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Obesity at Menopause: An Expanding Problem

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Introduction

Postmenopausal women are usually troubled by increasing weight and waist circumference caused by obesity and androidal fat redistribution [1-3]. This is mostly attributed to estrogen depletion though other factors such as chronological aging and decline in physical activity play a significant role [4-7].

The deleterious health consequences of obesity and visceral fat deposition after middle age encompass a variety of problems; from dyslipidemia and metabolic syndrome to increased risk of cardiovascular disease (CVD), osteoporosis, malignancies and mortality [8-11].

The mean age at natural menopause is reported to vary from 45-52.8 years [12,13]. With the increase in life expectancy resulting in women living one half to one third of their lives after menopause, the high incidence of overweight and obesity in women during menopause transition and beyond have become important public health concerns [4].

Obesity in postmenopausal women is attributed to both genetic [14] and environmental factors, with adverse lifestyle practices playing a major role in the increase in body mass index (BMI) and waist circumference [15,16].

The management of obesity, central adiposity and associated health problems mainly concentrates on lifestyle changes such as restriction of caloric intake and increase in physical activity, with pharmacotherapy and bariatric surgery added when necessary [17-19].

This review focuses obesity associated with menopause, its pathophysiology, impact on health and management.

Changes in Adipose Tissue during Menopause Transition

Major changes in fat distribution and function occur throughout life [2]. Fat tissue mass increases though middle age and declines in old age, with menopause transition being associated with significant weight gain of 2-2.5 kg over 3 years on average [17]. The prevalence of overweight or obesity in middle-aged women, around and after menopause is high and is rising worldwide, more rapidly in women over the age of 40 years, with up to 65% being either overweight or obese and up to 30% or more being obese [1,3,20-22].

Fat is redistributed among different fat depots especially during and after middle age, from subcutaneous to intraabdominal visceral depots causing an androidal fat distribution [2]. This results in an increase in abdominal circumference of 4 cm every 9 years in adult women [23].

Menopause transition is characterized by a change in the hormonal milleu, especially a decline in circulating estrogen levels, which is thought to be a major contributor to the central abdominal fat accumulation, reduction in subcutaneous fat and increase in total adiposity [24-27]. Longitudinal comparisons of menopausal and non-menopausal women of similar age revealed an accelerated increase in visceral fat depots caused by a peripheral to central redistribution of fat and increases in total adiposity [24,25,27-29]. Total body fat mass as well as abdominal fat mass are reduced with estrogen therapy in both human and animal studies [24]. Women after menopause are thus thrice as likely as premenopausal women to develop obesity and metabolic syndrome [30].

Pathophysiology

Obesity is a chronic low-grade inflammatory and prothrombotic state, with white adipose tissue releasing free fatty acids (FFA) and inflammatory adipokines including tumour necrosis factor (TNF), interleukin (IL)-1 and IL-6 which are proinflammatory, atherogenic, hypertensive, procoagulant and predisposing to insulin resistance [31,32] (Table 1). Other adipokines such as adiponectin, modulate endothelial function, are atheroprotective and enhance insulin sensitivity [4,31].

Modes of action	Adipokines
Pro-inflammatory action	TNF-α, IL-1, IL-6, leptin, IFN-α, IFN-b, IL-8, TGF-b, MCP-1, IP-10, resistin
Stimulating lipogenesis	angiotensinogen, angiotensin II, acylation-stimulating protein, IGF-1, visfatin,
Promoting insulin resistance	TNF-α, IL-6, resistin
Procoagulant activity	TNF-α, IL-6, TGF-b, PAI-I, tissue factor

Promoting angiogenesis	Leptin, IL-8, VCAM, ICAM, VEGF, FGF-2, MCP-1, IP-10, monobutyrin

Table 1: Substances released by adipocytes contributing to obesity-related morbidity, IL-1, interleukin 1; IL-6, interleukin 6; TNF-α, tumor necrosis factor alpha; IFN-α, interferon alpha; IFN-b, interferon beta; IL-8, interleukin 8; TGF-b, transforming growth factor beta; MCP-1, Monocyte chemoattractant protein-1; IP-10, Interferon gamma-induced protein 10; PAI-I, Plasminogen activator inhibitor-1; VEGF, Vascular endothelial growth factor VCAM-1, vascular cell adhesion molecule 1; , FGF-2, Fibroblast Growth Factor 2, ICAM-1, Intercellular adhesion molecule; IGF-I, insulin-like growth factor 1.

