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Understanding weight gain at menopause

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ABSTRACT

Objective The aim of this review was to summarize the literature regarding the impact of the menopause transition on body weight and body composition.

Methods We conducted a search of the literature using Medline (Ovid, 1946–present) and PubMed (1966–2012) for English-language studies that included the following search terms: 'menopause', 'midlife', 'hormone therapy' or 'estrogen' combined with 'obesity', 'body weight' or 'body composition'.

Results Whereas weight gain *per se* cannot be attributed to the menopause transition, the change in the hormonal milieu at menopause is associated with an increase in total body fat and an increase in abdominal fat. Weight excess at midlife is not only associated with a heightened risk of cardiovascular and metabolic disease, but also impacts adversely on health-related quality of life and sexual function. Animal and human studies indicate that this tendency towards central abdominal fat accumulation is ameliorated by estrogen therapy. Studies mostly indicate a reduction in overall fat mass with estrogen and estrogen–progestin therapy, improved insulin sensitivity and a lower rate of development of type 2 diabetes.

Conclusion The hormonal changes across the perimenopause substantially contribute to increased abdominal obesity which leads to additional physical and psychological morbidity. There is strong evidence that estrogen therapy may partly prevent this menopause-related change in body composition and the associated metabolic sequelae. However, further studies are required to identify the women most likely to gain metabolic benefit from menopausal hormone therapy in order to develop evidence-based clinical recommendations.

INTRODUCTION

For women aged 55–65 years, weight gain is one of their major health concerns[1]. This is understandable as obesity is one of the most common nutrition-related disorders globally, and its prevalence is increasing. World-wide, the prevalence of obesity has more than doubled since 1980. In 2008, 1.5 billion adults, 20 years and older, were overweight (body mass index (BMI) 25–29.9 kg/m^2), affecting both developed and developing countries. Of these, over 200 million men and nearly 300

million women were obese (BMI ≥ 30 kg/m^2)[2]. Moreover, the rates of obesity have increased notably in developing countries adopting a Western lifestyle (decreased physical activity and overconsumption of cheap, energy-dense food). The sharp increase in overweight and obesity rates observed in the last 20 years is dependent on, or controlled by, several factors and is only in part attributable to changes in lifestyle.

The deleterious effects of obesity are diverse, ranging from an increased risk of premature death to several non-fatal diseases with an adverse impact on quality of life. Obesity is a major risk factor for diabetes mellitus and the cardiovascular diseases, coronary heart disease, infarction, stroke, and hypertension[2]. However, the relationship between obesity and metabolic disease is complex. There is increasing recognition of a metabolically healthy but obese phenotype, observed in about 9% of men and 16% of obese women[3]. The lower rate of cardiometabolic abnormalities in metabolically healthy obese individuals is not explained by diet composition or level of physical activity, highlighting the importance of a genetic contribution to the predisposition to the co-morbidities of obesity[4]. Obesity is also a major risk factor for urinary incontinence, dementia, some cancers (endometrial, breast and colon) and musculoskeletal disorders, especially osteoarthritis, a highly disabling degenerative disease of the joints[2].

Obesity has substantial psychosocial consequences. Depression and depressive symptoms are common among obese patients. As increasingly evidenced in the literature, obesity substantially affects health-related quality of life (HRQOL)[5-7]. It affects physical competence, appearance, self-esteem and social functioning. There are no clear differences between gender and ethnicity in these outcomes.

In general, obesity is characteristically more prevalent in females than in males. Several explanations have been proposed to explain this sex difference in obesity; however, none have been conclusive. Fluctuations in sex hormones at different stages of reproductive life, such as menarche, pregnancy, and menopause transition, may play a role in the adipose tissue expansion.

The menopause transition begins with the onset of menstrual irregularities and ends with the last menstrual period. Numerous studies have demonstrated that the menopausal transition is associated with unfavorable changes in body composition, abdominal fat deposition and general health outcomes;

for this reason, it is mandatory to investigate the changes in these risk factors during the menopausal transition. This review summarizes and discusses the contribution of the menopause transition to obesity in women.

