MAYO CLINIC

Weight Gain in Women at Midlife: A Concise Review of the Pathophysiology and Strategies for Management

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Learning Objectives: On completion of this article, you should be able to (1) summarize the weight and body composition changes in women during aging and menopause, (2) describe a practical approach to weight management in midlife women, and (3) describe the role of menopausal hormone therapy, weight loss medications, and bariatric surgery in the management of overweight and obesity in midlife women.

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Abstract

Weight gain accompanied by an increased tendency for central fat distribution is common among women in midlife. These changes are a result of aging, decreasing estrogen levels after menopause, and other unique influences in menopausal women that interfere with the adoption of healthy lifestyle measures. Central obesity, in particular, results in several adverse metabolic consequences, including dysglycemia, dyslipidemia, hypertension, and cardiovascular disease. Given that cardiovascular disease is the leading cause of death in postmenopausal women, the importance of weight management in midlife cannot be overemphasized. In addition, weight gain in midlife contributes to other health risks including cancer, arthritis, mood disorders, and sexual dysfunction. It is imperative that primary care physicians screen midlife women for overweight/obesity and offer appropriate advice and referral. In addition to counseling regarding lifestyle change, behavioral modification, and psychological support, it is important to address the unique barriers to adoption of healthy lifestyle measures in postmenopausal women, including the presence of vasomotor symptoms, mood disorders, and sleep disturbance. When indicated, menopausal hormone therapy should be considered to manage bothersome symptoms. Despite its favorable influence on body fat distribution, menopausal hormone therapy cannot be recommended as a treatment for central obesity in midlife women.

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Weight gain is common among aging women, especially during the menopausal transition.[1] On average, women gain about 1.5 pounds (0.7 kg) per year during midlife (fifth and sixth decades of life), independent of their initial body size or race/ethnicity.[2,3] In the United States, nearly two-thirds of women aged 40 to 59 years and about three-fourths of women 60 years and older are overweight (body mass index [BMI; calculated as weight in kilograms divided by height in meters squared], >25 kg/m^2). Furthermore, almost half of the women in these age groups are obese (BMI ≥30 kg/m^2).[4] Postmenopausal women also have important changes in body fat distribution—primarily a greater tendency for central fat distribution (android pattern) compared with age- and BMI-matched premenopausal counterparts, who have a gynoid (lower body) fat distribution.[3]

Obesity and increased central body fat, particularly visceral fat, are associated with adverse metabolic consequences and an increased risk of cardiovascular disease, which is the leading cause of death in postmenopausal women.[5] Obese midlife women are also more likely to report more frequent and/or severe hot flashes and symptoms of sexual dysfunction.[6,7]

Apart from aging, midlife women are exposed to several unique and potentially interrelated influences that promote weight gain. These influences include estrogen deprivation, mood disorders, and sleep disturbance, among others.[4] These factors need to be identified and addressed, along with lifestyle recommendations, for optimal weight management in midlife women.

In this concise review, we discuss the pathophysiology of weight gain and offer practical recommendations regarding management of weight gain in women in midlife and beyond.

AGING VS MENOPAUSE

Aging has been associated with weight gain in both sexes, and controversy exists regarding the relative contributions of aging vs menopause to weight gain in midlife women.[3] However, most of the existing literature supports the theory that weight gain in midlife women is primarily the result of aging and lifestyle changes, and that menopause per se does not result in significant weight gain after adjustment for aging.[3] Although estrogen deprivation after menopause leads to an increase in total body fat, it also results in a decrease in lean body mass, such that there is little net effect on weight related to menopause alone.[8] Women have a tendency to gain weight with age, independent of menopausal status[3,9,10]; this weight increase is a result of physiologic changes of aging and lifestyle changes. Aging results in a decrease in lean body mass, which decreases the resting metabolic rate.[11] Aging is also associated with a decrease in physical activity (PA), which may be subtle and therefore not easily perceived by the individual.[12] The decrease in PA further compounds the decrease in lean body mass.[13] Among the environmental factors affecting weight in studies of female twins, PA has emerged as the most important.[14] In a study among women aged 50 to 64 years, only about half reported regular PA, and only one-fourth reported high-intensity exercise.[15] Aging can result in a decrease in both basal and total energy expenditure, and unless a woman adjusts her caloric intake and/or consciously increases her PA level, a state of positive energy balance results, with associated weight gain.

Sleep disturbance also contributes to weight gain in midlife women.[4] Several potential contributors to sleep disturbance in midlife women include nocturnal vasomotor symptoms (night sweats), mood problems, obstructive sleep apnea, and a direct effect of the low-estrogen state.[16] Chronic sleep deprivation can lead to increased daytime fatigue and decreased PA. In a study of more than 68,000 women, those who slept 5 hours or less gained more weight than those sleeping more than 7 hours every night.[17] Mood changes, which affect up to one-fourth of perimenopausal and postmenopausal women, can also interfere with the adoption of healthy lifestyle habits and contribute to weight gain.[18]

Although menopause itself does not seem to substantially influence weight gain, it does result in central fat distribution, an effect that persists after adjustment for aging, total body fat, and PA level, all of which independently increase central body fat.[3,5,19] In other words, in age- and BMI-matched women, those who are postmenopausal tend to have a greater percentage of body fat in the central distribution as compared with premenopausal women. In fact, visceral fat depots may increase to 15% to 20% of the total body fat,

compared with 5% to 8% in the premenopausal state.[20]

