Obesity at Menopause: An Expanding Problem

Piyusha M Atapattu*

Department of Physiology, Faculty of Medicine, University of Colombo, Kynsey Road, Colombo, Sri Lanka

*Corresponding author: Atapattu PM, Department of Physiology, Faculty of Medicine, University of Colombo, Kynsey Road, Colombo 8, Sri Lanka, Tel: +94779501610; E-mail: piyusha.atapattu@yahoo.com

Received date: Nov 17, 2015; Accepted date: Dec 21, 2015; Published date: Dec 29, 2015

Copyright: © 2015 Atapattu PM. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Introduction

Menopause is a life-changing event that occurs when a woman stops menstruating and ceases to produce eggs. This transition is typically marked by a decrease in estrogen levels, which can lead to various health issues. One of the significant health concerns during menopause is obesity, which is increasingly becoming a public health issue due to the aging population and changes in lifestyle. Weight gain during menopause 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].

Table 1: Adipokines and their modes of action

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

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 milieu, 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].
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.

### Table 1: Substances released by adipocytes contributing to obesity-related morbidity

| Substance | Description |
|-----------|-------------|
| Leptin    | IL-8, VCAM, ICAM, VEGF, FGF-2, MCP-1, IP-10, monobutyrin |

### 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).

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

| 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 |

### 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 estradiol [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]. Orlistat, Phentermine, Topiramate, and Lorcaserin, Natrexone/bupropion, Diethylpropion, Phendimetrazine serotonin receptor activation [120]. Orlistat, Phentermine, Topiramate, and Benzphetamine are available for managing obesity [117,120,121].

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/m² or >35 kg/m² 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.