METHODS

The literature was searched using Medline (Ovid, 1946–present) and PubMed (1966–2012) for English-language studies that included the following search terms: 'menopause', 'midlife', 'hormone therapy' or 'estrogen' combined with 'obesity', 'body weight' or 'body composition'.

IS WEIGHT GAIN AT MIDLIFE A CONSEQUENCE OF MENOPAUSE OR AGING?

The studies that have focussed on the question of whether midlife weight gain is simply a function of age or due to the hormonal changes that occur in relation to menopause have concluded that the steady weight gain of about 0.5 kg annually is due to age rather than the menopause itself[8-10]. These include both cross-sectional comparisons of weight in women of similar chronological age but varying menopausal status (premenopause, perimenopause and postmenopause) and longitudinal studies that have examined the rate of weight change and the impact of menopausal status and hormonal change. In addition, consideration of both ethnicity and physical activity is important since these have a profound effect on both obesity and fat distribution[11-13].

The Study of Women's Health across the Nation (SWAN) included five ethnic groups in the US: Caucasians, African-Americans, Hispanic, Chinese and Japanese[14]. In a telephone survey of 16 000 study participants, no difference in self-reported BMI was found between premenopausal and postmenopausal women, adjusting for age and other covariants[15]. This result was confirmed in a small cross-sectional study of energy expenditure, body composition and menopausal status conducted as part of the SWAN, which also considered impact of ethnicity. This sub-study reported that the median weight of the Chinese pre- and early postmenopausal women was not statistically different from that of the late perimenopausal and postmenopausal women[16]. The median weight of the white women in the study was significantly greater than that of the Chinese, and it also did not differ by menopausal status. The mean weight gain over 3 years in the SWAN cohort as a whole was 2.1 kg, but was unrelated to menopausal status[8].

In summary, weight gain does not appear to be affected by the hormonal changes of the menopause.

EFFECTS OF LOSS OF OVARIAN HORMONE PRODUCTION ON WEIGHT AND BODY COMPOSITION

Findings from animal models

Studies in animal models indicate that changes in the hormonal milieu at menopause contribute to changes in body composition and fat distribution. Studies in mice have demonstrated that the loss of ovarian function promotes a diet-independent increase in adipose tissue mass and associated metabolic pathologies[9]. Several studies have shown that oophorectomy results in obesity in mice[17,18]. Oophorectomized mice exhibit decreased energy expenditure, without concomitant change in energy intake, resulting in adipocyte hypertrophy, adipose tissue inflammation and the development of fatty liver[17]. However, when supplemented with 17β-estradiol, oophorectomized mice are protected from developing hepatic steatosis and insulin resistance[18]. In this model, estradiol supplementation also protected against adipocyte hypertrophy and adipose tissue oxidative stress and inflammation[18]. That central fat accumulation is a consequence of estrogen deficiency is also supported by studies of aromatase gene knock-out (ArKO) mice, which cannot synthesize endogenous estrogens. Female ArKO mice exhibit obesity by as early as 3 months of age, which is characterized by marked increases in the gonadal and infra-renal fat pads[19]. This increased adiposity is not simply due to hyperphagia or reduced resting energy expenditure but, as in oophorectomized mice, is associated with reduced energy expenditure due to reduced physical activity[20]. Studies of female mice with total body deletion of the estrogen receptor-α (ERα) (ERα-knock-out mice), have reported similar findings[21]. Estradiol replacement in female ArKO mice primarily results in reduced adipocyte volume with little change in factors that control *de novo* adipocyte fatty acid synthesis, suggesting that changes in the uptake of lipids from the circulation are the main mechanisms by which estradiol regulates fat accumulation[19].

In addition to estrogen deficiency being associated with reduced energy expenditure, there is also evidence from animal models that estrogen is important for feeding behaviors and meal size[21]. Estrogen may have direct actions through ERα or act indirectly to decrease orexigenic peptides and decrease food intake, as reviewed in detail by Brown and Clegg[21].

