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REVIEW ARTICLE

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Obesity and menopause

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ABSTRACT

Obesity is not a choice or a result of lack of willpower, but a multifactorial, chronic, progressive, and relapsing disease. During menopause, hormonal and body composition changes lead to greater visceral adiposity, that aggravates women's health at a cardiometabolic, mechanic and mental level. Adiposity has been identified as an important modifier of reproductive hormones. During female midlife, obesity has been associated with menstrual cycle alterations (anovulatory cycles ending with abnormal bleedings), menopausal symptoms including hot flashes, poor quality of sleep, aches and joint pain, genitourinary symptoms, and reduced quality of life. However, the relationships between weight, the menopausal process, aging, and hormone levels remain poorly understood. Women with obesity have an increased risk of thromboembolic disease when using menopause hormone therapy (MHT), and it is probably the main medical condition to prescribe or not MHT. However, this risk depends on the route and type of MHT. The use of estrogen-only or combined transdermal MHT does not increase the risk of a thrombotic event in women with obesity.

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Introduction

Obesity is not a 'choice', it arises from a complex interplay of biological, psychological, environmental and social factors. Obesity is not simply related to an individual's lack of willpower [1], rather, it is a chronic, progressive, and relapsing disease that affects women at higher rates than men [2]. According to the World Health Organization (WHO), overweight and obesity are defined as the abnormal or excessive accumulation of fat, that imposes risks to health, quality of life and life expectancy [3]. Excess of ectopic body fat can lead to the production of adipocytokines and inflammatory mediators, that disrupt glucose and fat metabolism, thus, increasing cardiometabolic and cancer risks [4].

In a gynecological setting, complications frequently encountered related to obesity include menopause problems/symptoms [5] and the increased risk of breast and gynecological cancers [6]. The endocrine tumult of the menopausal transition also exposes racial and socioeconomic disparities regarding the onset, severity, and frequency of symptoms [5,6]. There is ever-growing evidence of the impact that the excess of adiposity observed during the menopause and after, mainly due to biological changes resulting from decreased estrogen levels, has on various health indicators [7]. On the other hand, obesity can influence the decision to prescribe menopausal hormone therapy (MHT) [5,7].

Literature search

For this narrative review we performed a literature search using PubMed©, Embase©, and Scopus© to cover all publications up to November 2023. The search terms included the following keywords in the title and/or the abstract: obesity, menopause, fat mass, hormone therapy, vasomotor symptoms, osteoporosis. The search included studies in English language. A manual check was performed for potential additional studies.

How does the menopause affect fat mass?

Studies suggest that both estradiol (E2) and follicle-stimulating hormone (FSH) play roles in regulating energy balance, and hence, their known variations during the menopausal transition may influence fat mass quantity and composition [8,9]. E2 affects numerous energy homeostasis pathways, such as central nervous system (CNS) control of food intake and energy expenditure, regulation of lipid storage and metabolism in the adipose tissue, and insulin sensitivity [8]. Experiments involving laboratory animals (e.g. estrogen receptor Knockout and Knock-in models and ovariectomy with and without hormone supplementation) have shown that, in the absence of estrogens, a general mechanism for fat gain operates by reducing the metabolic rate at rest, decreasing spontaneous physical activity, and increasing caloric intake [10].

Several cross-sectional and longitudinal observational studies have found that resting energy expenditure (REE) is lower during the postmenopause than in the premenopause [11,12]. In premenopausal women, pharmacologic suppression of sex hormones through sustained administration of a gonadotropin-releasing hormone agonist (GnRH-a) reduces REE, whereas adding back

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transdermal E2 compensates for this GnRH-a induced decrease [13]. Notably, this paradigm of pharmacological hormone suppression, with and without the addition of transdermal E2, results in loss of lean mass, as assessed by Dual energy X-ray absorptiometry (DXA) only in women not receiving E2 treatment [14].

In a sample of 130 women of the Women's Health Across the Nation (SWAN) study showed no effect of the time since the last menstrual period over fat mass or lean mass (as determined by bioelectrical impedance). Indeed, the trend showed a linear increase in fat mass and a slight linear decrease in lean mass over time [15]. Similar results were corroborated in another study involving 191 healthy women (35 to 45 years) who were evaluated every 5 years and 75 women (46 or more years) who were still menstruating and evaluated every 6 months [16]. Most existing studies that examine the relationship between advancement of the menopausal stage based on menstrual pattern (i.e. pre-, peri-, or postmenopause) and changes in body composition or weight have concluded that the menopause had no effect on these parameters [17–24]. Although weight increased over time, in most studies [17–22], they often have important limitations such as the lack of details within such broad periods of pre-, peri- and postmenopause and in some cases had long periods between evaluations [16–21].

