SYMPOSIUM OBESITY AND REPRODUCTIVE HEALTH

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# Obesity and menopausal transition
## Obesidad y transición a la menopausia

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**ABSTRACT**
Obesity is a chronic multifactorial disease influenced by biological, psychological, and environmental determinants, with a higher prevalence in women. It is associated with chronic inflammation, metabolic disturbances, and an increased risk of cardiovascular diseases and cancer. In postmenopause, the hormonal changes characteristic of this stage affect body composition and energy metabolism, promoting an increase in visceral adiposity. Oestrogen decline favours fat redistribution towards the abdomen, which increases insulin resistance and the prevalence of metabolic syndrome. This process is accompanied by a reduction in resting energy expenditure and lean mass, without significant variations in body mass index (BMI). It is important to emphasise that body fat distribution is a more accurate predictor of cardiometabolic risk than BMI. Additionally, obesity influences the menopausal transition, exacerbating symptoms such as hot flushes, sleep disorders, and sexual dysfunction, as well as increasing the risk of urinary incontinence, sleep apnoea, and cognitive impairment, partly due to systemic inflammation induced by adipokines. Moreover, obesity also increases the risk of cancer, particularly endometrial and breast cancer, as it is associated with greater exposure to endogenous oestrogens. Given the increase in life expectancy, a growing number of women will spend a significant portion of their lives in postmenopause, a stage in which obesity is highly prevalent. This underscores the need to address obesity as a priority public health issue due to its impact on quality of life and the risk of chronic diseases.
Keywords: Obesity, Menopause, Perimenopause, Postmenopause, Climacteric (source: MeSH NLM).

**RESUMEN**
La obesidad es una enfermedad crónica multifactorial, influenciada por determinantes biológicos, psicológicos y ambientales, con una mayor prevalencia en mujeres. Se asocia con inflamación crónica, alteraciones metabólicas y un mayor riesgo de enfermedades cardiovasculares y cáncer. En la postmenopausia, los cambios hormonales propios de esta etapa afectan la composición corporal y el metabolismo energético, promoviendo un aumento de la adiposidad visceral; el declive estrogénico, favorece la redistribución de la grasa hacia el abdomen, lo que incrementa la resistencia a la insulina y la prevalencia del síndrome metabólico. Este proceso se acompaña de una reducción del gasto energético en reposo y de la masa magra, sin variaciones significativas en el índice de masa corporal (IMC). Hay que enfatizar que la distribución de la grasa corporal es un predictor más preciso del riesgo cardiometabólico que el IMC. Asimismo, la obesidad influye en la transición menopáusica, exacerbando síntomas como sofocos, trastornos del sueño y disfunción sexual, además de aumentar el riesgo de incontinencia urinaria, apnea del sueño y deterioro cognitivo, en parte debido a la inflamación sistémica inducida por adipocinas. Por otro lado, la obesidad también incrementa el riesgo de cáncer, especialmente de endometrio y mama, asociado a una mayor exposición a estrógenos endógenos. Dado el aumento en la esperanza de vida, un número creciente de mujeres pasará una parte significativa de su vida en la postmenopausia, etapa en la que la obesidad es altamente prevalente. Esto subraya la necesidad de abordar la obesidad como un problema prioritario de salud pública, dado su impacto en la calidad de vida y en el riesgo de enfermedades crónicas.
Palabras clave: Obesidad, Menopausia, Perimenopausia, Posmenopausia, Climaterio (fuente: DeCS BIREME).

## Introduction

Obesity is not a "choice," but rather the result of a complex interaction of biological, psychological, environmental, and social factors[1]. Obesity is not simply related to an individual's lack of will to control their appetite[2], but rather a chronic, progressive, and relapsing disease that affects women more than men[3]. According the World Health Organization (WHO), overweight and obesity are defined as an abnormal or excessive accumulation of body fat that poses risks to health, quality of life, and life expectancy[4]. Particularly, excess body fat can lead to the production of adipocytokines and inflammatory mediators, which alter glucose and fat metabolism, increasing the risk of cardiometabolic diseases and cancer[5,6].

Obesity generates a proinflammatory state induced by the increased production of inflammatory cytokines such as TNF-alpha, resistin, and leptin by obese adipocytes. These molecules are linked to most chronic diseases and cancer[5-7].

According to the WHO[8], metabolic syndrome is the leading cause of death. Although its prevalence increases with age, menopause contributes to increased body weight, insulin resistance, and visceral fat accumulation[9]. During the menopausal transition, the severity of metabolic syndrome tends to worsen, which could increase cardiovascular risk at this stage[10].

There is growing evidence of the impact of excess adiposity observed during and after menopause, primarily as a consequence of reduced estrogen levels, on various health indicators[2,11]. The physiological and metabolic changes associated with menopause are a direct effect of estrogen deficiency, influencing lipid metabolism, energy expenditure, insulin resistance, and body fat distribution. This leads to a transition from a gynecoid fat distribution to an android, with greater accumulation of abdominal and visceral fat, increasing cardiovascular and metabolic risk[12].

