirectly through their effect on growth hormone [13]. However, Homma and his colleagues found that estrogen markedly decreased the LPL mRNA using genetically manipulated cells and demonstrated a special sequence that was responsible for suppressing the LPL gene transcription by estrogen [14]. There might be a nongenomic mechanism existing for the regulation of ovarian hormone, which responses more rapidly, since ER was found in cellular membranes of subcutaneous abdominal and omental human adipose tissues. But the mechanism has not been completely elucidated. It appears that various components of the membrane signaling systems were involved, including the cAMP cascade and the phosphoinositide cascade [5].

2.1.2 Menopausal hormone therapy-related body fat distribution

Since the increases in total body fat and abdominal fat are associated with hormonal changes during menopause transition period, MHT may help to ameliorate the unfavorable body fat redistribution and reduce the overall fat mass.

Our team found that in ovariectomized mice, the estrogen-treated group gained less weight and had significantly lower visceral adipose mass and smaller adipocyte size than nontreated group [15]. A randomized study found that hip and abdominal circumferences and fat mass/fat-free mass ratio over the abdomen in women who received only estrogen therapy were significantly declined [16]. Postmenopausal women who used continuous combined regimen of 17-β estradiol plus norethisterone acetate showed significantly reduced central fat accumulation as assessed by waist circumference and subcutaneous abdominal fat thickness after a 6-month follow-up [17]. One study concerning the randomized controlled clinical trial of the Women's Health Initiative (WHI) showed that after 3 years of intervention with estrogen plus progestin, the treated group of women lost less lean soft tissue mass than the placebo group. Additionally, the women in the treated group had less upper-body fat distribution than the women in the placebo group [18]. Other studies compared different routes of estrogen replacement therapy and discovered that oral estrogen treatment resulted in an increase in fat mass of 5% and a decrease in lean body mass of 2%, which is equivalent to those occurring spontaneously over a 5–10-year period, whereas the transdermal estrogen did not bring a significant change in fat mass and lean mass [19, 20]. Though the conclusion is controversial, the International Menopause Society (IMS) puts it in their recommendation that menopausal abdominal fat accumulation can be ameliorated by estrogen therapy, with a reduction in overall fat mass, and maintain that a healthy diet and physical activity should also be included in weight management [21].

2.2 The influence of menopause on glucose metabolism and menopausal hormone therapy

2.2.1 Glucose metabolism at menopause

The incidence of glucose intolerance and insulin resistance increases after menopause [22]. The underlying pathogenesis of impaired glucose metabolism, although not yet fully understood, has been linked to estrogen deficiency, which is one of the characteristic changes arising with menopause. Estrogen exerts its protective effects on glycometabolism via various ways:

1. Increase insulin synthesis: Estradiol-stimulated estrogen receptor α (ERα) activates the Src/MAPK pathway, phosphorylates the transcription factor

PDX-1, and enhances NeuroD1 nuclear localization and its binding to the insulin promoter [23]. As a result, insulin gene transcription is upregulated, and insulin synthesis increased.

2. Regulate insulin release: On one hand, estrogen inhibits basal insulin secretion, which is mainly mediated by estrogen receptor β (ERβ). After an overnight fast, ERβ knockout mice carry lower blood glucose level than their counterparts in the control group and ERα gene knockout group [24]. On the other hand, estrogen promotes glucose-stimulated insulin secretion, which is mainly mediated by its plasma membrane receptor. This pathway regulates the activity of membrane-bound guanylate cyclase and activates protein kinase G. Subsequently, ATP-sensitive K+ channels close, and calcium channels open, triggering the insulin release [25].

3. Decrease insulin-mediated glucose uptake: Study suggests that the use of estrogen or combined estrogen-progesterone therapy in women may alter glycogen synthesis, GLUT4 translocation, and other early steps in the insulin-signaling pathway, which in turn decreases whole-body glucose uptake [26].

4. Reduce insulin resistance: Low estrogen is found to be an independent predictor of insulin resistance [27]. Elevated cytosolic free calcium may be the basis of insulin resistance. It is believed that estrogen as a calcium channel blocker may reduce cytosolic calcium, antagonizing the process of insulin resistance [28].

5. Protect pancreatic β cells against inflammation-induced apoptosis: Estrogen activates Src/MAPK, PI3K/Akt signaling pathway, upregulates liver receptor homolog −1, promotes glucocorticoid synthesis, suppresses interleukin-1 and interleukin-6 transcription, and thus protects human islets against inflammation-induced apoptosis [29].