Menopause transition associated with estrogen depletion has deleterious influence on inflammatory markers and adipokines, leading to increased visceral adiposity [33]. The pattern of distribution of excess fat rather than the actual increase in the total body fat stores has a greater impact on health with excess central fat deposition having a significant contribution to cardiovascular morbidity and mortality in postmenopausal women [10].

It is unclear if menopause transition itself is the cause for the weight gain. Declining estrogen levels however, appear to have a major influence on weight gain by several mechanisms. Diminished activity of estrogen receptor alpha (ERα) is shown to be linked to obesity in both women and men [34] and both male and female mice lacking ERα receptors develop central obesity and insulin resistance [4]. Estradiol appears to selectively promote antilipolytic activity in subcutaneous adipocytes [35] and increases muscle fat oxidation [4]. Estrogen influences the central control of appetite and deletion of hypothalamic ERα has shown to cause hyperphagia visceral obesity in mice [36]. Plasma adiponectin levels are inversely proportionate to estradiol levels, and estrogen replacement has shown to reduce both plasma adiponectin levels and adipocyte resistin levels in mice [37,38]. Estradiol increases lipoprotein lipase (LPL) which utilizes triglycerides in muscle and is crucial in lipid metabolism and transport. LPL activity declines at menopause contributing to visceral adiposity and alteration of plasma lipid concentrations [39]. Furthermore, low estrogen at menopause via increased cortisol promotes accumulation of abdominal fat [6].

There are many other factors that are attributed to the changes in body composition at menopause, such as genetic factors, aging, dietary practices, ethnicity, reduced lean mass, resting metabolic rate and drug treatment (e.g. steroid) [5,40]. Physical inactivity and aging affect adipose tissue fatty acid storage and oxidation, contributing to increased body fat in women after menopause [5].

The role of genetic factors in the aetiology of obesity needs special mention. The heritability of body mass index in adults in twin studies is reported as between 55% to 85% [14]. Genetic influence on weight gain and fat distribution has been confirmed in population-based and genome-wide association studies (GWAS) [41-45]. Visceral adiposity, measured by waist circumference is strongly associated with increased CVD risk in postmenopausal women [3,8,46]. However, heritability for waist circumference and waist:hip ratio in postmenopausal women appears to be greater than that for premenopausal women [14]. This suggests that the effects of therapeutic lifestyle changes on reducing the waist circumference in postmenopausal women may be less than expected.

Health Issues Related to Obesity in Postmenopausal Women

Inflammatory adipokines (eg. IL-1, IL-6, leptin, resistin and TNF-α) play a central role in the pathophysiology of CVD, metabolic syndrome, diabetes mellitus, insulin resistance, dyslipidemia, hypertension, atherosclerosis, non-alcoholic steatohepatitis (NASH) and malignancies [31]. Obesity is also linked to other problems in menopause, such as osteoporosis, vasomotor symptoms, sexual dysfunction, urinary disorders and chronic kidney disease (Table 2).

Cardiovascular disease
Metabolic syndrome
Diabetes mellitus and insulin resistance
Dyslipidemia
Hypertension
Atherosclerosis
Non-alcoholic steatohepatitis
Malignancies
Osteoporosis
Vasomotor symptoms
Sexual dysfunction
Urinary disorders
Chronic kidney disease

Table 2: Summary of health issues related to obesity in postmenopausal women.

Metabolic syndrome and CVD risk

Visceral adiposity is the primary derangement causing metabolic syndrome. The increase in visceral fat predisposes to metabolic syndrome, a proatherogenic lipid profile, type 2 diabetes mellitus, hypertension, and cardiovascular disease in women after menopause [3,8,46]. There is ample evidence to show that obesity and visceral adiposity increase CVD risk factors in postmenopausal women. Postmenopausal women with high BMI have a significant negative effect on blood pressure, blood glucose and lipid profile with high triglyceride and low HDL cholesterol [21]. It has been found that in women after menopause, with the increase in waist circumference, the number of metabolic syndrome components increase significantly [47,48]. Waist circumference shows significant positive correlation with systolic and diastolic blood pressure, fasting blood glucose, glycated hemoglobin (HbAC), total cholesterol, Low-density

lipoprotein cholesterol, and triglycerides [49]. Visceral adiposity is significantly associated with coronary heart disease in women [50]. Menopause and central obesity were both independently associated with an increase in CVD risk factors in Chinese women [51]. An independent association of increased weight with CVD risk was shown in black women without metabolic syndrome in analysis using the Women's Health Initiative (WHI) data where adjusted CVD risk was higher in overweight women compared to normal weight women [52].

