Body Composition as an Important Determinant of Metabolic Syndrome in Postmenopausal Women

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Abstract

Menopause-related hormonal changes are associated with an increased prevalence of various cardiometabolic risk factors, components of the metabolic syndrome, and an excess risk of all-cause and cardiovascular mortality. Estrogen withdrawal and the subsequent androgenicity interact in a synergistic manner to predispose post menopausal women to an increase in total body weight but also to a pronounced change of body composition. Central fat accumulation and ectopic fat storage constitute potent determinants of the increased cardiometabolic risk in post menopausal women. In contrast, peripheral subcutaneous fat has an independent cardioprotective and anti-atherogenic impact. Data are less conclusive regarding the contribution of lean body mass to metabolic syndrome and cardiometabolic health in post menopausal women.

Keywords: Menopause; Body composition; Fat distribution; Metabolic syndrome; Fat mass; Lean body mass; Post menopausal women

Introduction

Menopause constitutes a transitional period from reproductive to non-reproductive life, which is mainly characterized by a major reduction in estrogens production and androgenicity [1]. It can be officially defined as the absence of menstruation for one complete year and occurs between late 40’s and early 50 are, depending on the race, ethnicity, lifestyle and coexistent diseases [1].

Post menopausal women (PMP) exhibit an increased risk for all cause and cardiovascular mortality which is attributed to the increased prevalence of obesity, dyslipidemia, hypertension, insulin resistance and diabetes mellitus, all of which are components of the metabolic syndrome (MS) [2,3]. Total body fat mass as well as its regional distribution, consisting of central fat accumulation, decreased peripheral fat mass and ectopic fat storage, constitute potent determinants of the increased prevalence of MS in PMP women [4-6], whereas data are less conclusive regarding the contribution of lean body mass [7].

Menopause and body composition

During menopause transition, women tend to gain weight with an average increase of 2-2.5 Kg in a period of three years, which seems to be related to both menopause and normal aging [8]. In addition to an evident increase in total fat mass, a remarkable change in body composition is observed in menopause, which is mainly characterized by a marked increase in subcutaneous and visceral abdominal fat and a concomitant reduction in lean body mass (LBM) [4,9,10]. The decreased physical activity observed in PMP women as a result of reduced cardiorespiratory fitness and exercise capacity, seems to contribute both to reduced LBM and to increased total and abdominal fat mass accumulation [11,12], the combined presence of which is termed “sarcopenic obesity” and constitutes a relatively common entity in older subjects including PMP women [13].

Menopause-related hormonal changes represent the major factor underlying the effects of menopause on fat mass and distribution. Estrogens promote peripheral fat storage mainly in the gluteal and femoral subcutaneous region, and thus estrogen deficiency is expected to result in decreased peripheral fat mass [14]. Furthermore, it has been shown that androgens can have an appreciable effect on fat distribution in PMP women, by promoting visceral abdominal fat accumulation at different stages of menopause, independently of age, race, total fat mass and other cardiovascular risk factors [15]. As a result, menopause-related estrogen decline and the subsequent androgenicity, interact in a synergistic manner to predispose PMP women to a preferential decreased peripheral fat mass and upper body fat accumulation [16]. In addition, an increased expression and activity of enzyme 11-beta-hydroxysteroid-dehydrogenase type 1 (11βHSD1) has been documented in the adipose tissue and liver of normal-weight PMP women, leading to an increased conversion of cortisone to cortisol and excess abdominal adiposity [17]. Whether all these unfavorable changes of body composition could be prevented or improved by hormone replacement treatment in PMP women, remains still unresolved [18].

Figure 1 summarizes the most representative body composition changes associated with menopause.