Taken together, the available data from animal models indicate that estrogen depletion favors central abdominal fat accumulation, and studies in animals indicate that this is ameliorated by estrogen therapy.

Findings from human studies

The prevalence of abdominal obesity is almost double that of general obesity, with rates in the US in 2008 of 65.5% in women aged 40–59 years and 73.8% in women aged 60 years or more[22]. It has been suggested that BMI but not menopausal status determines central adiposity in postmenopausal women. However, there is substantial evidence that the perimenopause is associated with a more rapid increase in fat mass and redistribution of fat to the abdomen, resulting in a transition from a gynoid to an android pattern of fat distribution and an increase in total body fat[11]. Studies using a range of radiological modalities have shown that postmenopausal women have greater amounts of intra-abdominal fat compared to premenopausal women[23,24]. Waist circumference represents both subcutaneous and visceral adipose tissue depot size and correlates closely with cardiovascular disease risk. In women, it is also closely associated with dyslipidemia[25]. The waist-to-hip ratio is another indicator of accumulation of visceral fat which can also be quantitated by CT scanning[26].

Abdominal fat can be considered an endocrine organ due to its capacity to secrete adipokines and other substances that are closely associated with metabolic diseases such as insulin resistance, type 2 diabetes and the metabolic syndrome[27]. Aging and the menopause transition are each associated with changes in adipose tissue metabolism, which may contribute to the accumulation of body fat after menopause[28].

Deleterious changes in inflammatory markers and adipokines correlate strongly with increased visceral adiposity at menopause[29]. The transport protein, serum sex hormone binding globulin (SHBG), is a strong independent marker of insulin resistance[30-32] and type 2 diabetes risk[33] and has been increasingly implicated in the pathogenesis of type 2 diabetes and cardiovascular disease[33-35]. SHBG levels in postmenopausal women are negatively correlated with visceral fat[26,36] and an adverse adipokine profile[37]. Importantly, the relationship between SHBG and insulin resistance in postmenopausal women is independent of both endogenous estrogens and androgens[38]. Thus, a high waist circumference, indicating accumulation of excessive central abdominal fat, and a low SHBG level are independent predictors of metabolic disease risk in postmenopausal women.

A significant change in waist circumference in relation to final menstrual period has been observed[39] and significant increases in central abdominal fat have been reported from longitudinal studies of Caucasian and Asian women[40,41]. Significant increases in total fat mass, percentage fat mass, truncal fat mass and visceral fat have been seen in non-obese premenopausal women followed over several years[40]. The women who became perimenopausal or postmenopausal by the third follow-up year showed a significant increase in visceral fat ($p < 0.01$) compared with baseline. Weight circumference and fat mass (measured by bio-electrical impedance) have also been observed to increase in relation to the final menstrual period[42]. These changes occurred similarly in both African-American and Caucasian women.

Within Asia, different ethnic groups exhibit different levels of insulin resistance, and ethnicity modifies the relationship between insulin resistance and type 2 diabetes that is related to an increase in central adiposity[43,44] and possibly decreased activity[43]. Women of Indian origin have a significantly elevated risk of type 2 diabetes but the impact of menopause itself on this risk is unclear. Studies of the menopause transition and changes in body composition in Chinese women suggest that the menopause has an independent effect on the increase in fat mass as well as an increase in central adiposity[41].

Consistent with weight gain primarily being influenced by age, not menopause, the published literature does not support an adverse effect of spontaneous premature ovarian failure (POF) on body weight and, in general, women with POF tend to be leaner[45]. However, data pertaining to fat distribution in women with spontaneous POF are lacking. Central obesity is common in women with premature ovarian failure due to Turner syndrome. The distinct anthropometrical composition of women with Turner syndrome is associated with higher BMI and waist-to-hip ratio, as well as increased fat mass, central adiposity and liver adiposity when compared with age-matched normal controls[46]. Even so, Turner syndrome patients show a different metabolic pattern than the seen in natural menopause: they frequently have abnormal glucose tolerance and high triglycerides, but with decreased insulin secretion instead of the expected hyperinsulinemia. It is speculated that these women may have impaired pancreas β-cell function, hypothetically due to the involvement of still unknown X-chromosome genes[47].

