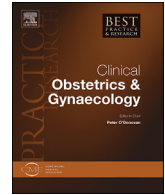




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Obesity and menopause

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ABSTRACT

The global obesity pandemic continues to rise, with figures from the World Health Organization showing that 13% of the world's adult population was obese in 2016. Obesity has significant implications, with an increased risk of cardiovascular diseases, diabetes mellitus, metabolic syndrome, and several malignancies.

The menopausal transition is associated with increased obesity, a transition from a gynecoid to an android body shape, and increased abdominal and visceral fat, which further worsens the associated cardiometabolic risks.

Whether this increased obesity is a consequence of menopause, age, genetics, or environmental factors has long been debated. Increasing life expectancy means women spend a significant part of their lives in the menopause. As such, understanding this complex interplay of obesity and menopause is important to providing the right advice/management.

We review the current evidence on obesity and menopause, focusing on the implications of increased obesity during menopause, the impact of menopause on obesity, and the effect of available treatments on associated morbidities.

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Multiple choice questions

1. Regarding vasomotor symptoms (VMS)-
 - a. Includes hot flushes and night sweats - T
 - b. Causes sleep disturbance and affects the quality-of-life - T
 - c. Obese perimenopausal women have more VMS than normal-weight women - T
 - d. Obese postmenopausal women have more VMS than normal-weight women - F
 - e. Premenopausal obese women have higher estrogen and FSH levels compared with normal-weight women – F

2. Regarding the menopausal transition (MT) -
 - a. There is robust evidence linking smoking to an earlier age at natural menopause. - T
 - b. Obesity is generally associated with a later onset of natural menopause
 - c. Women of different ethnicities experience the same changes in weight and body shape around menopause - F
 - d. The menopausal transition lasts on average 2 years - F
 - e. There is robust evidence linking genetics to an earlier age at natural menopause. - T

3. Menopause is associated with a change from a gynecoid to an android body shape, with increased abdominal and visceral adiposity.
 - a. BMI (body mass index) is a good measure of abdominal and visceral obesity. - F
 - b. Abdominal and visceral obesity are associated with higher cardiometabolic risk and mortality. - T
 - c. Menopause associated body shape changes only occur in obese women. - F
 - d. A body shape index (ABSI) and lipid accumulation product (LAP) are more accurate measures of visceral adiposity. – T
 - e. The menopausal body shape changes are mediated by estrogen decline and increased follicle-stimulating hormones (FSH)- T

Introduction

Menopause is a retrospective diagnosis made 12 months after the permanent cessation of menstruation that is caused by a decline in ovarian hormone production. The current median age of menopause is 52 years in the United States [1], ranging from 45 to 55 years [2]. There is a progressive transition from the late reproductive years, through the perimenopause, to the final menstrual period and the early and late menopause, characterized by menstrual irregularity, vasomotor symptoms (VMS), sleep disturbances, and the genitourinary syndrome, as well as increased risks of cardiovascular (CVS) disease, metabolic syndrome (MetS), osteoporosis, and several malignancies (STRAW + 10 classification) [3].

The physiologic and metabolic changes associated with the menopause are a direct effect of estrogen deficiency, which has been shown to affect lipid metabolism, energy consumption, insulin resistance, and body fat composition, with a transition from a gynecoid to an android body shape and increased abdominal and visceral fat accumulation associated with increased CVS and metabolic risks [1,4–8].

Worldwide, obesity is considered a pandemic, with the rate continuing to rise. Currently, approximately 13% of the world's adult population is obese, according to the latest World Health Organization figures [9], and 50% of the US adult population is projected to be obese by 2030 [10]. Obesity is more prevalent in women than men, especially in the middle and older age groups [11,12]. Population statistics from the United Kingdom, China, and worldwide show a similar trend [13–15].