After menopause, there is a clear increase in fat mass, and a decrease in lean mass. This likely explains why there is no observable accelerated increase in weight or body mass index (BMI) across the menopausal transition. Data are consistent with the growing observation that, while BMI is a well-established indicator of cardiometabolic risk, it is not nearly as informative as the adiposity index. Specific aspects of adiposity, such as fat distribution, are not detected by BMI [25,26], making this index a less useful indicator of cardiometabolic risk in older women [27]. Despite this, recently more value, as a risk predictor, has been given to the abdominal circumference measurement [28].

Ultimately, the menopausal transition is associated with accelerated gain of fat mass and the simultaneous loss of lean mass; but their combined rates of change do not result in a detectable acceleration in weight or BMI gain at the onset of the menopausal transition [29].

How does obesity/overweight affect menopause?

Adiposity has been identified as an important modifier of reproductive hormones. During female midlife, obesity is associated with menstrual cycle alterations (e.g. anovulatory cycles ending with abnormal uterine bleeding), menopausal symptoms including hot flashes, poor sleep, aches and joint pain, urinary symptoms, and reduced quality of life [30]. However, the relationship between weight, the menopausal process, aging, and hormone levels remains poorly understood [31].

In a longitudinal study conducted in the population-based Penn Ovarian Aging Cohort ($n = 436$), which evaluated during 12 years anthropometric measures, menopausal status, and reproductive hormone quantifications [30], the findings clearly indicate that obesity is an important factor influencing the hormonal changes observed during the menopausal transition independent of age, race, and smoking.

Effect of obesity on age at menopause

Obesity at different ages (e.g. early versus mid-adulthood) may have different effects on the timing of menopause [32], due to changes in the reproductive function over time; however, few studies have directly and closely examined this. Furthermore, weight change and weight regain may be associated with menopause timing, especially in the context of overall adiposity.

Current evidence on the association between BMI and age at menopause remains unclear. The SWAN found no association between obesity and the age at natural menopause, although an association was found between surgical menopause and obesity [33]. However, an international pooled analysis of 11 prospective studies [34] supported a previously reported association between higher BMI and later menopause.

A prospective cohort study examined a variety of adiposity measures in 78,759 premenopausal women from the Nurses' Health Study who were followed from 1989 to 2011 in order to determine the incidence of early natural menopause [35]. The authors observed a non-linear, J-shaped association between BMI and the risk of early natural menopause. Compared to lean-normal weight women with a BMI of 18.5–22.4 kg/m^2, those with underweight significantly had 30% higher odds of early menopause. In contrast, women with overweight had a significant 21–30% lower odds. Intermediate abdominal adiposity was associated with a lower risk when compared to the lowest level, which persisted after BMI adjustment. The heterogeneity of study populations, assessment methods, and definitions of obesity may explain the observed discrepancies between findings.

Interestingly, according to a systematic review and meta-analysis [36], ovarian reserve markers, Anti–Müllerian hormone (AMH) and FSH, were significantly lower in women with obesity than in those without obesity, and BMI was negatively correlated with AMH levels in all study populations. Beyond its value as a marker of ovarian reserve and potential for ovulation, it has been suggested that lower AMH serum levels during the menopausal transition could be associated with higher markers of obesity and may be predictive of future obesity-related cardiometabolic complications [37].

Effect of obesity on vasomotor symptoms

The association between BMI and vasomotor symptoms (VMS; hot flashes and night sweats) remains highly controversial. Menopause-induced changes in thermoregulatory neurons result in a narrowing of the thermoneutral zone which is coupled with a reduction of the temperature threshold for a compensatory vascular response [38]. To date, two contradictory hypotheses have been proposed to explain the mechanisms that determine the relation between BMI and VMS. The 'thermoregulatory model' [32,33] that suggests that higher BMI and adiposity are linked to a greater prevalence of hot flashes due to body adipose tissue acting as a thermal insulator, hindering heat dissipation, thus women with obesity would suffer more VMS [39,40]; on the other hand there is the so-called 'thin hypothesis' that proposes that women with excess body weight experience fewer VMS because the cytochrome P450 aromatase enzyme in fat tissue converts androgens to estrogens [41,42]. In this second model, body fat would serve as a supplementary source of estrogen by aromatizing androstenedione, converting it into estrone [43].