OTHER FACTORS INFLUENCING WEIGHT GAIN IN MIDLIFE

Obesity is substantially influenced by genetic, demographic, social and behavioral factors. Globally, obesity in women is inversely associated with poorer education and urbanization[48,49]. Other factors that have been found to significantly predict obesity in women include a low level of activity, parity, family history of obesity and marriage at earlier age[48]. Although traditionally obesity has been related to food intake and activity, there is increasing evidence that disruption of circadian rhythms and timing of food intake, as seen with shift work, and sleep deprivation may contribute to weight gain[50]. Although it seems intuitive that factors such as skipping breakfast, daily eating frequency, snacking, irregular meals, eating away from home, consumption of fast food, take-away food intake, consumption of large food portions and eating until full might predict obesity, the literature in this area remains inconclusive due to methodological discrepancies between studies[51,52].

Obesity is associated with psychological distress and low self-esteem and there is evidence for obesity predicting development of depression. However, intrapersonal and contextual factors may confound the relationship between obesity and depression due to the variable perception of body image issues by women according to culture. Furthermore, a spectrum of depression can be increased food intake and decreased physical activity[53] and women who experience depression tend to gain more weight across adulthood[54]. Most population-based studies report an association between obesity and depression[55] and a bidirectional relationship has been found in women between depression and type 2 diabetes[56]. The perimenopause is associated with a higher vulnerability to depression, with the risk increasing from early to late perimenopause and decreasing during postmenopause[57]. Weight gain and increased BMI have been related to anxiety and depression and low life satisfaction during the menopause transition[58,59].

Diverse psychotropic drugs are also associated with weight gain, with negative metabolic consequences. Second-generation antidepressants are the mainstay of management of major depression. These include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other drugs with related mechanisms of action that selectively target neurotransmitters. Some SSRIs and SNRIs are more associated with weight gain than others. Other commonly used psychotropics associated with weight gain include clozapine, imipramine, and amitriptyline[60]. These drugs have been found to up-regulate sterol regulatory element-binding proteins,

which are involved in cellular cholesterol and fatty acid biosynthesis[60]. In contrast, the antidepressants which in general are not associated with weight gain, ziprasidone and buproprion, have little effect on these proteins[60].

Many studies have provided evidence that weight gain is common during chemotherapy. There is consistency in the observation of a significant change in body composition with an increase in total body fat and in abdominal and visceral adiposity, while lean mass stays unchanged or slightly decreases[61]. These changes are not attributable to a change in resting energy expenditure[61]. Decreased voluntary energy expenditure, not increased food intake, appears to contribute to the observed weight gain[61]. Women who experience ovarian failure during treatment have significantly more weight gain than those who remain premenopausal[62], with greater gains observed in truncal fat[63].

DOES OBESITY OR WEIGHT GAIN ALTER THE MENOPAUSE TRANSITION?

When analyzing weight increase during the menopausal transition, there are two important considerations: first, the effect of body weight over the course of the transition, including its effect on age at natural menopause (ANM), and, second, its effect on menopausal symptoms.

Excessive body weight and age at natural menopause

It is well established that obesity may be associated with altered menstrual cycle length and hormone patterns in premenopausal women, with longer cycles due to increase in length of the follicular phase. The rate of premenopausal BMI increase and premenopausal episodic weight loss of more than 5 kg have been independently associated with a later ANM[64]. A later ANM has also been associated with being a non-smoker, higher adult weight, higher BMI, greater alcohol consumption, regular strenuous exercise and not being vegetarian[65]. In contrast, premenopausal smoking and type 2 diabetes predict an earlier ANM.

Longitudinal studies indicate that the greater the BMI, the later the ANM[66]. In the Penn Ovarian Aging Study, there was a positive association between BMI and the odds of transitioning from pre- to perimenopause but not from peri- to postmenopause[67].