Whether this increase in obesity is a consequence of menopause, age, genetics, and/or environmental factors is a subject of ongoing debate. With increased life expectancy, more women will spend an estimated thirty to forty percent (30–40%) of their lives in the menopause stage, with the attendant health and quality of life implications [2,16,17].

The complex interaction between age, obesity, and menopause is the subject of several ongoing studies. Current evidence from several large and long-running cohort studies, such as the Study of Women's Health Across the Nation (SWAN) and the Women's Health Initiative (WHI), suggests that the perimenopausal increase in obesity, measured by body mass index (BMI), is a consequence of age. Menopause is, however, associated with an increase in truncal obesity and visceral adiposity (measured by waist circumference and waist-to-hip ratio), which are more associated with increased CVS risk, MetS, and hormone-related malignancies like endometrial and breast cancers. [1,18–20].

In this review, we discuss and appraise current evidence on the interaction between obesity, the menopause, and long-term health indexes.

Obesity and menopausal transition

Several factors have been postulated to affect the age of natural menopause (ANM); there is, for example, robust evidence for an association between genetics and smoking and younger age of onset of menopause. The median age at menopause has progressively increased, which is most likely because of a combination of factors, including genetic and environmental, especially that there remains a variance in the age at menopause from one country/region to another: for example, 49 years in Korea and Iran, 51 years in the United Kingdom, and 52 years in the United States and Australia [1,14,21,22].

Obesity has been shown in most studies to be associated with a later onset of menopause. Although most cross-sectional studies show obesity to be linked to a later age at the onset of menopause, longitudinal cohort studies either show no association or a modest association. This discrepancy has been attributed to confounding factors, such as reliance on patients' recall of their weights, smoking, and the inability to determine the timing of menopause in some women who were surgically amenorrhoeic [16,23–25].

One plausible explanation given for the association between obesity and the later onset of menopause is that the increasing peripheral conversion of androstenedione to estrone that occurs in adipose tissue delays the onset of menopause, which is manifested by estrogen deficiency [25].

A recent population-based study from China found that compared with women with normal weight and normal waist circumference (WC), women who are overweight with both normal WC and central obesity were significantly more likely to enter menopause after the reference median of 51 years for these populations. Interestingly, some women who are overweight with central obesity also have a significantly higher risk of early menopause at younger than 45 and 45–49 years [13].

Obesity and menopausal symptoms

An important symptom of menopause is the hot flush, a sudden sensation of heat, usually starting from the face or chest, spreading through the body, and lasting 1–5 min [23]. This, together with night sweats, make up the VMS experienced by fifty to eighty percent (50–80%) of perimenopausal women, causing sleep disturbances, irritability, and poor quality of life [1,17].

Several studies have shown that perimenopausal women with obesity experience more severe VMS than women of normal weight. One explanation given for this is that excess subcutaneous adipose tissue in women with obesity acts as an extra layer of insulation, preventing heat dissipation. Pre-menopausal obese women are known to have lower estradiol and follicle-stimulating hormone (FSH) levels, partly due to the aromatization of androgen to estrogens in adipose tissue that causes negative feedback to the hypothalamic-pituitary-ovarian axis, decreasing FSH and, in effect, ovarian estrogen secretion. This production of extra ovarian estrogen, however, has a positive impact on vasomotor and other symptoms in obese women after the menopause [1,18].

An observational cross-sectional study from South Korea found that compared with women with normal weight, obesity was associated with more physical menopausal symptoms (bloating, sleep disturbance) in the perimenopausal period and increased VMS in the postmenopausal period, contrary to the common perception of increased peripheral estrogen in postmenopausal women with obesity resulting in less VMS [26].

Another cross-sectional study from Qatar in a mostly obese population did not show any association between obesity and VMS or sleep disturbance but showed a positive association between obesity,

genitourinary symptoms, and shortness of breath. Muscle aches also had a linear relationship with obesity, with a threshold effect plateauing after a BMI of 38 [27].