Risk factors for metabolic syndrome and CVD have both genetic and environmental components [53,54]. Oestrogen depletion, changes in body composition and lifestyle factors as previously discussed contribute to the increase in CVD risk in women after menopause. CVD risk factors including the components of metabolic syndrome, have shown heritability in many studies: with high or moderate heritability of plasma high density lipoprotein cholesterol (HDL-C), triglyceride, waist circumference, blood pressure, plasma glucose, insulin and non-traditional risk factors such as C-reactive protein, serum creatinine and fibrinogen [54-58].

Malignancy

Obesity, both general and visceral is associated with increased risk of many cancers [11,59,60]. In postmenopausal women, high BMI is especially associated with increased risk of breast and endometrium [11,59,60] and increased waist:hip ratio with breast cancer [11]. In the million women study, it was found that in the UK among postmenopausal women, being overweight or obese was attributed to 5% of all cancers, and [59]. In the nurses' health study, among postmenopausal women who underwent weight loss more than 10 kg, breast cancer risk was lowered by 50% [61]. Obesity may predispose to cancers of breast and endometrium by adipose tissue synthesizing increased amount of unopposed estrogen [11,62,63]. It may also be linked to the hyperinsulinemia in insulin resistance associated with visceral obesity, as insulin is a mitogenetic agent, which may predispose to breast cancer [11].

Osteoporosis

As low BMI is a well-known risk factor for osteoporosis, high BMI has conventionally been thought to confer protection against osteoporosis [64], with higher estrogen and leptin levels stimulating bone formation, estrogen inhibiting bone resorption and greater skeletal loading contributing to increased bone density in obese women [65,66]. However, the increase in overweight among older women in the US was not projected to be associated with a proportionate reduction in osteoporosis [67]. Emerging evidence suggests that obesity may not increase bone mineral density in proportion to the increase in weight or BMI [68], and may even increase the risk of both vertebral [69,70] and non-vertebral [71-73] fractures in postmenopausal women. This could be attributed to bone loss promoted by inflammatory adipokines, diabetes and metabolic syndrome prevalent in obese postmenopausal women [74,75].

Other problems

Increased BMI is linked to other problems in middle aged women.

The association of vasomotor symptoms (VMS) with BMI reveals contrasting results, with studies reporting both higher [76-80] and lower [81,82] incidence of VMS with increasing BMI. Exacerbation of VMS seen with high BMI may be attributed to the insulating effect of adipose tissue preventing heat dissipation [76], whereas the lower incidence of VMS in obese women may be explained by the increased estrone production by adipose tissue stabilizing hypothalamic thermoregulatory center and vascular reactivity [80,83].

The prevalence of sexual disorders in postmenopausal women varies between 68% and 86.5% [84]. Obesity has been found to reduce the sexual quality of life, with less desire, enjoyment and performance with avoidance of sexual encounters with poorer sexual quality of life seen in women with class III obesity [85]. High BMI is linked to sexual dysfunction in postmenopausal women [86-89]. Obesity is associated with diabetes, cardiovascular disease, urinary incontinence, low self-esteem and poor psychosocial well-being, all of which contribute to sexual dysfunction in older women [84,86]. However, other studies report the relationship of sexual disorders with obesity in perimenopausal women as inconclusive [89].

Obesity and metabolic syndrome increase the risk of developing chronic kidney disease (CKD) in adults [90-93]. Obesity-related glomerulopathy is characterized by focal segmental glomerulosclerosis with glomerulomegaly and fusion of foot processes [94,95]. In one study among perimenopausal women, the prevalence of CKD increased with age with the highest prevalence of 46.6% found in women over 60 years [96]. In women aged between 50-60 years, metabolic syndrome was found to be associated with CKD [97]. The withdrawal of the protective effect of estrogen on the kidneys may contribute to increasing renal disease in postmenopausal women [98,99]. Thus obesity per se, and obesity associated increase in metabolic syndrome may worsen the occurrence of CKD in postmenopausal women.

Mortality

Obesity is linked to excess all-cause mortality in women [100-102]. Bea et al 2015 found increased mortality in postmenopausal women linked not only to their BMI, but also to the total body fat percentage [103].