The ANM is determined by genetic factors. There are several possible pathways and genomic regions which have been associated with ANM. Nevertheless, findings to date are not conclusive. That obesity is in part genetically determined is known. Enzymes involved in steroid production such as aromatase and type 1 17β-hydroxysteroid dehydrogenase (HSD) can exert influence over estradiol levels during the menopausal transition, particularly in obese women. The decline in estradiol is more rapid in non-obese women[68]. For obese women, selected variations in the aromatase gene and type 1 17β-HSD gene result in different estradiol trajectories around the final menstrual period and, hence, different postmenopausal estradiol levels[68]. Thus, genetic factors may link both ANM and BMI.

In conclusion, there is a potential circular relationship between adiposity and the menopause. It seems that there is a substantial effect of obesity and adiposity on the magnitude of the hormonal changes experienced during the transition. Nevertheless, there are other factors aside from BMI influencing the ANM which may be more relevant such as genetic predisposition, intrauterine development and subclinical ovarian pathology.

Effect of increased weight during the menopausal transition over menopausal symptoms

The prevalence and severity of menopausal symptoms depend on several factors. These include not only the hormonal changes imposed by the transition, but also psychosocial factors. During the menopausal transition, as weight increases so do menopausal symptoms. Obesity is an independent risk factor for more severe menopausal symptoms[69-71].

Obesity and menopausal bone loss

Obese women appear to lose bone at a lower rate than non-obese women across the menopause transition[72]. However, the relationship between osteoporosis, fracture risk and excessive BMI is complex. Low BMI has been associated with osteoporosis and women with long-standing obesity have been observed to be less at risk for osteoporosis and fracture[73]. These views have recently been challenged by the results provided by the Global Longitudinal study of Osteoporosis in Women[74]. This study included 60 393 women $\geq$ 55 years from ten countries and assessed patient characteristics, fracture history, fracture risk factors, and anti-osteoporosis medications. Using fracture as the endpoint, the risk of incident ankle and upper leg fractures was significantly higher in obese women, while the risk of wrist fracture was significantly lower. Obese women with fracture were more likely to have

experienced early menopause and to report two or more falls in the past year. In this population, self-reported co-morbid conditions were highly prevalent, including asthma, emphysema, and type 1 diabetes, and more common in obese women with incident fracture. These data clearly suggest that obesity is not protective against fracture in postmenopausal women[74].

Impact of weight gain on psychosexual well-being at menopause

Apart from being at increased risk for a variety of chronic diseases, overweight women may suffer from psychosocial consequences, with a significant impact on self-esteem and general well-being[75].

A review of eight studies examining HRQOL among women aged over 55 years old concluded that obese postmenopausal women have lower HRQOL in physical functioning, energy, and vitality compared with normal-weight women[76]. Given the evidence that mood disorders are one of the most important co-morbid conditions of sexual dysfunction in postmenopausal women, it is plausible that weight gain and obesity at menopause may be risk factors for poor sexual functioning. However, little is known of the specific impact of weight gain on sexual function at menopause as a consequence of the 'domino' effect of other menopausal symptoms, especially psychological symptoms. Indeed, loss of fitness and weight gain were not the sole factors influencing the intensity of sexual complaints in a clinical sample of menopausal women[77]. In peri- and postmenopausal women with urinary incontinence, increased BMI early in menopause represents a risk not only for urinary incontinence, but also for sexual dysfunction. Arousal, orgasm, lubrication and satisfaction are inversely correlated with BMI[78].

Amongst obese postmenopausal women, the percentage of women with sexual problems is greatest in those with abdominal obesity[79]. Sexual well-being is adversely affected by insulin-resistance and the metabolic syndrome[80], and sexual dysfunction is more prevalent in postmenopausal women with metabolic syndrome in comparison with healthy controls[81]. The third Princeton Consensus Conference reported that women with the metabolic syndrome/obesity have more sexual dysfunction than those without, and treatment of the metabolic syndrome/obesity improves sexual function[82]. Although cardiometabolic risk factors, diabetes, and coronary heart disease are associated with more sexual dysfunction in women, there are no data showing that sexual dysfunction is a predictor of future cardiovascular events in women, as is evident in men[82].