With increasing life expectancy, a significant percentage of women will live between 30% and 40% of their lives postmenopausally, with important implications for health and quality of life[4-14]. The complex interaction between age, obesity, and menopause is the subject of numerous ongoing studies[15]. Also, obesity may influence the decision to prescribe menopausal hormone therapy (MHT)[2,16].

## Pathophysiology

Body fat distribution is altered in postmenopause, predominantly in the abdominal region[17], unlike during reproductive years. For this reason, simple assessment of the waist-to-hip ratio becomes more relevant for diagnosis. In animal models, ovariectomy affects leptin function and promotes adipocyte formation[18]. In humans, body composition densitometry studies indicate that abdominal fat gain is greater in postmenopausal women than in premenopausal women. This difference is attributed to estrogen deficiency, which would increase cardiovascular risk[19]. Also, abdominal circumference is a better predictor of metabolic syndrome than body mass index[20].

Another relevant aspect is that obesity stimulates the secretion of resistin and leptin, increasing the risk of insulin resistance. In turn, it decreases adiponectin and ghrelin, increasing cardiovascular risk[21]. Another adipocytokine, vizofin, is increased in postmenopausal women with metabolic syndrome[22]. Fat also produces a series of cytokines such as TNF-alpha, IL-6, which contribute to decreased insulin sensitivity[21] and increase cardiovascular risk.

## Obesity and the menopause transition

The menopausal transition (MT), defined as the period of physiological change preceding menopause, is characterized by menstrual irregularity and transient symptoms such as hot flashes, depressive symptoms, and persistent changes in bone density and lipids. It can last from 4 to 10 years and is marked by a progressive decline in ovarian follicular reserve and decreased ovarian sex hormone production, leading to an increase in FSH. This decrease in ovarian follicles leads to a decrease in inhibin B, which is secreted by the granulosa cells of the antral follicles. The decrease in inhibin B secretion decreases the inhibition of pituitary FSH secretion, resulting in an increase in FSH levels. Initially elevated FSH causes sustained or even increased levels of estradiol (E2) until the decline in antral follicles is so pronounced that E2 levels finally decline[14,23-26].

Estradiol (E2) and follicle-stimulating hormone (FSH) play a role in regulating energy balance, so their variations during the menopausal transition may influence the amount and composition of fat mass[2,16]. Observational studies have indicated that resting energy expenditure (REE) is lower during postmenopause than during premenopause[2,6,27].

Weight gain is observed in women during the menopausal transition[28]. After menopause, there is a clear increase in fat mass and a decrease in lean mass, which explains why there is no observable accelerated increase in weight or body mass index (BMI) during the menopausal transition. These data reinforce the idea that BMI is not the best predictor of cardiometabolic risk, the adiposity index and the distribution of body fat[5,29,30].

## Obesity and menopause

Obesity is a growing global problem[15]. Currently, approximately 13% of the world's adult population is obese, according to the latest WHO figures[4], and it is estimated that by 2030, 50% of the US adult population will be obese[31].

Obesity is associated with menstrual cycle disturbances, menopausal symptoms such as hot flashes, sleep disturbances, joint aches and pains, urinary symptoms, and reduced quality of life[31]. Obesity is a determining factor in the hormonal changes observed during the menopausal transition, independent of age, race, and smoking status[31,32].

The relationship between BMI and age at menopause remains controversial. The SWAN study did not find an association between the age of natural menopause, although an association was observed with surgical menopause[33,34].

A systematic review and meta-analysis[35] found that anti-Müllerian hormone (AMH) and FSH levels were significantly lower in obese women, suggesting a possible relationship with future cardiometabolic complications[2,36].

As mentioned, menopause is associated with an increase in cardiometabolic risk factors through several mechanisms, including weight gain, abdominal and visceral adiposity, and the loss of the protective effect of estrogen on cardiovascular disease (CVS)[11,37]. Obesity exacerbates this risk, quadrupling cardiovascular mortality in obese postmenopausal women[11,38]. Several studies point to the increase in visceral adipose tissue (VAT) during MRI as the main driver of increased cardiometabolic risk, with elevated blood pressure, increased carotid artery atherosclerosis, elevated LDL-C levels, a decreased ratio of total cholesterol to high-density lipoprotein cholesterol, insulin resistance, and chronic inflammation[11,39,40].

Abdominal fat is considered a metabolically active endocrine organ that produces many adipokines and substances associated with insulin resistance, type 2 diabetes, and metabolic syndrome[11,41,42]. During menopause, decreased SHBG concentrations and increased bioavailable testosterone are observed, another factor that increases the risk of insulin resistance and type 2 diabetes in postmenopausal women[11].

## Obesity and menopause transition

A major symptom of menopause is hot flashes, a sudden sensation of warmth, usually beginning in the face or chest, spreading throughout the body, and lasting 1 to 5 minutes[39]. This, along with night sweats, constitutes VMS syndrome, which is experienced by between fifty and eighty percent (50 to 80%) of perimenopausal women, causing sleep disturbances, irritability, and poor quality of life[12,14]. Its origin in menopause-induced changes in thermoregulatory neurons, resulting in a narrowing of the thermoneutral zone, accompanied by a reduction in the temperature threshold for a compensatory vascular response[5,43].