Management of Obesity

The main aspects of obesity management are diet control and physical exercise, which is true for obesity at all ages in both sexes. A review by Wadden et al., in 2007 concluded that lifestyle modification caused clinically significant weight which was associated with prevention or improvement of cardiovascular risk factors [104]. Lifestyle approaches with diet and exercise significantly decreased weight, BMI, waist circumference and body fat percentage in overweight-to-obese post-menopausal women [105]. Weight reduction improves all aspects of metabolic syndrome and all-cause and cardiovascular mortality [19,106-108]. However, being physically active and fit appear to be more important than losing weight [46].

Physical activity

There is a vast body of literature showing the impact of physical activity on obesity and related disorders in middle-aged pre and post menopausal women. In postmenopausal women, a higher level of physical activity was associated with a more optimal body composition, including lower adiposity and higher lean mass [19]. Regular physical activity regardless of the type reduced body weight and body fat [109,110]. In addition to reducing body fat, regular exercise has positive effects on most deleterious consequences of obesity, i.e.; insulin resistance, cardiovascular disease, hypertension, atherogenic lipid profile and even malignancies [19,106-108]. Walking

or light jogging for one hour daily will produce significant loss of visceral fat, leading cardiovascular risk reduction. The aim is to lose 10% of basal weight in 6-12 months, until the target body mass index is reached and to maintain a waist circumference <80 cm in women [111]. It is important to exercise regularly, for at least 30 min on at least 5 days of the week, amounting to 150 minutes a week, while consuming a healthy diet [46].

Diet

Reducing calorie intake is effective in the management of obesity [105,112] as the mainstay in management is that energy intake should be less than energy expenditure [113]. In a study comparing the effect of exercise and diet in overweight-to-obese post-menopausal women, a total daily energy intake of 1200-2000 kcal/day based on baseline weight, less than 30% daily energy intake from fat resulted in a more significant weight loss than the use of exercise alone [105]. Many different dietary regimes have been used by various studies but 600 kcal/day deficit or low-fat diet and low-calorie diet (800-1600 kcal/day) are recommended for weight reduction and reducing cardiovascular risk factors [113]. Very low calorie diets less than 800 kcal per day when used should be under supervision of physician [114]. The dietary requirements of individuals should be calculated before prescribing the diet for an individual [112].

Pharmacotherapy

Medical management with drugs, and surgical approaches with bariatric surgery have been found to be effective in morbid obesity [18,115,116]. Pharmacotherapy, be used only as an adjunct to lifestyle measures [117]. Pharmacotherapy used as an adjunct to lifestyle measures even lead to a greater weight loss and cardiometabolic improvements than lifestyle measures alone [118-120].

The mechanisms of action of pharmacological agents include noradrenergic activation, gastrointestinal lipase inhibition and serotonin receptor activation [120]. Orlistat, Phentermine, Topiramate, Lorcaserin, Natrexone/bupropion, Diethylpropion, Phendimetrazine and Benzphetamine are available for managing obesity [117,120,121]. The antiobesity drugs rimonabant was discontinued due to increased suicide risk [122] and sibutramine banned in many countries from 2010 as it was associated with an increased risk of non-fatal myocardial infarctions and strokes [123].

Hormone replacement therapy (HRT)

In a meta-analysis of over 100 randomized trials on HRT, it was found that in postmenopausal women without diabetes, estrogen replacement orally or transdermally reduced visceral fat, improved insulin resistance, improved lipid profile and decreased blood pressure whereas in women with diabetes reduced insulin resistance and fasting glucose [124].

Surgery

Bariatric surgery is recommended for obese subjects with BMI >40 kg/m^2 or >35 kg/m^2 with comorbid conditions in whom non-surgical interventions have failed. Bariatric surgery improves both morbidity and mortality in obese subjects [116].

However, in the long term, there is no substitute for a healthy lifestyle which should be adhered to even when treated with medical management or surgery [40,46].

Conclusion

Obesity is a rapidly growing problem globally. Both obesity and central adiposity are more common in women in middle age, especially after menopause. This is mainly caused by estrogen depletion during menopause transition leading to a change in body composition, with fat redistribution resulting in central adiposity. Obesity is also attributed to genetic and environmental factors, with adverse lifestyle practices playing a major role in both overall and central adiposity. Obesity and visceral adiposity increases inflammatory markers and adipokines, leading to increased visceral adiposity leads to a variety of problems; from dyslipidemia and metabolic syndrome to increased risk of cardiovascular disease, malignancies and mortality. Lifestyle modification by exercise and dietary calorie restriction are the mainstay of its management with pharmacotherapy and bariatric surgery being useful adjuncts. More research is needed on etiology, pathophysiology and management of this growing problem of adiposity associated with menopause.

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