Menopause and metabolic syndrome

Menopause is associated with an increased prevalence of obesity, dyslipidemia, hypertension and glucose intolerance or diabetes mellitus, all of which being components of MS [3,19]. PMP women exhibit a 60% increased risk of MS, even after adjusting for traditional risk factors such as age, BMI and physical inactivity [20]. Both the onset and the duration of menopause are important risk factors for MS, independently of age. Early menopause, and specifically surgical menopause induced by bilateral oophorectomy before the age of 50 years old, has been significantly associated with increased cardiovascular risk and the presence of MS [21,22]. Age at menopause has been also

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closely related to cardiovascular risk in PMP women, indicating that late menopause has a favorable impact on cardiovascular risk [23]. Concerning menopause duration, a prospective Korean cohort study has shown an increased risk for development of MS within the first 14 years since the menopause onset, while this risk decreased thereafter [24]. The major pathogenetic mechanisms accounting for the development of MS in PMP women are related to central fat distribution. As illustrated in Figure 2, menopause-related visceral fat accumulation promotes systemic and hepatic insulin resistance, which is the predominant underlying substrate for the subsequent manifestation of several cardiometabolic abnormalities, including hyperglycemia, dyslipidemia and hypertension [25]. The relationship between visceral fat and insulin resistance is mediated by adipokines, proinflammatory cytokines and free fatty acids (Figure 2).

A very common and clinically relevant manifestation of MS in PMP women is atherogenic dyslipidemia, expressed as a constellation of lipid and lipoprotein abnormalities promoting atherosclerosis. The most typical lipid derangements that have been reported in cohorts of PMP women include increased levels of total cholesterol, LDL (low density lipoprotein) cholesterol, VLDL particles (very low density lipoprotein), small dense LDL particles, triglycerides and lipoprotein (a), and decreased levels of anti-atherogenic HDL2 (high density lipoprotein) particles [26-31].

PMP women do not only present with the typical features of MS, but they are also characterized by enhanced inflammation [32], impaired fibrinolysis [33] and signs of subclinical atherosclerosis, such as an increased carotid artery intima-media thickness and coronary calcification, which are both associated with increased cardiovascular risk [34-37]. Subclinical atherosclerosis in PMP women is mediated by increased circulating androgen levels. In a large multiethnic cohort of PMP women, total and bioavailable testosterone displayed a strong positive correlation with atherosclerotic markers, independently of traditional cardiovascular risk factors [38]. These findings are consistent with experimental data suggesting direct receptor-mediated effects of androgens on several critical steps of the atherosclerotic process, such as transformation of macrophages into foam cells through oxidized LDL uptake [39], proliferation of vascular smooth muscle cells [40] and human monocyte adhesion to vascular endothelium [41].

**Fat mass and metabolic syndrome in post menopausal women**

Total and regional adiposity of PMP women can be reliably assessed with Dual-energy X-ray Absorptiometry (DXA), since it seems convenient to combine the annual osteoporosis screening with an additional evaluation of fat mass and distribution, when the DXA instrument in the specific clinical setting is equipped with the advanced software option for body composition analysis.

It has been suggested that trunk fat mass constitutes a strong and independent predictor of insulin resistance and dyslipidemia in PMP women, whereas leg fat mass has shown to confer protective effects against metabolic dysfunction [42]. Similar contrasting associations between central and peripheral fat have been found in a longitudinal study of PMP women on the long-term progression of cardiovascular risk factors and aortic calcification [43]. In PMP women, the beneficial effects of peripheral fat depots such as leg and femoral fat mass are independent of the adverse effects of central fat [5,44]. It has been also shown that the presence of MS in PMP women is associated with a high degree of ectopic fat storage, expressed as mid-thigh muscle fat infiltration [6].

In pathophysiological terms, visceral fat is causally involved in the pathogenesis of MS, while peripheral fat can effectively counterbalance the detrimental metabolic effects of visceral fat accumulation. More analytically, as a result of the high lipolytic rate of visceral fat, there is an increased flux of free fatty acids to the liver through the portal vein, which promotes hepatic insulin resistance. Hepatic insulin resistance can lead to increased endogenous glucose production and increased synthesis of triglyceride-containing very low density lipoprotein particles. Visceral fat can also secrete a large number of proinflammatory cytokines, which promote peripheral insulin resistance, leading to impaired insulin-mediated glucose disposal and thus hyperglycaemia. On the other hand, subcutaneous gluteofemoral adipocytes are much more resistant to lipolysis. This means that they are more likely to take up free fatty acids from circulation rather than release them, acting as a fat sequestering storage depot. This “free fatty acids trapping” within peripheral fat stores may protect vital organs such as liver, pancreas, skeletal muscle and myocardium, from the metabolically detrimental effects of free fatty acids. It has been also recently shown that femoral fat has the unique capacity to respond with hyperplasia to overfeeding, in order to prevent or delay abdominal fat cell hypertrophy with all the subsequent adverse cardiometabolic effects [45].