Obesity, particularly that associated with an increased abdominal girth, has been linked to sleep apnea and other sleep disturbances in menopausal women, as have genitourinary symptoms [24,28].

Obesity and reproductive hormones associated with menopausal transition

Menopausal transition (MT), defined as a critical period of physiologic change leading up to the final menstrual period, is characterized by menstrual irregularity, and transitory symptoms such as hot flashes and depressive symptoms, and persistent changes in bone density and lipids. It can last from 4 to 10 years. It is characterized by increased attrition and progressive depletion of ovarian follicles, with decreased ovarian sex hormone production resulting in a reflex elevation of FSH. This decline in ovarian follicles leads to a decrease in inhibin B, which is secreted by the granulosa cells of antral follicles. The decrease in inhibin B secretion decreases inhibition of pituitary FSH secretion, resulting in rising FSH levels. Elevated FSH initially causes sustained or even increased estradiol (E2) levels until the decline in antral follicles is so pronounced that E2 levels ultimately decrease [3,16,17,19,24].

Studies have shown that obese premenopausal women have lower E2 and FSH levels than non-obese women, with a more blunted rate of change in E2 levels perimenopause and higher E2 levels post menopause. Whereas the increased postmenopausal E2 is easily explained by the peripheral aromatization of androgens in adipose tissue, explanations given for the lower premenopausal E2 include adiposity-induced suppression of sex hormone-binding globulin (SHBG) synthesis, which then leads to greater clearance of E2, and a possible negative effect of obesity on granulosa cell function, thereby decreasing inhibin B levels [1,16,23,24].

Effect of menopause on obesity

The MT has been shown to be associated with an accelerated increase in obesity and central obesity, compared with the premenopausal years, with simultaneous loss of lean body mass. This has been shown in several longitudinal cohorts using BMI, waist-to-hip ratio, computed tomography, magnetic resonance imaging, and dual-energy X-ray absorptiometry measurements [7,20,24,29,30]. There are distinct ethnic differences highlighted in the SWAN study, with Black and White women having similar trajectories in weight and visceral fat gains during the MT but, interestingly, different trajectories after menopause, with White women continuing to gain visceral fat but not Black women. Japanese women, on the other hand, did not show the increased trend of visceral fat around the MT but then displayed an increase in central adiposity after menopause [1].

A decline in E2 may preferentially lead to central fat accumulation and promote visceral adiposity. Animal studies in mice and rats, as well as human ovarian suppression using gonadotropin-releasing hormone agonists, resulted in visceral but not overall fat mass gain; when E2 was added back, the visceral fat gain was reversed [16,24,31].

FSH has also been implicated in the postmenopausal increase, especially in visceral adiposity. Although FSH receptors were originally thought to be restricted to the gonads, they are now known to be present in visceral fat in both men and women. In vitro administration of FSH to pre-adipocytes in mice resulted in the redistribution of visceral fat mass and an increase in adipocyte lipid droplets and adipocyte lipid synthesis. Moreover, serum levels of adipokines (cytokines secreted by adipose tissue), including leptin and adiponectin, and lipid subgroups, including triglycerides, were altered, thereby suggesting that FSH might stimulate fat distribution and contribute to a pro-inflammatory milieu [16,24,32].

Importantly, the MT-associated increase in abdominal and visceral adiposity has been shown to increase cardiometabolic risk and mortality in postmenopausal women. The accumulation of abdominal fat in postmenopausal women appears to be a critical factor in the development of insulin resistance and type 2 diabetes. These are often accompanied by an abnormal lipid profile, characterized by an increase in low-density lipoprotein cholesterol (LDL-C) and a decrease in the ratio of total cholesterol to high-density lipoprotein cholesterol [23,33,34].

These metabolic alterations occur in both women with obesity and normal weight who may miss out on health screenings using BMI; hence, it has been suggested that either the BMI threshold for health screening should be lowered in menopausal women to capture the excess risk in the non-obese or other measures that are more indicative of abdominal and visceral adiposity, such as WC and waist-to-hip ratio, and newer anthropometric indexes, such as a body shape index and lipid accumulation product, which have been suggested as being more accurate but at present are not practical to use in clinical settings, are used [29,31,35,36].