References

1. Stachowiak G, Pertyński T, Pertyska-Marczewska M (2015) Metabolic disorders in menopause. Prz Menopauzalny 14: 59-64.
2. Tchikonia T, Morbeck DE, Von Zglinicki T, Van Deursen J, Lustgarten J, et al. (2010) Fat tissue, aging, and cellular senescence. Aging Cell 9: 667-684.
3. Teede HJ, Lombard C, Deeks AA (2010) Obesity, metabolic complications and the menopause: an opportunity for prevention. Climacteric 13: 203-209.
4. Lizzano E, Guzmán G (2014) Estrogen Deficiency and the Origin of Obesity during Menopause. Biomed Res Int 2014: 757461.
5. Maltais ML, Desroches J, Dionne IJ (2009) Changes in muscle mass and strength after menopause. J Musculoskeletal Neuronal Interact 9: 186-197.
6. McKinnes KJ, Andersson TC, SimonyTA K, Saderstram I, Mattsson C, et al. (2012) Association of 11-hydroxysteroid dehydrogenase type 1 expression and activity with estrogen receptor β in adipose tissue from postmenopausal women. J Obstet Gynecol Res 38: 109-117.
7. Toth MJ, Tchernof A, Sites CK, Poehlman ET (2000) Effect of menopausal status on body composition and abdominal fat distribution. Int J Obes Relat Metab Disord 24: 226-231.
8. Carr MC (2003) The emergence of the metabolic syndrome with menopause. J Clin Endocrinol Metab 88: 2404-2411.
9. Villalbana AC, Jayachandran M, Banka C (2010) Atherosclerosis and sex hormones: current concepts. Clin Sci (Lond) 119: 493-513.
10. Matvienko OA, Alekel DL, Bhupathiraju SN, Hofmann H, Ritland LM, et al. (2010) Fat tissue, aging, and cellular senescence. Aging Cell 9: 667-684.
11. Harvie M, Hooper L, Howell AH (2003) Central obesity and breast cancer risk: a systematic review. Obes Rev 4: 157-173.
12. Schoenaker DA, Jackson CA, Rowlands JV, Mishra GD (2014) Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analyses of studies across six continents. Int J Epidemiol 43: 1542-1562.
13. Gold EB (2011) The timing of the age at which natural menopause occurs. Obstet Gyneol Clin North Am 38: 425-440.
14. Kellemen LE, Atkinson EJ, de Andrade M, Pankratz VS, Cunningham JM, et al. (2010) Linkage analysis of obesity phenotypes in pre- and post-menopausal women from a United States mid-westERN population. BMC Med Genet 11: 156.
15. Bray GA, Bellanger T (2006) Epidemiology, trends, and morbidities of obesity and the metabolic syndrome. Endocrine 29: 109-117.
16. Gravena AA, Brischiliari SC, Lopes TC, Agnolo CM, Carvalho MD, et al. (2013) Excess weight and abdominal obesity in postmenopausal Brazilian women: a population-based study. BMC Womens Health 13: 46.
17. Polotsky HN, Polotsky AJ (2010) Metabolic implications of menopause. Semin Reprod Med 28: 426-434.
18. Mastorakos G, Valsamakis G, Paltoglou G, Creatas G (2010) Management of obesity in menopause: diet, exercise, pharmacotherapy and bariatric surgery. Maturitas 65: 219-224.
19. Asikainen TM, Kukkonen-Harjula K, Miihupalo S (2004) Exercise for health for early postmenopausal women: a systematic review of randomised controlled trials. Sports Med 34: 753-778.
20. Flegal KM, Carroll MD, Ogden CL, Curtin LR (2010) Prevalence and trends in obesity among US adults, 1999-2008. JAMA 303: 234-241.
21. Bagnoi VR, Fonseca AM, Arie WM, Das Neves EM, Arzevedo RS, et al. (2014) Metabolic disorder and obesity in 5027 Brazilian postmenopausal women. Gynecol Endocrinol 30: 717-720.
22. Xi B, Liang Y; He T, Reilly KY, Hu Y, et al. (2012) Secular trends in the prevalence of general and abdominal obesity among Chinese adults, 1993-2009. Obes Rev 13: 287-296.
23. Koutsari C, Ali AH, Nair KS, Rizza RA, O'Brien P, et al. (2009) Fatty acid metabolism in the elderly: effects of dehydroepiandrosterone and testosterone replacement in hormonally deficient men and women. J. Clin. Endocrinol. Metab 94: 3414-3423.
24. Davis SR, Castelo-Branco C, Chedraui P, Lumsden MA, Nappi RE, et al. (2012) Understanding weight gain at menopause. Climacteric 15: 419-429.
25. Toth MJ, Poehlman ET, Matthews DE, Tchernof A, MacCoss MJ (2001) The pathophysiology of obesity and its clinical manifestations. Gastroenterology 50: 976-982.
26. Simpson ER, Misso M, Hewitt KN, Hill RA, Boon WC, et al. (2005) Estrogen- the good, the bad, and the unexpected. Endocr Rev 26: 322-330.
27. Douchi T, Yamamoto S, Nakamura S, Iijim T, Oki T, et al. (1998) The effect of menopause on regional and total body lean mass. Maturitas 29: 247-252.
28. Kanaley JA, Sames C, Swisher L, Swick AG, Ploutz-Snyder LL, et al. (2001) Abdominal fat distribution in pre- and postmenopausal women: The impact of physical activity, age, and menopausal status. Metabolism 50: 976-982.
29. Tchernof A, Desmeules A, Richard C, Laberge P, Daris M, et al. (2004) Ovarian hormone status and abdominal visceral adipose tissue metabolism. J Clin Endocrinol Metab 89: 3425-3430.
30. Eshtiaghi R, Esteghamati A, Nakhjavani M (2010) Menopause is an independent predictor of metabolic syndrome in Iranian women. Maturitas 65: 262-266.
31. Redinger RN (2007) The pathophysiology of obesity and its clinical manifestations. Gastroenterology 50: 856-863.
