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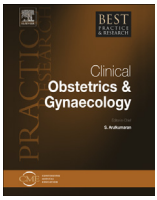

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Obesity and Menopause

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Over the recent decades, the prevalence of obesity in the United States has increased to epidemic proportions to more than 35% of adults, along with an increased risk of a number of health conditions, including hypertension, adverse lipid concentrations, and type 2 diabetes. The relationships between menopausal transition, weight gain, and obesity are reported but incompletely understood. The association between menopause and these measures has been the subject of many studies, along with examining their effect on reproductive hormones and menopausal symptoms. The purpose of this review is to summarize what is published in the literature on this subject and examine it through: (1) the possible impact of obesity on the timing of menopause; (2) the effect of obesity on menopausal symptoms and reproductive hormones around the time of menopause; and (3) the effect of menopause on obesity, weight gain, and body composition.

Introduction

Menopause is the permanent cessation of menses, with a median age of 51 years in North America. In the 21st century, Western women are expected to spend more than a third of their lifetime beyond the menopausal transition. The Stages of Reproductive Aging Workshop (STRAW) staging system was developed in 2001 to describe various stages of the menopausal transition. This staging system was revised in 2012 [1] to take into account more hormonal changes and to pinpoint more precisely the timing of symptoms (Fig. 1). With increasing longevity, the proportion of women who are menopausal in the general population is on the rise. Most women undergo physiological changes associated with menopause in the 3–5 years preceding the final menstrual period (FMP). Several short-term changes in

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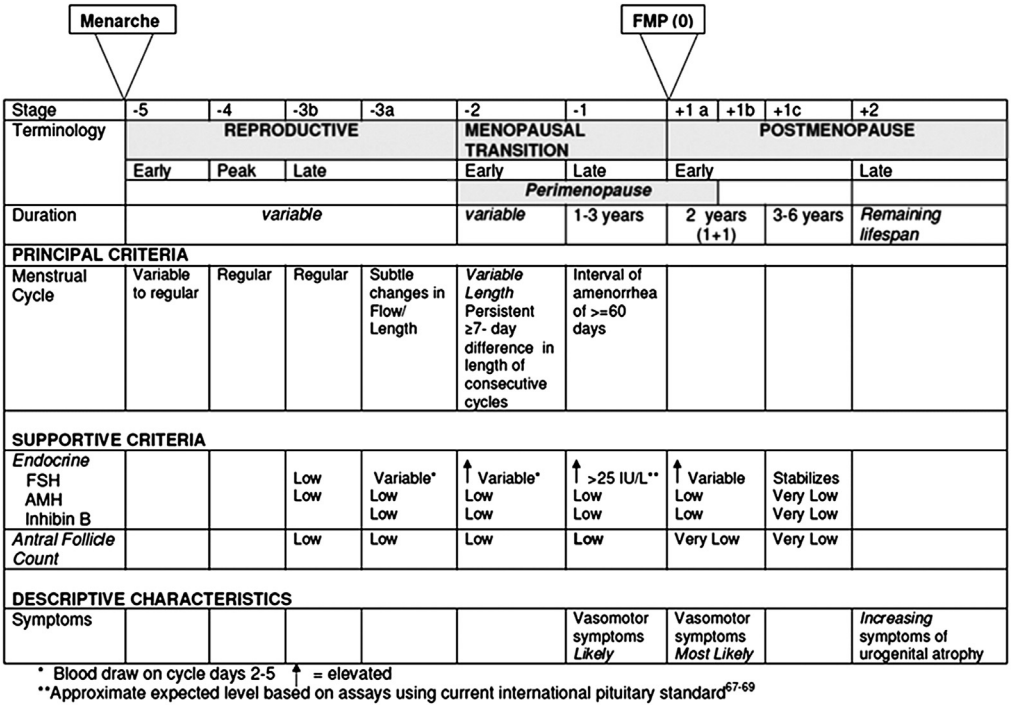

Fig. 1. The Stages of Reproductive Aging Workshop +10 staging system for reproductive aging in women. From: Harlow, S.D., et al., *Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging.* Fertil Steril, 2012.

health and quality of life, such as vasomotor symptoms, sleep disturbance, and affective symptoms, are frequent causes to seek medical attention. At the same time, some long-term changes in several health outcomes (i.e., urogenital symptoms, bone, and lipids) may result in significant morbidity [1]. This review will describe the latest evidence on the impact of obesity on menopause and menopausal transition.