6. Reduce pro-inflammatory cytokines: Estrogen reduces pro-inflammatory cytokines in adipose tissue. It is noted that the level of TNFα, MCP-1, IL6, and macrophages increases after oophorectomy in mice [30]. By inhibiting inflammatory responses, estrogen can improve the insulin sensitivity.

After menopause, the above protective effects are impaired due to a dramatic reduction in estrogen, leading to a decreased level of insulin synthesis and glucose-stimulated secretion. At the same time, however, the inactivation and clearance of insulin are slowed in aging liver and kidney, and the serum insulin concentration exhibits an overall upward trend.

2.2.2 Menopausal hormone therapy-related glucose metabolism

MHT improves the quality of life in postmenopausal women by treating a range of symptoms with exogenous hormone supplement, using estrogen together with other hormones. However, current evidence concerning the effects of MHT on glycometabolism remains controversial.

It was found that a low estrogen status is more detrimental to glycometabolism. The second national health and nutrition survey in the United States revealed that the risk of Type 2 diabetes in postmenopausal women was significantly higher than premenopausal women. Moreover, 40~50% of menopausal women were reported to have reduced insulin sensitivity.

Further studies confirmed that estrogen has a dual effect on insulin sensitivity: appropriate estrogen improves insulin sensitivity, while high dose estrogen promotes insulin resistance. In one study, insulin tolerance test was undertaken following the estrogen replacement using conjugated equine estrogen. *K* value indicating insulin sensitivity increased by 25% with the dosage of 0.625 mg but decreased by 24.7% with the dosage of 1.25 mg [31].

Borissova et al. found that estrogen in MHT can promote insulin secretion after glucose administration, improve insulin sensitivity, and correct fasting hyperinsulinemia in postmenopausal women with Type 2 diabetes [32]. Two large randomized, double-blind trials also found that estrogen replacement significantly reduced the incidence of diabetes compared with the control group, the incidence rates were 3.5 versus 4.2% and 6.2 versus 9.5%, respectively [33, 34].

However, some scholars believe that estrogen is unfavorable for glycometabolism in view that high level of estrogen could result in a decrease in glucose tolerance in oral contraceptives users. Studies also showed that estrogen, when given beyond its physical dosage, induced the glucocorticoid secretion and thus increased the blood glucose level [35].

Lack of standardization for insulin sensitivity measurement, differences in the studied population, as well as types and routes of administration of hormone therapy may contribute to the discrepancies of effects of estrogen replacement on glycometabolism [36].

2.3 The influence of menopause on lipid metabolism and menopausal hormone therapy

2.3.1 Lipid metabolism at menopause

It is well known that estrogen has a significant effect on modulate lipid metabolism. A variety of research show that total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (Apo B) increased in perimenopausal women, while menopause-related alternation in high-density lipoprotein cholesterol (HDL-C) is inconsistent [1, 37–42]. Some studies reported a significant reduction, others found an increase in menopausal transition, and rest showed no changes in HDL-C, which El Khoudary has suggested that menopause-related alterations may influence other metrics of HDL that could not be fully reflected by just the cholesterol contents of HDL particles as measured by HDL-C [43].

The underlying mechanisms that estrogen and lipid interact at a molecular level to contribute to the risk of CVD are not clear. It has been reported that estrogen-related receptor γ (ERRγ) regulates hepatic TG metabolism through the action phospholipase A2G12B [44], and polymorphic hepatic lipase is associated with estrogen modulate lipolysis of TG [45]. Della Torre et al. showed that liver ERα activity was essential for balanced lipid and TC metabolism, lack of ERα might lead to hepatic fat accumulation and nonalcoholic fatty liver disease [46]. Enza Distefano et al. suggested that estrogen activates the expression of LDL-receptor gene in HepG2 cells by tyrosine kinase signaling pathway [47]. Several research studies have suggested that estrogen can reduce circulating LDL-C but not cholesterol synthesis by downregulation of hepatic and plasma PCSK9, which is a suppressor of LDL receptors, in both animals and humans [48, 49]. Liu et al. reported that estrogen antagonizes oxidized LDL-induced secretion of macrophage matrix metalloproteinase-12 (MMP12,) and arterial stiffness that prevent from atherosclerosis in women [50].