Similarly, the effect of obesity on menopause-related symptoms may differ in relation to age (early versus mid-adulthood) [33]; higher BMI is significantly associated with more hot flashes during the menopausal transition, whereas it would be linked to a lower risk of hot flashes in the postmenopause [44], where a higher level of estrone might reduce hot flash frequency [42].

Recent studies have explored the role of adipose tissue-derived cytokine-like substances, collectively known as adipokines, as an additional mechanism that might potentially explain the link between adiposity and flushing. Adiponectin, the most abundant adipokine in the body, which is anti-inflammatory, has been associated with improved cardiovascular health, including a lower risk of cardiovascular disease (CVD) events [45]. In women with obesity, low circulating adiponectin levels, as well as central resistance to leptin, may contribute to a greater severity of menopause-related symptoms [44]. High leptin levels and low adiponectin levels have been observed in premenopausal and perimenopausal women [38], as well as in postmenopausal women with hot flashes compared to those without hot flashes [46]. However, a cross-sectional analysis of 898 postmenopausal women found an association between self-reported VMS and higher levels of ghrelin, the orexigenic peptide hormone released by endocrine cells in the stomach [47], but not adiponectin [44]. Therefore, although there appears to be links between VMS and adiponectin [48], this association remains underexplored.

Some research seems to point out at the link between VMS and adverse adipokine profiles or cytokines produced by the adipose tissue. Physiologic VMS have been associated with lower adiponectin levels, after considering potential confounders, indicating that the potential role of adipokines in producing VMS and their links to health warrant further attention [46]. Understanding the relationship between menopausal symptoms and obesity may help identify new strategies to prevent weight gain during female midlife, and thus, reduce adverse outcomes related to obesity and the severity of VMS [49].

Obesity, osteoporosis, and fracture risk: the 'obesity paradigm'

The belief that obesity is protective against fractures has influenced clinical practice, with BMI being part of the fracture risk assessment tool (FRAX). Studies have shown a positive correlation between bone mineral density (BMD) and BMI [50] and a lower incidence of hip fractures in adults with obesity [51]. However, accumulating evidence challenges this perception, which is known as the 'obesity paradigm'. While BMD is higher in obesity [52], it may not be sufficiently increased to compensate for the negative factors affecting bone health, including biomechanical factors such as bone geometry and quality.

A systematic review and meta-analysis [53] of 121 studies reported higher lumbar spine, total hip, femoral neck, and radius BMD among men and women (pre- and postmenopausal) with obesity compared to their counterparts with normal weight. Contrary to this, a recent retrospective study [54] identified abdominal obesity as a negative predictor of bone health among older adults, independent of BMI, with an inverted U-shaped association, and a point of inflection at a waist circumference of 95 cm, considered as a clinical parameter of abdominal obesity.

Although the underlying mechanisms linking obesity and bone health remain unknown, the common origin of osteoblasts and adipocytes from stromal cells may be the explanation of the link between adiposity and bone health [55]. The coexistence of a higher BMD and a higher prevalence of fractures suggests that in these patients, bone density is either more fragile or they are more prone to falls. Both could be partly explained by the consequences of impaired glucose metabolism. Changes in the properties of bone collagen material, due to the accumulation of advanced glycation end-products have been described [56]. Chances of falling are increased in patients with diabetes due to polyneuritis or episodic-hypoglycemia. Over time, it can be assumed that the accumulation of advanced glycation end products, as well as vascular and neural complications, may contribute to a greater tendency to fracture instead of offering protection against fractures due to greater bone mass [57].

Effect of obesity on other specific parameters of the menopause

Obesity has been associated with several other specific menopausal parameters or aspects including urinary symptoms, sexual functioning and quality of life. Women with overweight or obesity are more likely to experience urinary incontinence (UI) substantially affecting their quality of life [58,59]. Overweight and obesity have been identified as an important predictor of UI, with the risk being significantly elevated in cases of obesity. A recent meta-analysis reveals a strong association between high BMI, abdominal pressure, and bladder pressure [60]. Therefore, currently, obesity and overweight are considered independent risk factors for UI [59,60].

An important clinical condition to consider in postmenopausal women is the presence of sarcopenic obesity defined by excess adiposity and low skeletal muscle mass and/or function [61]. Sarcopenic obesity is a predictor of disability and survival, dramatically increasing the risk of obesity and age-related diseases [61].