Obesity and age at menopause

The age at the FMP is of intrinsic clinical and public health interest as it could represent a marker of general aging and health [2]. The impact of body mass and obesity has been extensively studied as a potential determinant of the FMP [3]. Weight gain among midlife women has been frequently reported, but the interrelationships between obesity, weight gain, and the menopausal transition remain incompletely understood. Due to differences in study designs, analysis, or varying control of confounding variables, inconsistent findings were seen when examining the relationship between body mass and age at menopause. Some studies have reported that both increased body mass index (BMI) and upper body fat distribution (indicated by waist-to-hip ratio) were associated with later age at natural menopause [4–6], while many other studies have reported no significant association of BMI with age at natural menopause [7–11]. In the Study of Women's Health Across the Nation (SWAN), cross-sectional analysis showed no relationship between obesity and age at natural menopause, but obesity was associated with a higher likelihood of surgical menopause [3].

Obesity and menopausal symptoms

Vasomotor symptoms (VMS), commonly known as hot flushes and night sweats, are sudden episodes of intense heat that usually begin in the face or chest and spread throughout the body,

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accompanied by sweating and flushing that typically last 1–5 min. VMS may also interfere with sleep and cause chronic sleep disruption in some women. Although for many years obesity was thought to be protective against VMS because androgens are aromatized to estrogens in body fat, it has been found through large observational studies that obesity is a key risk factor for perimenopausal, but not postmenopausal, VMS. Women with higher abdominal adiposity, particularly subcutaneous adiposity, are more likely to report VMS during the menopausal transition and early postmenopause [12]. This association between VMS and higher BMI persisted after controlling for related risk factors. The mechanism for this association is not well understood; it has been hypothesized that adipose tissue functions as an insulator and interferes with normal thermoregulatory mechanisms of heat dissipation. Adipose tissue may also have an endocrine function that mediates VMS [13]. Vulvovaginal atrophy with its symptoms of vaginal dryness, itching, dyspareunia, and irritation is strongly and consistently linked to estrogen deficiency and is highly prevalent in menopausal and perimenopausal women. Data from the observational cohort of the Women's Health Initiative (WHI) [14] have shown that obesity is an important correlate for multiple urogenital symptoms, and obese women were twice as likely to report severe vaginal discharge and almost four times more likely to report severe itching/irritation compared with low, normal-weight women, controlling for diabetes.

Obesity and reproductive hormones associated with menopausal transition

A number of studies looked at the pattern of hormonal changes during the menopausal transition between obese and nonobese women. In both SWAN and Penn Ovarian Aging Study (POAS), obese women had lower estradiol (E2) and follicular stimulating hormone (FSH) levels than nonobese women, and in the POAS, lower luteinizing hormone and inhibin B levels as well [15–18]. More rigorous analysis of hormonal changes before and after the FMP between obese and nonobese women has found that the patterns of change in FSH and E2 in relation to the FMP were not statistically different when comparing obese to nonobese women, although significant differences in the mean FSH and estradiol levels were observed [19]. In that analysis from SWAN, the E2 change was less pronounced in obese women when compared with nonobese women, because obese women had lower premenopausal mean E2 levels but higher postmenopausal mean E2 levels. The rate of E2-blunted decline observed among obese women is physiologically corroborated by a similarly blunted FSH rise surrounding the FMP in obese versus nonobese women [19]. Ultrasound data have shown no difference in antral follicle count between obese and nonobese women in their late reproductive age (40–52 years) [20]. This lack of difference does not support low ovarian reserve as the mechanism underlying lower E2 levels in obese women premenopausally, and this mechanism is currently unclear [21]. In POAS, anti-müllerian hormone was found to be lower in obese women compared to nonobese women in the late reproductive years [22], demonstrating the complex relationship between obesity and reproductive hormones in women approaching menopause. Follicular dysfunction and alterations in central nervous system regulation of hormonal levels among obese women may be factors, but additional research in this area is needed. The blunted magnitude of change in reproductive hormones in obese women during menopausal transition may be related to the change in the primary source of circulating E2 as the menopause transition progresses; the primary source of circulating estradiol premenopausally is the ovary, whereas post menopause, the primary source of circulating estradiol is the aromatization of androgens within the adipose tissue. This change in estradiol source provides postmenopausal obese women with a non-ovarian reservoir of estrogen that normal-weight women do not have, which may blunt the gonadotropin rises and mitigate ovarian estrogen loss with menopause. These hormonal alterations may also blunt menopause-associated adverse health effects [21].

Effect of menopause on obesity

The menopausal transition is associated with weight gain in many women [23,24]. Body weight also increases with age in both normal-weight and obese individuals [25]. These changes in weight and lipids seen during the transition were independent of age in some studies [26,27] but not others [23,28]. This weight gain during menopausal transition has been examined as potentially a major contributing factor to midlife body weight. However, a similar increase in adiposity has been observed

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in men of the same age, implying that chronologic rather than reproductive aging is the main culprit. Weight gain at midlife is partially attributed to the reduction in energy expenditure (EE), as women who have undergone menopause have shown a larger decrease in EE when compared with premenopausal controls at 4-year follow-up [29]. The possible explanations for this observed reduction in EE include a reduction in leisure-time physical activity, loss of lean body mass causing basal EE decline, as well as a loss of the luteal phase increases in EE described in the premenopausal years [25]. A cross-sectional study on 292 Brazilian women showed that sedentariness rather than menopause is associated with an increased risk of overweight/obesity (odds ratio 2.1; 95% confidence interval 1.233–3.622, $p = 0.006$) [30].