Menopausal weight gain has also been explained by the effect of estrogen deficiency on energy intake and expenditure. E2 has been shown to have an inhibitory effect on appetite, and post-menopausal E2 depletion is thought to centrally control energy intake [37].

A longitudinal study from Iran showed that the postmenopausal increase in obesity had an interesting inverse relationship with ANM. Relative to their mean age of 49 years, women with an earlier ANM had an increase in obesity, whereas women with a higher ANM had a decreasing tendency of obesity after menopause. They rationalize that this relationship is because of menopause/estrogen deficiency-related depression, decreased appetite, and energy expenditure [38].

Menopause, obesity, and cardiometabolic risk

The MT is associated with increased cardiometabolic risk factors through several mechanisms, including increased weight, increased abdominal and visceral adiposity, and the removal of premenopausal estrogen-derived CVS protection [33,39].

Obesity is a well-known CVS risk factor and compounds the menopause-associated CVS risk. Postmenopausal women with obesity have a 4-fold increased risk of CVS mortality [4,39].

Ovarian estrogens promote peripheral fat storage in the gluteal and femoral subcutaneous regions and have a role in maintaining glucose homeostasis through their effects on insulin secretion and clearance. It is well established that E2 promotes peripheral (vs. central) fat distribution and improves insulin sensitivity in women [16].

After menopause, adipose tissue distribution in women shifts and instead accumulates in the viscera or abdominal region, coinciding with an increased risk of cardiometabolic diseases [29,40].

Several studies point to the increased visceral adipose tissue (VAT) during the MT as the main driver for the increased cardiometabolic risk, with elevated blood pressure, increased carotid artery atherosclerosis, elevated LDL-C levels, a decrease in the ratio of total cholesterol to high-density lipoprotein cholesterol, insulin resistance, and chronic inflammation [23,34,39].

Abdominal fat is considered a metabolically active endocrine organ that produces many adipokines and substances that are associated with insulin resistance, type 2 diabetes, and MetS. Changes in adipokine production from visceral fat trigger inflammation and contribute to insulin resistance, which eventually results in increased circulating insulin concentrations [5,39,40].

Because most VAT is drained by the portal vein, the hyperlipolytic state of large (hypertrophic) adipocytes associated with visceral obesity exposes the liver to high concentrations of free fatty acids and glycerol, leading to several impairments in liver metabolism, such as reduced hepatic extraction of insulin (exacerbating hyperinsulinemia) and increased production of triglyceride-rich lipoproteins, as well as increased production of hepatic glucose, which explains the link between visceral obesity and glucose intolerance and type 2 diabetes [33].

In vitro and mice experiments also suggest that decreased concentrations of estrogen or estrogen receptor- α can cause insulin resistance in peripheral tissues. Estrogen decline could even affect insulin production by pancreatic β cells and insulin disposal in muscles, which are conditions that further exacerbate the risk of diabetes [39].

Another argument is that it is the increased bioavailability of testosterone during the menopause, as well as the balance of testosterone to estrogen, that drives the changes in body composition and increased CVS risk. Menopause is associated with decreased concentrations of SHBG and a resultant increase in bioavailable testosterone, which is associated with insulin resistance and type 2 diabetes [39]. According to a 5-year follow-up study from the original SWAN cohort, a higher baseline testosterone-to-estradiol ratio and its increase over time were strongly associated with a higher risk of obesity and MetS during the MT period [41].

Menopause, obesity, and risk of cancer

Obesity is a known risk factor for several malignancies, especially hormone-associated endometrial and breast cancers, both of which have an increased prevalence in postmenopausal women. Obesity is associated with later ANM—a risk factor for breast and endometrial cancers [25,42].