Higher BMI and adiposity are associated with a higher prevalence of hot flashes because body adipose tissue acts as a thermal insulator, hindering heat dissipation, so obese women may experience more VMS[2,44,45]. Obese premenopausal women are known to have lower levels of estradiol and follicle-stimulating hormone (FSH), and less aromatization of androgens to estrogens in adipose tissue. These changes cause negative feedback to the hypothalamic-pituitary-ovarian axis, decreasing FSH and, in turn, ovarian estrogen[15].

Adiponectin, the most abundant adipokine and an anti-inflammatory, has been associated with better cardiovascular health, including a lower risk of cardiovascular disease (CVD) events[5,46]. In women with obesity, low levels of circulating adiponectin, as well as central leptin resistance, may contribute to greater severity of menopause-related symptoms[5,47].

## Obesity, sleep, and urinary tract symptoms

Obesity, particularly that associated with a larger waist circumference, has been linked to sleep apnea and other sleep disorders in postmenopausal women, as well as genitourinary symptoms[23, 25]. Women who are overweight or obese are more likely to suffer from urinary incontinence (UI), which substantially affects their quality of life[5,48,49].

## Obesity and brain

Obesity is recognized as a significant risk factor for cognitive decline. Recent evidence suggests that excess body fat, especially during middle age, may increase the risk of cognitive decline in later life. An analysis involving five million participants found a significant association between obesity and an increased risk of cognitive decline and dementia, with an OR: 1.10 (95% CI: 1.05–1.15)[50]. Also, a global study[51] that synthesized data from 72 studies and included a total of 2 980 947 older adults reported a 32.5% prevalence of mild cognitive impairment in overweight or obese individuals. The same study identified a 12.6% prevalence of impairment in obese individuals in Latin America (51). Adipokines produced by adipose tissue would be involved in the etiopathogenesis, which activate systemic inflammation, which ultimately affects the brain[5,52].

## Obesity, menopause, and quality of life

Obesity in postmenopausal women negatively affects perceived quality of life, sleep quality, physical activity, and development[53]. Obesity also increases the severity of symptoms of impaired sexual function, unbalancing sex hormone levels, resulting in reduced sexual desire, arousal, and orgasm[5,54]. Also, obesity increases the likelihood of developing comorbidities such as type 2 diabetes and dyslipidemia[5,55]. Also, people with obesity are more likely to experience anxiety and/or depression, which are thought to directly or indirectly affect sexual function[54,56,57].

## Obesity, menopause, and cancer risk

Obesity is a known risk factor for several malignancies, especially hormone-related endometrial and postmenopausal breast cancers, both of which are more prevalent in postmenopausal women[58]. Obesity is the most important risk factor for endometrial cancer; for every 5 kg/m2 increase in BMI, a 60% increased risk is observed. Premenopausal obesity is associated with anovulatory cycles and unopposed estrogenic action on the endometrium, which increases endometrial hyperplasia, dysplasia, and neoplasia[59]. The risk of postmenopausal breast cancer increases by 11% for every 5 kg gained in adulthood. In overweight or obese, estrogen receptor (ER) positive postmenopausal women and progesterone receptor positive breast cancer risk is approximately 1.5 to 2 times higher, increasing ER breast cancer risk by 70%[58,60].

## Treatment

Hormone replacement therapy (HMT) remains the mainstay treatment for menopausal symptoms. As recommended for other medical interventions, HMT should be individualized according to the woman's needs, symptoms, and clinical condition[1]. Also, it is important to provide the optimal HMT in terms of type and route[2,61]. HMT has been indicated for women experiencing menopausal symptoms[1]; however, a high proportion of eligible women (54%–79%) are unwilling to receive this option[5,62].

The use of low-dose transdermal estradiol therapy in overweight/obese patients is a good alternative, as it increases repair markers and improves microvascular reactivity, without changes in inflammatory markers[63]. HMT should not be prescribed solely as an isolated indication for preventive purposes[2,64], except in cases of premature ovarian failure[65]. Women with a high BMI have an increased risk of thromboembolic disease (TED) when using oral MHT (OR 2.5, 95% CI 1.7-3.7 (overweight); OR 3.9, 95% CI 2.2-6.9 (obesity) compared to normal weight women[5,66]. TED is probably the main medical condition for prescribing or not prescribing MHT[1].

## Conclusions

Obesity in postmenopausal women represents a public health challenge to high prevalence and multiple metabolic, hormonal, and functional consequences. Its impact on systemic inflammation, cardiometabolic risk, and cognitive decline highlights the need for specific preventive and therapeutic strategies. Also, its association with cancer and chronic diseases reinforces the urgency of addressing it comprehensively. Given the increase in life expectancy, it is essential to implement health policies to mitigate its effects on this vulnerable population.

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