Longitudinal studies such as SWAN have confirmed that chronological aging is a significant contributor to the increase in weight and waist circumference during the fifth and sixth decades of life, while menopausal status was not associated with these changes over the 3-year follow-up period [31]. Moreover, within an SWAN ancillary study, body composition analyses demonstrated a positive, linear slope of fat mass by study year as a proxy for chronologic aging, but a curvilinear increase in fat mass was seen surrounding the FMP, whereby fat mass increased to a greater degree before menopause and thereafter leveled off, suggesting that accumulation of fat mass slowed after the FMP [32].

Obesity and metabolic correlates of menopause

As was discussed above, weight gain at midlife is primarily influenced by age alone rather than FMP. However, menopause is associated with an increase in abdominal subcutaneous and visceral fat as was seen in a study using computed tomography (CT), demonstrating an increase in subcutaneous adipose tissue with age, independent of menopausal status, whereas visceral and total body fat increased only in women who became postmenopausal during the 4 years of follow-up [29]. The change in visceral adiposity was accompanied by a decrease in circulating estradiol and increase in FSH, and it was attributed by the authors to influences of estrogen on lipoprotein lipase activity and lipolysis [29]; this was also reflected in a cross-sectional study showing increased waist circumference and waist–hip ratio in postmenopausal women, even after controlling for BMI and other confounding factors [33]. Another study using magnetic resonance imaging (MRI) showed an increase in abdominal subcutaneous and visceral fat with menopause, but no change in BMI or waist circumference [34]. These changes have been sometimes described as a transition from a gynecoid to an android pattern of fat distribution [35,36]. The accumulation of abdominal fat in postmenopausal women appears to be a critical factor in the development of insulin resistance and type 2 diabetes [37]. This constellation of adverse effects often includes abnormal lipid profile, with an increase in low-density lipoprotein cholesterol and a decrease in the ratio of total cholesterol to high-density lipoprotein cholesterol [34]. Interventions to treat obesity include physical activity, calorie-controlled diet, pharmacotherapy, or bariatric surgery. Menopausal hormone therapy is associated with a reduction in central adiposity and an increase in insulin sensitivity, as seen in most randomized controlled trials [38–40], but hormone therapy should not be prescribed solely for this purpose. Metformin is effective at delaying the progression of impaired glucose tolerance to type 2 diabetes [41]. Lifestyle modifications, such as diet and exercise, have been more effective in randomized controlled trials to reduce the incidence of diabetes in those at high risk [42]. Women in the menopausal transition are ideal candidates to begin preventative measures such as dietary modification and physical activity, and health-care providers should encourage these women to adhere to these lifestyle changes in order to prevent morbidities associated with obesity and aging.

Summary

Weight gain among midlife women has been frequently reported, but the associations between obesity, weight gain, and the menopausal transition remain incompletely understood. Studies have not shown a significant impact of obesity on the timing of menopause, but they have suggested that obese women have exacerbated VMS. This association is likely due to the insulating effects of adipose tissue, although this effect may decrease later in the menopause transition because of the blunted estradiol decrease in obese women. Studies have shown that chronological aging and lack of physical activity

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rather than menopause are the main culprits in weight gain and obesity in midlife women. Lifestyle modifications with healthy diet and exercise remain the best measures to prevent morbidities related to obesity and aging.

Conflict of interest statement

The authors have no conflicts of interest related to this article.

Practice points

- Age and sedentary life are the main contributors to weight gain around the time of menopause.
- Obese women are more likely to report vasomotor symptoms (VMS) during the menopausal transition and early postmenopause, possibly due to the insulating effects of the adipose tissue.
- Obese premenopausal women have lower estrogen levels than normal-weight women; this is shifted after menopause with higher estrogen levels in obese women.
- Health-care providers should encourage women in menopausal transition to adhere to healthy lifestyles in order to prevent associated morbidities.

Research agenda

- Additional longitudinal studies on the effect of menopause on increase in fat mass and abdominal fat redistribution are required.
- Further research is needed in which all potentially confounding variables are simultaneously controlled to be able to assess adequately the independent contribution or the interactive effect of body mass and composition and these other factors on the age at the natural final menstrual period and duration of menopause transition, using appropriate longitudinal study design and data analysis techniques.

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