That notwithstanding, there is a need for more research into the association between female sexual health and vascular risk factors.

Weight loss and menopausal symptom improvement

Reductions in weight, BMI and abdominal circumference have been associated with a reduction in vasomotor symptoms in overweight and obese women[83]. The combination of dietary modification and exercise also has positive effects on HRQOL and psychological health, which may be greater than that from exercise or diet alone[84]. Improvements in weight, aerobic fitness and psychosocial factors may mediate some of the effects of these interventions on HRQOL[84]. Weight loss in overweight and obese women improves psychological well-being, HRQOL, self-esteem and health practices[85,86]. In addition, dietary weight loss and exercise exert a positive effect over insulin resistance in postmenopausal women, which together with a decrease in menopausal symptoms may potentially decrease cardiovascular risk.

DOES MENOPAUSAL HORMONE THERAPY AFFECT WEIGHT AND BODY COMPOSITION?

A Cochrane Review published in 2000 reported no evidence of an adverse effect of estrogen-only or estrogen–progestin therapy on body weight or BMI[87]. There has been no subsequent research that would challenge this conclusion.

The effects of estrogen therapy in postmenopausal women on body composition vary, with most randomized, controlled trials showing a reduction in central adiposity[88-91] and a few not[92]. In a subsample of women participating in the Women's Health Initiative estrogen plus progestin (EPT) study, who had body composition measurements at baseline and year 3, the EPT intervention at 3 years significantly helped to maintain lean body mass and prevented a shift toward android fat distribution[90]. However, the size of the effect was small.

Although, overall, the effects of exogenous estrogen appear to be favorable in terms of body composition, the route of estrogen delivery may have subtle, but differing effects[93,94]. Oral estrogen has been associated with a small but significant increase in fat mass and a decrease in lean mass, whereas lean body mass and fat mass do not change significantly with transdermal estradiol[93,94]. Neither route

appears to alter visceral fat mass[93]. The differing effect of oral versus transdermal estrogen therapy may relate to the differing effects of oral versus transdermal estrogen on growth factors and substrate oxidation. Oral estrogen, but not transdermal estrogen, is associated with a significant decline in circulating insulin-like growth factor 1 (IGF-1)[95-98]. This appears to be due to oral estrogen impairing hepatic IGF-I production, which then causes increased secretion of growth hormone through reduced feedback inhibition[99]. Divergent effects on fat mass have also been seen for oral raloxifene and transdermal estradiol. In growth hormone-replaced hypopituitary women, treatment with transdermal estradiol was associated with a reduction in fat mass. This effect was attenuated when the women were treated with raloxifene[100].

Despite the divergent effects of oral and transdermal estrogen noted above, improved insulin sensitivity has been observed with oral EPT[92], and both oral estrogen-alone and EPT may reduce the incidence of type 2 diabetes[101].

In summary, menopausal hormone therapy is not associated with increased weight or increased visceral adiposity. Studies mostly indicate a reduction in overall fat mass with estrogen and estrogen–progestin therapy, improved insulin sensitivity and a lower rate of development of type 2 diabetes.

STRATEGIES TO PREVENT/MANAGE WEIGHT GAIN

Management strategies for weight reduction in obese individuals include physical activity, calorie-controlled diet, pharmacotherapy or bariatric surgery. Complementary and alternative treatments such as acupuncture, yoga, and herbal supplements may also aid in weight loss. These strategies may be used alone or in combination for greater efficacy.

Physical activity

Physical activity has an inverse relationship with weight and waist circumference independent of aging and change in menopausal status[11]. Hence, active midlife women have an advantage as they approach menopause with a lower BMI, lower fat mass, greater lean mass and less central obesity. Even though physical activity may not entirely prevent weight gain with age, it may protect against the development of obesity[14]. Sixty minutes/day of moderate-intensity activity are essential to maintain normal weight[102]. One unit increase in physical activity score decreases 4 cm^2 of intra-abdominal fat[12]. There is

concern about loss of muscle and bone mass with weight loss in older women. Resistance exercise has been shown to preserve lean mass during weight loss[103].