**Figure 1: Major body composition changes induced by menopause**

**Figure 2: A summary of the major pathogenetic mechanisms underlying the relationship of menopause with metabolic syndrome.**
Another critical question related to fat mass and MS in PMP women, is what amount of visceral fat should be lost in order to achieve a clinically significant improvement in cardiometabolic risk factors. According to an interesting study which tried to address this issue, either achieving or not achieving visceral adipose tissue levels below the proposed threshold of 110 cm² after a weight loss program resulted in similar improvements in lipids, insulin sensitivity and blood pressure, suggesting that even moderate losses of visceral fat are clinically meaningful and not inferior to larger and more difficult to attain losses of visceral fat [46].

**Lean body mass and metabolic syndrome in post menopausal women**

LBM has been traditionally considered a beneficial component of human body composition, since muscle tissue is highly metabolically active and accounts for 85% of whole-body insulin-mediated glucose disposal, promoting peripheral insulin sensitivity and systemic glucose homeostasis [47]. Recently, National Health and Nutrition Examination Survey III (NHANES III) has shown, that increased skeletal muscle mass relative to body weight was associated with a reduced incidence of insulin resistance at a population level [48]. However, this study has a number of limitations. Skeletal muscle mass was estimated by BIA, which appears to be methodologically problematic in ethnically diverse populations such as the NHANES cohort. Furthermore, the study population of NHANES III was mainly consisted of relatively young and lean participants with unknown levels of physical activity. On the other hand, a Chinese population-based study including a large number of PMP women, has demonstrated that both fat and fat-free mass are independently associated with MS, after adjusting for age, gender, smoking habits, physical activity, medications and family history [49].

The majority of data suggesting a paradoxically adverse contribution of LBM to cardiometabolic risk have been derived from overweight and obese sedentary PMP women. It has been shown that a high amount of LBM correlates significantly with both the presence and the severity of MS in obese PMP women [50,51]. Furthermore, visceral fat accumulation has shown to promote insulin resistance and subclinical inflammation, by interacting with LBM, in obese sedentary PMP women [7]. In addition, lower values of LBM have been found in the “metabolically healthy” compared to “unhealthy” obese phenotypes in PMP women [52], while sarcopenic obese PMP women exhibited a significantly better lipid profile compared to non-sarcopenic women, because of their reduced LBM [53]. The major pathophysiological mechanism explaining the unfavorable association of LBM with insulin resistance is related to androgens. Insulin resistance is very commonly accompanied by a suppressed hepatic production of sex hormone binding globulin and increased circulating levels of free androgens, exerting anabolic effects on skeletal muscle protein mass [54]. Besides, it cannot be precluded that the increased LBM observed in women with insulin resistance and MS might be an adaptive alteration, in order to compensate for potential qualitative defects of skeletal muscle tissue related to insulin resistance, such as intramyocellular or intermyocellular lipid accumulation [35]. Another theory for interpreting the adverse cardiometabolic effects of LBM is provided by a Chinese study in middle-aged men and women, showing that interleukin 18 (IL-18), a well-established proatherogenic and diabetogenic cytokine, is primarily secreted by LBM rather than fat mass, and might be the missing link in the relationship between LBM and MS [56].

**Conclusions**

Menopause is associated with an increased prevalence of MS and an increased mortality risk, independently of aging. Body composition changes regarding total fat and lean mass and their distribution, mediate most of the menopause-related cardiometabolic abnormalities. Increased central fat deposition, decreased peripheral fat mass accumulation and ectopic fat storage promote cardiometabolic abnormalities, leading to increased prevalence of MS after menopause. On the other hand, LBM - contrary to what was originally thought - might contribute to the increased cardiometabolic risk in PMP women, which needs to be further evaluated. In practical terms, efforts aiming at the prevention of the adverse body composition changes during the perimenopause and early menopause period through lifestyle changes or other interventions seem to be important in order to decrease the menopause-related cardiometabolic morbidity and mortality.

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