Recent studies of our group have linked glycerol channel aquaporin 7 (AQP7) to protective effect of estrogen against body fat redistribution and hepatic steatosis in ovariectomized mice, indicating that AQP7 might be a novel checkpoint involved in the regulatory network of estrogen during menopausal obesity [15, 51]. Following up these studies, the molecular details that link AQP7 to estrogen were examined by analyzing the physical interactions between the promoter site of AQP7 and ER in our latest publication [52]. From there, we provided the first evidence that ER directly bound the estrogen response elements (EREs) in the promoter area of the Aqp7 gene and transcriptionally controlled AQP7 expression upon estrogen exposure. Therefore, there is solid ground for suggesting that Aqp7 is a direct target gene of ERs and may serve as a potential molecular target for the prevention of menopausal obesity.

In a recent study performed by Song et al., research focuses on the effects of FSH on lipid metabolism and has suggested that the marked increase of FSH expression postmenopausal combined with its receptors in liver may also reduce LDL-receptor level and subsequently result in a weakness of LDL-C endocytosis and an elevation of circulating LDL-C level [53].

Taken together, the above observations emphasize the gender differences and age independent on the lipid changes around the final menstrual period and suggest that ovarian hormone may influence the hepatic lipid synthesis, reduce the lipid circulation, upregulate the lipolysis, and lead to protective cardiometabolic effects. Growing body of literatures indicated several related functional proteins might play a crucial role in sex hormone's regulation of lipid metabolism; however, presented findings of the studies as well as the conclusion need further verification, but they are promising. Therefore, the complex association of menopause, ovarian hormone, especially estrogen, and lipid metabolism needs further extensive experimentation.

2.3.2 Menopausal hormone therapy-related lipid metabolism

Prevention of weight gain and lipid metabolic disorder is important components in the healthcare of postmenopausal women. Although the latest guideline from IMS indicated that MHT may ameliorate perimenopausal intra-abdominal fat accumulation, whether the MHT might maintain the lipid level during menopause transition has not been mentioned [21].

Numerous studies have attempted to understand the metabolic consequences of MHT use and define the effects of different MHT regimens. Major studies have consistently found MHT decrease LDL-C, TC and lipoprotein (a) levels; however, findings regarding TG and HDL-C levels have been inconsistent [45, 54–57]. Godsland reviewed the effect of different MHT regimens, estrogen alone, estrogen plus progestogen, raloxifene, or tibolone on plasma lipid and lipoprotein levels and found estrogen alone raise HDL-C and lower LDL-C and TC. Oral and transdermal estrogen had opposite effect on TG. The increases in HDL-C and TG when using estrogen alone were opposed according to the additional progesterone type. Specifically, effects arranged from the least to the greatest are dydrogesterone, medrogestone, progesterone, cyproterone acetate, medroxyprogesterone acetate, transdermal norethindrone acetate, norgestrel, and oral norethindrone acetate [58]. Stevens et al. suggested that MHT-related metabolic pathways is linked to multiple cellular processes, and the different MHT regimens might lead to distinct intracellular signal transduction events which contributed to the disparate risks for some diseases, e.g. CVD and cancer, in menopausal women with MHT [59].

In conclusion, different MHT regimens have different effects on lipid metabolism, exerting favorable and unfavorable changes. The choice for a particular regimen should consider individual demands, indications, complications, and lipid profile.

2.4 Role of nonsex hormones in energy metabolism during menopausal transition

2.4.1 Role of leptin in energy metabolism at menopause

Leptin is a protein hormone encoded by obese genes and secreted by adipose tissue. It has two effects on energy metabolism: on the one hand, it causes weight loss mainly by suppressing appetite. On the other hand, it has a number of effects on peripheral tissues: it can regulate energy balance by reducing lipid release into the blood circulation, reducing the output of triglycerides in target cells, and reducing the newly formed apolipoprotein B, which reduces the production of chylomicrons and low-density lipoprotein and increases apoA1, apoA IV, and apoE [60]. In obese people, the serum concentration of leptin is significantly elevated, which may be the result of leptin resistance [61]. At the same time, leptin plays a special role in maintaining normal reproductive function. The maintenance of human reproductive function requires adequate nutrition and storage of metabolic fuels, and leptin is a messenger with this signal [62, 63]. People who are emaciated lack such a signal.