Calorie-controlled diet

Calorie restriction alone can elicit reduction in body weight, total body and visceral fat, similarly to exercise. The addition of exercise, with a weight loss of more than 5%, can reduce risk factors for cardiovascular disease, such as dyslipidemia, hypertension, and diabetes mellitus[104].

Conventional diets are defined as those providing calories below energy requirements but above 800 kcal/day[105]. Options include balanced low-calorie diets, low-fat low-calorie diets, moderate-fat low-calorie diets, low-carbohydrate diets, and the Mediterranean diet. An important determinant of weight loss is adherence to the diet, irrespective of the particular macronutrient composition. A diet based upon patient preferences may improve long-term adherence.

Ideally, any calorie-restricted diet should result in the lowest possible loss of protein, keeping the calories from fat to below 30% of total calorie intake. If a low-carbohydrate diet is chosen, healthy choices for fat (mono- and polyunsaturated) and protein (fish, nuts, legumes, and poultry) should be encouraged. If a low-fat diet is chosen, increases in healthy carbohydrates (fish, vegetables, whole grains) should be selected. It has been suggested that low carbohydrates may be more effective for weight loss than low-fat diets. However, weight losses at 6 months and at 2 years have been found to be similar for diets with differing carbohydrate and fat macronutrient contents[106].

Pharmacotherapy

Anti-obesity medications are pharmacological agents that reduce or control weight. These drugs act by suppressing appetite and increasing satiety, increasing the metabolism of the body and interfering with the body's ability to absorb specific nutrients in food[107].

Orlistat, sibutramine and rimonabant have been studied in trials of 1 year and longer. Attrition rates averaged 30–40%, limiting the validity of studies. All three anti-obesity agents significantly achieved 5–10% weight loss and had differing effects on cardiovascular risk and adverse effect profiles.

At present, only one anti-obesity medication, orlistat (gastrointestinal lipase inhibitor) is currently approved for long-term use. Sibutramine and rimonabant have been withdrawn due to side-effects, including myocardial infarction, stroke and serious psychiatric disorders, respectively[108]. Herbal products have been used as supplements to aid weight loss but have not been found to be significantly effective[109]. Weight loss with pharmacological intervention is not sustained when therapy is discontinued.

Metformin, a drug approved for treatment of diabetes mellitus[110], has been known to produce weight loss of 1–2 kg over a 12-month period. Although metformin does not produce enough weight loss (5%) to qualify as a 'weight-loss drug', it is a useful choice for overweight individuals who have diabetes or are at high risk for diabetes[111].

Bariatric surgery

Bariatric surgery is a clinical and cost-effective intervention for moderate to severely obese people compared to other non-surgical interventions. The different surgical procedures include gastric bypass, vertical banded gastroplasty, adjustable gastric banding, and laparoscopic sleeve gastrectomy. In a systematic review of the effect of surgical versus non-surgical options, a statistically significant difference was seen in five out of six randomized, controlled trials. In two cohort studies that reported the outcome at the end of 2 years, significant weight loss, varying between 16 and 28.6% was demonstrated as compared to the non-surgical group in which there was weight gain. On comparison of different surgical procedures, gastric bypass was found to be more effective than vertical banded gastroplasty. No statistically significant difference was found in the amount of weight loss and quality of life between open versus laparoscopic surgery[112].

Traditional health practices and medicines

Several studies of yoga among the middle-aged and elderly have shown improved metabolic parameters[113]. Long-term Hatha yoga practice is linearly associated with a decrease in BMI[114]. An intensive yoga intervention helped to decrease waist circumference and improve quality of life in overweight and obese breast cancer survivors[115]. Yoga improves adiponectin levels, serum lipids, and metabolic syndrome risk factors in obese postmenopausal women. Consequently, regular yoga practice may be effective in preventing cardiovascular disease caused by obesity[116].