32. Maury E, Ehala-Aleksejev K, Guiot Y, Detry R, Vandenhooft J, et al. (2007) Adipokines oversecreted by omental adipose tissue in human obesity. Am J Physiol Endocrinol Metab 293: E656-665.
33. Lee MS, Kim JJ, Ha JY, Boddy K, Ernst E (2009) Yoga for menopausal symptoms: a systematic review. Menopause 16: 602-608.
34. Clegg DJ (2012) Minireview: the year in review of estrogen regulation of metabolism. Mol Endocrinol 26: 1957-1960.
35. Pedersen SB, Kristensen K, Hermann PA, Katzenellenbogen JA, Richelsen B (2004) Estrogen controls lipolysis by upregulating α2A-adrenergic receptors directly in human adipose tissue through the estrogen receptor α Implications for the female fat distribution. J. Clin. Endocrinol. Metab 89: 1869-1878.
36. Xu Y, Nedungadi TP, Zhu L, Sobhani N, Irani BG, et al. (2011) Distinct hypothalamic neurons mediate estrogenic effects on energy homeostasis and reproduction. Cell Metab 14: 453-465.
37. Combs TP, Pajvani UB, Berg AH, Lin Y, Jelicks LA, et al. (2004) A transgenic mouse with a deletion in the collagenous domain of adiponectin displays elevated circulating adiponectin and improved insulin sensitivity. Endocrinology 145: 367-383.
38. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, et al. (2001) The hormone resistin links obesity to diabetes. Nature 409: 307-312.
39. Abdulnour J, Doucet E, Brochu M, Lavoie JM, Strychar I, et al. (2012) The effect of the menopausal transition on body composition and cardiometabolic risk factors: a Montreal-Ottawa New Emerging Team group study. Menopause 19: 760-767.
40. Samat A, Rahim A, Barnett A (2008) Pharmacotherapy for obesity in menopausal women. Menopause Int 14: 57-62.
41. Dina C, Myrge D, Gallina S, Durand R, Körner A, et al. (2007) Variation in FTO contributes to childhood obesity and severe adult obesity. Nat Genet 39: 724-726.
42. Chambers JC, Elliott P, Zabanah D, Zhang W, Li Y, et al. (2008) Common genetic variation near MC4R is associated with waist circumference and insulin resistance. Nat Genet 40: 716-718.
43. Liu Y, Liu XG, Wang L, Dina C, Yan H, et al. (2008) Genome-wide association scan identified CTNNBL1 as a novel gene for obesity. Hum Mol Genet 17: 1803-1813.
44. Thorleifsson G, Walters GB, Gudbjartsson DT, Steinhorsdottir V, Sulem P, et al. (2009) Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. Nat Genet 41: 18-24.
45. Lindgren CM, Heid IM, Randall JC, Lamina C, Steinhorsdottir V, et al. (2009) Genome-wide association scan meta-analysis identifies three loci influencing adiposity and fat distribution. PLoS Genet 5: e1000508.
46. Dubnov-Raz G, Pines A, Berry EM (2007) Diet and lifestyle in managing postmenopausal obesity. Climacteric 10 Suppl 2: 38-41.
47. Jouyandeh Z, Nayebrzad F, Forbani M, Asadi M (2013) Metabolic syndrome and menopause. J Diabetes Metab Disord 12: 1.
48. Marjani A, Moghaem S (2012) The Metabolic Syndrome among Postmenopausal Women in Gorgan. Int J Endocrinol 2012: 956327.
49. Dasgupta S, Salmon M, Lokes, S, Xaviour D, Saheb SY, et al. (2012) Menopause versus aging: The predictor of obesity and metabolic aberrations among menopausal women of Karnataka, South India. J Midlife Health 3: 24-30.
50. Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, et al. (1998) Abdominal adiposity and coronary heart disease in women. JAMA 280: 1843-1848.
51. Chang CJ, Wu CH, Yao WJ, Yang VC, Wu JS, et al. (2000) Relationships of age, menopause and central obesity on cardiovascular disease risk factors in Chinese women. Int J Obes Relat Metab Disord 24: 1699-1704.
52. Schmiegelow MD, Hedlin H, Mackey RH, Martin LW, Vitolins MZ, et al. (2015) Race and ethnicity, obesity, metabolic health, and risk of cardiovascular disease in postmenopausal women. J Am Heart Assoc 4.
53. Zarkesh M, Daneshpour MS, Faam B, Fallah M, Hosseinizadeh N, et al. (2012) Heritability of the metabolic syndrome and its components in the Tehran Lipid and Glucose Study (TLGS). Genet Res (Camb) 94: 331-337.
54. Elder SJ, Lichtenstein AH, Pittas AG, Roberts SB, Fuss PJ, et al. (2009) Genetic and environmental influences on factors associated with cardiovascular disease and the metabolic syndrome. J Lipid Res 50: 1917-1926.
55. Powel CM, Boer JM, Feskens EJ (2011) Shared genetic variance between the features of the metabolic syndrome: heritability studies. Mol Genet Metab 104: 666-669.
56. Lin HF, Boden-Albala B, Joo SH, Park N, Rundek T, et al. (2005) Heritabilities of the metabolic syndrome and its components in the Northern Manhattan Family Study Diabetologia 48: 2006-2012.
57. Bayoumi RA, Al-Yahyaee SA, Albarwani SA, Rizvi SG, Al-Hadabi S, et al. (2007) Heritability of determinants of the metabolic syndrome among healthy Arabs of the Oman family study. Obesity (Silver Spring) 15: 551-556.
58. Jermendy G, Horváth T, Littvay L, Steinbach R, Jermendy AL, et al. (2011) Effect of genetic and environmental influences on cardiometabolic risk factors: a twin study. Cardiomet J 10: 96.
59. Reeves GK, Pirie K, Beral V, Green J, Spencer E, et al. (2007) Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ 335: 1134.
De Pergola G, Silvestris F (2013) Obesity as a major risk factor for cancer. J Obes 2013: 291546.