Obesity is also the strongest risk factor for endometrial cancer, with every 5 kg/m² increment in BMI associated with a 60% increase in risk. Premenopausal obesity is associated with anovulatory cycles and unopposed estrogen action on the endometrium, increasing endometrial hyperplasia, dysplasia, and neoplasia. The postmenopausal increase in E2 in women with obesity from peripheral conversion of adipose tissue-derived androgens to estrone similarly drives endometrial changes, increasing the risk of cancer [43].

Postmenopausal obesity, especially visceral adiposity, also increases breast cancer risk. Many studies have found that accumulating abdominal adipose tissue increases the risk of breast cancer in postmenopausal women. The risk of postmenopausal breast cancer increases by 11% for every 5 kg gained as an adult. For women who are overweight or obese, postmenopausal estrogen receptor-positive (ER+) and progesterone receptor-positive breast cancer risk is about 1.5–2 times higher, increasing ER+ breast cancer risk by 70% [42,44].

It is widely recognized that higher circulating levels of estrogen in postmenopausal women are linked with an increased risk of breast cancer by increasing cell division and DNA damage as well as promoting cancer cell growth [44].

Postmenopausal obesity is also thought to increase breast cancer risk through other mechanisms, including insulin resistance, suppression of SHBG, thus increasing bioavailable E2, decreased adiponectin, increased leptin, and obesity-related mitogens, and chronic inflammation [44].

Management of menopause and related obesity

Hormone therapy

Menopausal hormone therapy (MHT), hitherto known as hormone replacement therapy, is the most effective treatment for menopausal symptoms. Current evidence supports its use in young, healthy menopausal women younger than 60 years and within 10 years of menopause, with benefits typically outweighing risks [4,11,45].

Perimenopausal women with obesity are more likely to be symptomatic and thus require MHT. MHT use, however, is associated with increased risks of venous thromboembolism, CVS complications, and breast and endometrial cancers, especially in women with obesity; as such, there should be a careful risk-benefit assessment in obese women requiring MHT. Where necessary, the lowest estrogen dose, preferably using patches with micronized progesterone, should be used for a short duration [11,46,47].

Estrogen replacement has been shown in both animal and human studies to reverse the estrogen depletion associated with weight gain and body fat redistribution [16,24,31]. Several studies have shown a beneficial effect of hormone therapy in the reduction of central adiposity and preservation of lean body mass, including the WHI and PEPI studies [4,23,47,48]. Current advice is not to use MHT to prevent or treat MT-associated weight gain and visceral adiposity because the risks outweigh the benefits [11,45–47].

Lifestyle changes and exercise

There is clear evidence that lifestyle changes, such as regular physical activity and dietary management, have a positive effect on health and prevention of chronic diseases. In addition, intensive lifestyle changes leading to weight loss have been shown to reduce hot flashes [40,45,49].

A 5-year intervention study of premenopausal women aged 44–50 years showed the beneficial impact of lifestyle changes on body composition in middle-aged women. The lifestyle intervention program included sessions on diet, cooking, and physical activity, as well as support and motivation to ensure adherence to the program. After 4.5 years, 55% of those in the intervention group were at or

below baseline weight, whereas only 26% of the control group maintained or lost weight. Maintained weight loss also correlated with improvements in LDL-C level, triglyceride level, and systolic blood pressure. This study showed that lifestyle intervention and education programs may prevent adverse changes in body composition during the peri- to postmenopausal period [50].

Age-related declines in resting energy expenditure are not seen among women who exercise regularly. In both humans and rodents, increasing physical activity is an effective strategy to protect against metabolic dysfunction after ovarian hormone loss, and physical inactivity, therefore, is an imperative modifiable risk factor that may prevent or attenuate adverse metabolic changes during menopause [24,40].

A recently published meta-analysis of walking intervention studies among peri- and post-menopausal women showed statistically significant improvements in BMI, body weight, and body fat percentage compared with the no-exercise groups [49].