The effectiveness and safety of traditional Chinese medicine, including Chinese herbal medicine (CHM) and acupuncture, provide an alternative established therapy. Acupuncture is believed to induce weight loss via its regulatory effects on nerve and endocrine functions. Laser acupuncture has been found to exert a therapeutic effect on BMI and weight[117].

A review of 96 randomized, controlled trials comprising 49 trials of CHM, 44 trials of acupuncture and three trials of combined therapy has found that CHM and acupuncture were more effective than placebo or lifestyle modification in reducing body weight. CHM and acupuncture were found to have a similar efficacy as anti-obesity drugs but with fewer reported adverse effects. However, these conclusions were limited by small sample size and low quality of methodologies[118].

In summary, various modalities are available for weight loss in obesity. Lifestyle changes such as healthy diet, physical activity and yoga are recommended for long-term results. Bariatric surgery is accepted as an obesity surgery, with excellent results related to weight loss and reduction in morbidity due to metabolic syndrome. The use of acupuncture and CHM merits further investigation. No effective and safe drug is yet available for weight loss.

CONCLUSIONS

Obesity is a public health problem, with overweight individuals representing approximately 20% of the adult world population[119]. Consistent findings are that age, not menopause, is the main determinant of weight gain at midlife, but that the hormonal changes across the perimenopause substantially contribute to increased central abdominal fat and abdominal obesity. Abdominal obesity is not only associated with increased cardiovascular and metabolic disease risk, and cancer, but also sexual dysfunction and poorer health-related quality of life.

Weight control has an essential role in postmenopause health and should be considered early in the perimenopause to safeguard the quality of life of women. Weight loss through diet and increased physical activity has been shown to alleviate menopausal symptoms. Contrary to widespread belief, menopausal hormone therapy is not associated with weight gain and may ameliorate perimenopausal accumulation of abdominal fat. Hormone therapy has also been associated with lower rates of type 2 diabetes. In addition to reducing food intake and increasing activity, interventions including

acupuncture and Chinese herbal medicine may be beneficial for weight loss. However, like dietary and activity modification, these approaches also require individual commitment. As central weight gain with menopause is associated with the development of insulin resistance, there is increasing interest in the use of metformin to ameliorate this metabolic change and thus prevent or delay progression to type 2 diabetes.

In summary, weight gain with age is a global sociodemographic issue that is not a consequence of the menopause. In contrast, increased central abdominal fat appears to be a direct consequence of the menopause. It may be prevented by estrogen therapy and possibly by the use of metformin.

KEY POINTS

- Weight gain is a major health concern for women at midlife.
- Weight gain *per se* does not appear to be affected by the hormonal changes of the menopause.
- The fall in estrogen at menopause favors central abdominal fat accumulation.
- Other factors that may contribute to obesity in women include a low level of activity, parity, lower level of education, a family history of obesity, use of psychotropic drugs and chemotherapy.
- In addition to the adverse physical consequences of obesity, weight excess is a major risk factor for psychological distress, low self-esteem, depression and sexual dysfunction.
- Obesity is an independent risk factor for more severe menopausal symptoms.
- Estrogen-only or estrogen–progestin therapy does not adversely affect body weight and may ameliorate accumulation of abdominal fat.
- Methods of weight loss must include increased exercise and calorific control although this can be enhanced by surgery, drug therapy and non-medical means.
- Metformin is a useful drug for selected overweight individuals who have diabetes or are at high risk for diabetes.
- Successful maintenance of weight loss involves lifestyle change.

Conflict of interest During the past 2 years, Professor S. R. Davis has had a financial relationship (member of advisory boards and/or consultant or investigator) with Bayer-Schering Pharma, Warner Chilcott, Biosante and Trimel Pharmaceuticals; Professor R. E. Nappi has had a financial relationship (lecturer, member of advisory boards and/or consultant) with Bayer-Schering Pharma, Eli Lilly, Merck

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