Hankinson SE, Colditz GA, Hunter DJ, Manson JE, Willett WC, et al. (1995) Reproductive factors and family history of breast cancer in relation to plasma estrogen and prolactin levels in postmenopausal women in the nurses' health study (United States). Cancer Causes Control 6: 217–224.

Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, et al. (2003) Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. J Natl Cancer Inst 95: 1218-1226.

Key TJ, Pike MC.(1988)

Sharma S, Tandon VR, Mahajan S, Mahajan V, Mahajan A (2014) Obesity: Friend or foe for osteoporosis. J Midlife Health 5: 6-9.

Looker AC, Flegal KM, Melton LJ 3rd (2007) Impact of increased overweight on the projected prevalence of osteoporosis in older women. Osteoporos Int 18: 307-313.

Sornay-Rendu E, Boutroy S, Vilayphiou N, Claustrat B, Chapurlat RD (2010) Obesity, sarcopenia and postmenopausal osteoporosis: a site-dependent: a population-based study in postmenopausal women. J Bone Miner Res 25: 67-74.

Premoar MO, Pilbrow L, Tonkin C, Parker RA, Compston J (2010) Obesity and fractures in postmenopausal women. J Bone Miner Res 25: 292-297.

Prieto-Alhambra D, Premoar MO, Fina Avilés F, Hermosilla E, Martínez-Laguna D, et al. (2012) The association between fracture and obesity is site-dependent: a population-based study in postmenopausal women. J Bone Miner Res 27: 294-300.

Compton JE, Watts NB, Chapurlat R, Cooper C, Boonen S, et al. (2011) Obesity is not protective against fracture in postmenopausal women: GLOW. Am J Med 124: 1043-1050.

Iishi S, Cauley JA, Greendale GA, Nielsen C, Karvonen-Gutierrez C, et al. (2014) Pleiotropic effects of obesity on fracture risk: the Study of Women's Health Across the Nation. J Bone Miner Res 29: 2561-2570.

Vaidya R (2014) Obesity, sarcopenia and postmenopausal osteoporosis: An interlinked triad! J Midlife Health 5: 1-2.

Herber-Gast GC, Mishra GD, van der Schouw YT, Brown WJ, Dobson AJ (2013) Risk factors for night sweats and hot flushes in midlife: results from a prospective cohort study. Menopause 20: 953-959.

Umland EM (2008) Treatment strategies for reducing the burden of menopause-associated vasomotor symptoms. J Manag Care Pharm 14: 14-19.

Utian WH (2005) Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: a comprehensive review. Health Qual Life Outcomes 3: 47.

Thurston RC, Sowers MR, Sternfeld B, Gold EB, Bromberger J, et al. (2009) Gains in body fat and vasomotor symptom reporting over the menopause transition: the study of women's health across the nation. Am J Epidemiol 170: 766-774.

Gold EB, Colvin A, Avis N, Bromberger J, Greendale GA, et al. (2006). Longitudinal Analysis of the Association Between Vasomotor Symptoms and Race/Ethnicity Across the Menopausal Transition: Study of Women's Health Across the Nation. Am. J. Public Health 96: 1226–1235.