In the peri-menopausal obesity, the role of leptin is still not clear. Several studies have found that the leptin level in the obese women was significantly higher than that in the nonobese women, but there is no significant difference in serum leptin levels pre and post menopause [64], and menopause does not significantly affect leptin production. Serum leptin levels were significantly positively correlated with BMI and waist circumference [65].

Moreover, in the studies of leptin level in different sexes, it was found that peri-menopausal women had significantly higher level of leptin than men (even after adjusting for differences in male and female body weights) [66]. In the relationship between leptin and fat mass, it is different from gender. On the one hand, it is because of the inhibitory effect of androgen in blood on leptin. On the other hand, the difference in the amount of leptin in different fat distributions may also play a role. In fact, subcutaneous fat expresses more leptin mRNA than visceral fat [67], while male subcutaneous fat is less than female, so adipose tissue in males may produce less leptin than female adipose tissue. This can explain the difference in fat content in different genders, but it cannot explain that women before and after menopause have different fat distributions but have similar leptin levels. Kastin et al. studied the transfer of peptides from the blood into the brain in mice after ovariectomy and found that the transport of leptin into the brain was lower than that before ovariectomy [68]. Thus, they suggested that the weight gain caused by the loss of ovarian function in mice might be related to the decrease in leptin transported into the brain.

2.4.2 Role of growth hormone in energy metabolism at menopause

Growth hormone (GH) levels are lower in postmenopausal women than that in premenopausal women. Postmenopausal women have changes in body weight and body fat distribution, which may also be caused by changes in growth hormone axis function [69]. Snel et al. found that the fat mass in GH-deficient adults increased, and lean mass decreased [70], and this change could be reversed after supplementation with GH, thus confirming the importance of GH in regulating fat content.

GH regulates body weight through the hypothalamic-pituitary axis. Two peptides, growth hormone releasing hormone (GHRH) and growth hormone release inhibiting hormone (GHRIH), secreted by the hypothalamus, activate and inhibit the release of pituitary GH. The stress response of GH to GHRH in postmenopausal women decreases [71]. This response is similar to that in obese and elderly population; MHT supplementation in postmenopausal women can reconstitute GH response to GHRH. This shows that the neuroendocrine release of GH plays an important role in the control of neutral steroid hormones. On the other hand, high GH concentration may have exerted negative feedback by hypothalamic GHRIH [72]. The use of arginine in postmenopausal women does reconstitute the response of GH to GHRIH [73], which has nothing to do with BMI [71]. Therefore, we can assume that obesity, menopause, and aging are the characteristics of normal neuroendocrine changes caused by excessive effects of GHRIH, but the intrinsic relationship between them remains to be further studied.

2.5 Dietary intake at menopause

Incidence of overweight and obesity is increased in perimenopausal and menopausal women, which is an important public health concern. One of the reasons for increasing obesity during the menopausal transition is the increase in food intake. A combination of biological and psychological factors exerts potent influence on the regulation of appetite and food intake.

2.5.1 Estrogen and the central control of appetite

Women during the menopausal transition had decreased estrogen. Estrogen participates in the regulation of energy homeostasis, as evidenced by an increase in food intake and obesity in ovariectomized rats. In concordance, clinical evidence showed that hunger, desire to eat, and prospective food consumption are all increased during the menopausal transition, while fasting fullness is decreased. This trend persisted in the later postmenopausal years [74]. However, both animal and human studies indicate that overeating due to the lack of estrogen can be ameliorated by estrogen replacement therapy [75].

Control of appetite is mainly performed in the hypothalamus of the central nervous system. Located in this region are arcuate, ventromedial, and paraventricular nuclei. Two major populations of arcuate neurons influence food intake in opposite directions. Neurons that extend projections to the lateral hypothalamic area express neuropeptide Y and Agouti-related peptide, which stimulate food intake and decrease energy expenditure. In other words, they extend orexigenic effects. Other arcuate neurons extend projections to the paraventricular nuclei and express proopiomelanocortin (POMC) and cocaine-amphetamine-regulated transcript (CART), which inhibit food intake and increase energy expenditure. Therefore, they extend anorexigenic effects [76, 77]. Estrogen acts as both a direct and an indirect control of appetite and food intake, modulating both anorexigenic and orexigenic signals in hypothalamus [78]. Estrogen regulates the function of the hypothalamic nuclei through complex processes. While ERα is abundantly expressed in the rodent brain in ventromedial, arcuate, and paraventricular and the medial preoptic area, ERβ expression is significantly lower [79]. Estrogens directly act on POMC neurons and regulate their cellular activity. ERα mRNA level in arcuate POMC neurons fluctuates over the course of the menstrual cycle, with the most dramatic increase on the day of proestrus, when E2 concentration is the highest [77]. In concordance, Xu et al. demonstrated that hypothalamic-specific deletion of ERa in steroidogenic factor-1 (SF1) neurons reduces energy expenditure. Deletion of ERa in POMC neurons alone increases appetite. Simultaneous deletion of ERa in POMC and SF1 neurons can add up these two effects and lead to hypometabolism and hyperphagia [80].