Consistent evidence shows a bidirectional link between overweight/obesity and emotional distress in the general population [62]. In fact, adipokines produced by the adipose tissue activate systemic inflammation, which eventually affects the brain causing mood dysregulation [63]. It has also been hypothesized that menopause-related mood disorders may lead to increased cytokine and free radical generation, contributing to increased fat accumulation [64].

Furthermore, obesity also increases the severity of symptoms of impaired sexual functioning, unbalancing the levels of sex hormones, hence, resulting in a reduction of sexual desire, arousal, and orgasm [65]. Additionally, as obesity favors the likelihood of developing comorbidities such as type 2 diabetes, dyslipidemia and hypertension, these conditions in turn increase the risk of reduced sexual activity [66]. Moreover, people with obesity are more likely to experience anxiety and/or depression, which are thought to directly or indirectly impact sexual function [65,67]. As BMI increases, the likelihood of urinary incontinence and shortness of breath also increases [68]; however, in contrast, the relationship between BMI and the likelihood of aches/stiffness is nonlinear, increasing to a threshold level [68].

Risks and benefits of menopause hormone therapy in women living with obesity

MHT has been indicated in women suffering from menopausal symptoms; however, a high proportion of eligible women (54%–79%) are unwilling to receive this option [69]. According to recent guidelines [70–72] MHT remains the primary treatment for menopausal symptoms, particularly VMS and this statement has not changed in the last few years [73]. As it is recommended for medical interventions, MHT should be individualized according to women's needs, symptoms, and clinical conditions. In addition, it is relevant to provide the best MHT in terms of type, route, dose, and duration considering efficacy, tolerability, adherence, and any other relevant aspects [72]. In this sense, obesity

should be kept in mind when prescribing MHT, because adipose tissue is an endocrine tissue that produces estrogens [74] and it is associated with other disorders, such as the metabolic syndrome [75].

Scientific societies agree on the fact of considering MHT as safe and a recommendable management option in symptomatic menopausal women under the age of 60 or less than 10 years after menopause [71,72]. Although the benefits of MHT in these women have been demonstrated, by reducing cardiovascular risk, osteoporosis, and bone fractures, while also improving genitourinary syndrome of menopause, and quality of life [76,77], MHT should not be solely prescribed, as an isolated indication, for preventive purposes [77], except in case of premature ovarian insufficiency [78].

Women with increased BMI have a higher risk of thromboembolic disease (TED) when using MHT (OR 2.5, 95% CI, 1.7-3.7 [overweight]; OR 3.9, 95% CI, 2.2-6.9 [obesity]) as compared to women with normal weight [79]. TED is probably the main medical condition to prescribe or not MHT. However, this risk depends on the route and type of MHT and the severity of obesity. Women with overweight face an increased risk of TED when using oral MHT (combined or estrogen-only), although the absolute risk, especially in women under the age of 60 is low [80]. Transdermal MHT (with or without progesterone), on the other hand, is not associated with an increased risk; hence, the transdermal route should be preferred in patients with a risk or history of TED [80].

There are few studies that analyze the risk of using any type of MHT in obese women (BMI $\geq 30\,kg/m^2$). This is the reason why currently the prescription of MHT must be individualized, taking into consideration risks and benefits. Despite this, data regarding transdermal MHT suggest that the use of estrogen-only or combined transdermal MHT does not increase the risk of a thrombotic event in women with obesity (BMI $\geq 30\,kg/m^2$ but $<35\,kg/m^2$) [81,82].

Conclusions

During the menopausal transition there are unfavorable changes in body composition that include an increase in fat mass, particularly in the abdominal region, and a decrease in fat-free mass [31,83]. Whether these modifications are primarily due to age or hormonal changes is still a matter of intensive research and debate [31,83,84].

We currently consider that BMI is an independent factor for the presence of hot flashes, along with urge incontinence and vaginal dryness, supporting the thermoregulatory theory [85]. While BMD is higher in obesity [52], it may not be sufficiently increased to compensate for negative factors that affect bone health, including biomedical and biomechanical factors such as bone geometry and quality. For this reason, our belief is that all these factors predispose a greater tendency for fractures instead of offering protection against them due to greater bone mass.

In women with obesity, combined oral MHT should not be the first choice because the evidence shows an increased risk of TED; although the absolute risk, especially in those under 60 years of age, is low. The use of estrogen-only or combined transdermal MHT does not increase the risk of thrombotic events in women with obesity [81].

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