Mishra GD, Kuh D (2012) Health symptoms during midlife in relation to menopausal transition: British prospective cohort study. BMJ 344: e402.

Soules MR, Bremner WJ (1982) The menopause and climacteric: endocrinologic basis and associated symptomatology. J Am Geriatr Soc 30: 547-561.

Atapattu PM (2015) Vasomotor Symptoms: What is the Impact of Physical Exercise? J South Asian Feder Menopause Soc 3:15-19.

Ambl er DR, Bieber EJ, Diamond MP (2012) Sexual function in elderly women: a review of current literature. Rev Obestet Gynecol 6: 16-27.

Kolotkin RL, Binks M, Crosby RD, Ostbye T, Gress RE, et al. (2006) Obesity and sexual quality of life. Obesity (Spring) 14: 472-479.

Pace G, Silvestri V, Gualà L, Vicentini C (2009) Body mass index, urinary incontinence, and female sexual dysfunction: how they affect female postmenopausal health. Menopause 16: 1188-1192.

Esposito K, Cirotola M, Giugliano F, Bisogni C, Schisano B, et al. (2007) Association of body weight with sexual function in women. Int J Impot Res 19: 353-357.

Addis IB, Van Den Feden SK, Wassel-Fyr CL, Vittinghoff E, Brown JS, et al. (2006) Reproductive Risk Factors for Incontinence Study at Kaiser (RRISK) Study Group. Sexual Activity and Function in Middle-Aged and Older Women. Obestet Gynecol 107: 755764.

J Zarzgeb-Bielecka G, Wilczak M, Potasinska-Sobkowska A, Pisarska-Krawczyk M, Mizgier M, et al. (2015) Overweight, obesity and female sexuality in perimenopause: a preliminary report. Prz Menopauzalny 14: 97-104.

Foster MC, Hwang SJ, Larson MG, Lichtman JH, Parikh NL, et al. (2008) Overweight, obesity, and the development of stage 3 CKD: the Framingham Heart Study. Am J Kidney Dis 52: 39-48.

Tazawa M, Iseki C, Tokashiki K, Chinen S, Kohagura K, et al. (2007) Metabolic syndrome and risk of developing chronic kidney disease in Japanese adults. Hypertens Res 30: 937-943.

Kurella M, Lo JC, Chertow GM (2005) Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. J Am Soc Nephrol 16: 2134-2140.

Thomas G, Sehgal AR, Kashyap SR, Srinivas TR, Kirwan JR, et al. (2011) Metabolic syndrome and kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol 6: 2364-2373.

Kambham N, Markowitz GS, Valeri AM, Lin J, D’Agati VD (2001) Obesity-related glomerulopathy: an emerging epidemic. Kidney Int 59: 1498-1509.

Tsiboi N, Koike K, Hirano K, Utsunami Y, Kawamura T, et al. (2013) Clinical features and long-term renal outcomes of Japanese patients with obesity-related glomerulopathy. Clin Exp Nephrol 17: 379-385.

Salve H, Mahajan S, Misra P (2012). Prevalence of chronic kidney diseases and its determinants among perimenopausal women in a rural area of North India: A community-based study. Indian J Nephrol:22: 438-443.

Li Y, Zhao L, Chen Y, Liu A, Liu X, et al. (2013) Association between metabolic syndrome and chronic kidney disease in perimenopausal women. Int J Environ Res Public Health 10: 3987-3997.

Dixon A, Maric C (2007) 17 beta-Estradiol attenuates diabetic kidney disease by regulating extracellular matrix and transforming growth factor-beta protein expression and signaling. Am J Physiol Renal Physiol 293: F878–90.

Ji H, Zheng W, Menini S, Pesce C, Kim J, et al. (2007) Female protection in progressive renal disease is associated with estradiol attenuation of superoxide production. Gend Med 4: 56-71.

Flegal KM, Graubard BI, Williamson DF, Gail MH (2005) Excess deaths associated with underweight, overweight, and obesity. JAMA 293: 1861-1867.

Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, et al. (1995) Body weight and mortality among women. N Engl J Med 333: 677-685.
102. Mehta NK, Chang VW (2009) Mortality attributable to obesity among middle-aged adults in the United States. Demography 46: 851-872.

103. Bea JW, Thomson CA, Wertheim BC, Nicholas JS, Ernst KC, et al. (2015) Risk of Mortality According to Body Mass Index and Body Composition Among Postmenopausal Women. Am J Epidemiol 182: 585-596.

104. Wadden TA, Butryn ML, Wilson C (2007) Lifestyle

105. Foster-Schubert KE, Alfano CM, Duggan CR, Xiao L, Campbell KL, et al. (2012) Effect of diet and exercise, alone or combined, on weight and body composition in overweight-to-obese postmenopausal women. Obesity (Silver Spring) 20: 1628-1638.

106. Zois C, Tokmakidis SP, Volaklis KA, Kotsa K, Touvra AM, et al. (2009) Lipoprotein profile, glycemic control and physical fitness after strength and aerobic training in post-menopausal women with type 2 diabetes. Eur J Appl Physiol 106: 901-907.

107. Roussel M, Garnier S, Lemoine S, Gaubert I, Charbonnier L, et al. (2009) The periodized resistance training promotes similar changes in lipid profile in middle-aged men and women. J Sports Med Phys Fitness 52: 286-292.

108. Augusto Libardi C, Bonganha V, Soares Conceição M, Vergínia De Souza G, Fernandes Bernardes C, et al. (2012) The influence of a walking program on the metabolic risk profile of obese postmenopausal women. Menopause 16: 566-575.

109. Aragão FR, Abrantes CG, Gabriel RE, Sousa MF, Castelo-Branco C, et al. (2014) Effects of a 12-month multi-component exercise program on the body composition of postmenopausal women. Climacteric 17: 155-163.

110. Irwin ML, Yasui Y, Ulrich CM, Bowen D, Rudolph RE, et al. (2003) Effect of exercise on total and intra-abdominal body fat in postmenopausal women: a randomized controlled trial. JAMA 289: 323-330.

111. Rao SS, Singh M, Parkar M, Sugumaran R (2008) Health maintenance for postmenopausal women. Am Fam Physician 78: 583-591.

112. Brończyk-Puzoń A, Piecha D, Nowak J, Koszowska A, Kulik-Kupka K et al. (2015) Guidelines for dietary management of postmenopausal women with simple obesity. Prz Menopauzalny 14: 48-52.

113. NICE guidelines [CG89] 2006 (revised in 2015) Obesity: Guidance on the prevention of overweight and obesity in adults and children http://www.nice.org.uk/guidance/cg89/chapter/1-recommendations#dietary

114. Johansson K, Neovius M, Hemmingsson E (2014) Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 99: 14-23.

115. Rucker D, Padwal R, Li SK, Curioni C, Lau DC (2007) Long term pharmacotherapy for obesity and overweight: updated meta-analysis. BMJ 335: 1194-1199.

116. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, et al. (2007) Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med 357: 741-752.

117. Apovian CM, Aronne LJ, Bessesen DH, McDonell MH, et al. (2015) Pharmacological management of obesity: an endocrine Society clinical practice guideline. J Clin Endocrinol Metab 100: 342-362.

118. Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, et al. (2012) Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. Am J Clin Nutr 95: 297-308.

119. Wadden TA, Berkowitz RI, Womble LG, Sarwer DB, Phelan S, et al. (2005) Randomized trial of lifestyle modification and pharmacotherapy for obesity. N Engl J Med 353: 2111-2120.

120. Yanovski SZ, Yanovski JA (2014) Long-term drug treatment for obesity: a systematic and clinical review. JAMA 311: 74-86.

121. Rubio MA, Gargallo M, Isabel Millán A, Moreno B (2007) Drugs in the treatment of obesity: sibutramine, orlistat and rimonabant. Public Health Nutr 10: 1200-1205.

122. Topol EJ, Bousser M, Fox KAA, Creager MA, Despres J, et al, for the CRESCENDO Investigators (2010) Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. Lancet 376: 517-523.

123. James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, et al. (2010) Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med 363: 905-917.

124. Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, et al. (2006) Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Diabetes Obes Metab 8: 538-554.