Peptidergic systems known to regulate ingestive behavior include ghrelin, neuropeptide Y (NPY), and melanin-concentrating hormone (MCH). Ghrelin peptide is a hunger-stimulating hormone, which is not only produced in the stomach by parietal cells but also produced in different areas of the hypothalamus, such as the aforementioned arcuate and paraventricular nuclei [81, 82]. Ghrelin regulates food intake by activating the growth hormone receptor according to the fluctuation in carbohydrate and lipid levels. Ghrelin also antagonizes the function of leptin, which promotes a sense of fullness. The antagonizing effect acts through the neuropeptide Y/Y1 receptor pathway, which increases gene expression of NPY and augment food intake [83].

NPY increases food intake potently through the function of the arcuate and paraventricular area in hypothalamus [84]. Estrogen inhibits the orexigenic activity of NPY. This inhibitory action stems from the reduced NPY mRNA expression and receptor activity by estrogen [85].

Melanin-concentrating hormone (MCH) promotes feeding behavior by direct action on the lateral nucleus in hypothalamus [86]. The arcuate and POMC neurons can stimulate the MCH activity [87]. Ovariectomized rats treated with estradiol demonstrated reduced orexigenic effect of MCH [88], which is hypothesized to be a direct effect of the reduced expression of MCH mRNA or the decreased affinity of the MCH receptor [89].

2.5.2 Stress and feeding behavior

Stress has been tied to a tendency to overeat and a preference for high-fat and high-sugar foods. Animal studies showed that chronic stress stimulates food intake and inhibits hypothalamic-pituitary-adrenal axis activity induced by acute stress [90]. In humans, food craving after stress can be predicted by high cortisol reactivity in response to stress. Epel et al. found that premenopausal women exposed to a stressful situation had higher cortisol levels and experienced higher calorie consumption, and they also tend to prefer sweets. Negative mood induced by stress also leads to greater food consumption [91]. As women experiencing menopausal transition, they are exposed to a lot of distressing symptoms, such as hot flashes, negative mood, poor sleep, recurring infections of the urogenital tract, and so on. Stress arises, which may increase their eating behavior.

Further, stress situations can decrease gastric motility. Estrogen has synergistic actions with stress mediators and interacts with neuromodulators [92]. Estrogen also influences gut function by inhibiting smooth muscle contraction. Premenopausal and postmenopausal women demonstrated a decrease in gastric motility under stress, which was similar to the general population. However, the perimenopausal women exhibited lower basal gastric motility but did not reveal a decreased gastric motility in response to stress. This indicated that many gastric changes during menopause are a rapid response to decreased estrogen levels, which happens quickly and can recover with time even without estrogen replacement [93].

Gaining better understanding of the mechanisms of increased appetite during menopausal transition promises to open novel therapeutic solutions for this population. Since the lack of estrogen plays a key role in the disturbances of food intake, MHT is one of the solutions to prevent unfavorable overeating, metabolic disturbances, and obesity.

3. Conclusions

With the aging of world population, the health issue of postmenopausal women has been unprecedented concerned. Obesity is associated with a decline of lifespan. Especially, the increased risk of weight gain, centrally accumulation of body fat, and energy metabolism disorders during the menopausal transition lead to further CVD and rise overall mortality in women. An early intervention of

MHT perimenopause is recommended, which may maintain the energy metabolic homeostasis and increase the average life expectancy. Numerous research studies have elucidated that menopause-related obesity is the combined effects of a variety of neuroendocrine and metabolic pathways, and it is well recognized that ovarian hormone plays a key role. Besides, different regimens of MHT may cause delicate difference on energy metabolism. More studies are necessary to characterize the complex effects of ovarian hormone on the energy metabolism, in which multiple organs and systems are involved.

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Conflict of interest

The authors declare no conflict of interest.

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