Summary

The global trend of obesity continues to rise, with higher prevalence in middle-aged women than men. Obesity is a well-known risk factor for CVS disease, MetS, and several malignancies.

The MT is associated with increased obesity, which is thought to be age related, and, importantly, an increase in abdominal and VAT accumulation, which leads to increased cardiometabolic risks and increased risks of hormone-related breast and endometrial cancers. Because increased visceral adiposity and associated risks occur in non-obese perimenopausal women using traditional BMI definitions, there is an argument to either modify BMI cut-offs in menopausal women or use alternate measures, such as WC and waist-to-hip ratio, in clinical and research settings because these better reflect truncal obesity.

Obesity is associated with a later ANM and increased vasomotor symptoms in perimenopause but less VMS after menopause, which potentiates the menopause-related health risks.

MHT is an effective treatment for menopausal symptoms but should be used with caution in women with obesity because the risks may outweigh the benefits. MHT has been shown to reverse the MT-associated increase in abdominal and visceral adiposity, but it is currently not recommended for this.

There should be an increased focus on lifestyle modification in pre- and perimenopausal women because this has been shown to prevent MT-associated visceral adiposity and improve menopausal symptoms and adverse cardiometabolic risks.

Practice points

- Increased obesity in middle age is age related.
- Menopausal transition is associated with increased visceral and abdominal obesity, which increases cardiometabolic risk.
- Menopause-associated increased visceral and abdominal obesity occurs in women with normal weight and obesity; as such, specific measures of abdominal obesity should be incorporated into health screenings for menopausal women.
- Lifestyle modifications, such as increased physical activity and dietary modification, can ameliorate the menopausal increase in obesity and should be included in health advice.

Research agenda

- Additional research highlights the menopausal increase in abdominal and visceral adiposity in both women with obesity and normal weight and the associated health risks.
- More research is needed on the beneficial impact of lifestyle changes on mitigating menopause-associated body shape changes and incident cardiometabolic risks.

Explanation

1. Vasomotor symptoms consist of hot flushes and night sweats and are experienced by 50–80% of perimenopausal women. Obese premenopausal women are thought to have more severe vasomotor symptoms compared with normal-weight women, as their extra layers of subcutaneous adipose tissue act as an insulator, preventing heat dissipation.

Obese premenopausal women have lower estradiol and FSH levels, partly due to the aromatization of androgens to estrogens in adipose tissue, which negatively feeds back to the hypothalamus and pituitary glands, suppressing FSH secretion. Other explanations given for the lower premenopausal E2 include adiposity-induced suppression of sex hormone-binding globulin (SHBG) synthesis, which then leads to greater clearance of estradiol, and a possible negative effect of obesity on granulosa cell function.

The excess adipose tissue-derived estradiol has a beneficial effect in postmenopausal obese women who have less severe vasomotor symptoms.

2. The menopausal transition is a critical period of physiological and metabolic change leading up to the final menstrual period. It can last between 4 and 10 years. The SWAN study and other large longitudinal studies have shown that there are distinct ethnic differences in the physical and metabolic changes that occur during the menopausal transition.

There is robust evidence linking smoking and genetics to an earlier age at natural menopause. Obesity is generally associated with a later age at natural menopause.

3. Menopause is associated with a change from a gynecoid to an android body shape, with increased abdominal and visceral adiposity, which have been shown to be associated with a higher cardiometabolic risk and mortality.

These changes have been shown to be mediated by a decline in estrogen and rising FSH and occur in both obese and normal-weight women. BMI is an easy-to-use measure for obesity and associated health indices but not an accurate measure for abdominal and visceral obesity.

Waist circumference, waist-to-hip ratio, and other anthropometric measures like a body shape index (ABSI) and lipid accumulation product (LAP) are more accurate measures of visceral adiposity.

Declaration of competing interest

The authors have no conflict of interests to disclose.

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