MEDICAL COMPLICATIONS OF OBESITY AND CENTRAL BODY FAT DISTRIBUTION

Obese postmenopausal women have a higher overall mortality risk, with as much as a 4-fold increase in cardiovascular deaths in women with a BMI greater than 29 kg/m^2.[21] Obesity, particularly in the presence of increased visceral fat, raises the risk of several adverse metabolic health consequences, including dysglycemia or frank type 2 diabetes mellitus, dyslipidemia, and hypertension.[14] Obesity also increases the risk of certain cancers including breast[22] and uterine[23] cancers. Moreover, the risk of death from all cancers combined was approximately 62% higher in women with a BMI of 40 kg/m^2 or greater compared with normal-weight women in a large prospective study of US adults.[24] Women who are overweight or obese also tend to have more severe or more frequent hot flashes during the menopausal transition and tend to report these symptoms more often than their normal-weight counterparts.[6] Weight loss, however, is associated with improvement in vasomotor symptoms. From a psychosocial standpoint, weight gain at midlife can adversely affect emotional health, self-image, and intimate-partner relationships. Any of these factors alone or in combination can contribute to sexual dysfunction.[7]

MULTIDISCIPLINARY APPROACH TO MANAGEMENT

Clinicians caring for perimenopausal and postmenopausal women should routinely screen for obesity and offer appropriate weight-management counseling to all women with an increased BMI, even when not specifically sought by the patient. An ideal weight management program is a multicomponent behavioral intervention[25] that includes changes in eating habits, PA, and psychological support to enable these behavioral changes. Although specialized services are not available to many patients, weight loss interventions are best executed with a team-based approach involving medical practitioners, behavioral psychologists, dietitians, exercise specialists, and lifestyle coaches.[25] Weight loss medications, bariatric surgery, and endoscopic bariatric therapies may also be discussed in appropriate situations (to be discussed subsequently).

Physicians should assess for medical obstacles to implementation of lifestyle changes, such as joint pain, unrecognized obstructive sleep apnea, or medications that affect weight. Lifestyle changes are a lifelong journey, not a short-term strategy.

Physicians have a pivotal role in offering appropriate education, encouragement, support, and realistic goal setting to avoid disappointment. An intensive lifestyle intervention program is expected to result in a mean weight loss of about 6% to 8% in 6 to 12 months; weight loss of 5% or more is considered clinically meaningful.[26]

Dietary Modification

The optimal diet for weight loss has been debated, whether low-fat, low-carbohydrate, or high-protein diet.[27] However, one is not necessarily superior to another for achieving sustained weight loss.[28] Patients can achieve success at weight loss with various calorie-restricted diets, regardless of the macronutrient composition, as long as they adhere to the hypocaloric dietary plan.[29,30] The fundamental importance of caloric restriction for weight loss has been unequivocally proved.[27] The ability to adhere to a particular diet varies among patients and must be considered when making recommendations.[27] The obesity guidelines from the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society[26] recommend a daily caloric deficit of 500 to 750 kcal, which translates to a caloric intake of 1200 to 1500 kcal/d for most women and is expected to result in an average weight loss of 0.5 to 0.75 kg/wk.[25]

Although it does not affect weight loss, the macronutrient composition of weight loss diets may affect cardiometabolic risk.[25] Low-fat diets may lead to greater improvement in low-density lipoprotein cholesterol levels, whereas low-carbohydrate diets may result in greater improvement in triglyceride and high-density lipoprotein cholesterol levels. The differences are small, however, and the health benefits are mainly the result of calorie restriction—induced weight loss.[27]

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The optimal macronutrient composition for obese women with specific comorbid conditions needs further investigation.[25] The Mediterranean diet, however, deserves special mention because it is compatible with weight loss and has been shown conclusively to decrease cardiovascular disease risk.[31] This diet emphasizes moderate fat intake and plant-based foods, including fruits, vegetables, whole grains, nuts, and legumes.[27] Intermittent energy restriction is a novel strategy (periods of fasting alternating with feeding) that has weight loss outcomes comparable to those with continuous caloric restriction; however, long-term studies on sustained efficacy and effects on cardiovascular disease outcomes are lacking.[27]

Multiple dietary restrictions are difficult for patients to implement; therefore, whenever possible, meal replacement diets can be considered to provide structured portion control. For example, partial meal replacement diets are 1200- to 1400-kcal diets that replace 2 meals per day with a bar or shake and provide a low-fat meal in addition to 2 low-calorie snacks.[27]

If the services are available, consultation with a registered dietitian should be offered to formulate individualized dietary plans that fit the patient's needs, preferences, and lifestyle. Patients should be encouraged to use weight-management tools such as calorie-counting apps (eg, MyFitnessPal, Lose It!) and online resources (eg, the National Weight Control Registry [www.nwcr.ws]). Remote interventions for weight loss, via e- mail, telephone, or websites, appear to be at least as effective as in-person counseling.[32]

Physical Activity

Women who enter midlife with a greater level of PA and maintain it, or those who increase their PA after menopause, have a lower tendency to gain weight than do their less-active peers.[2,33] It is never too late to make lifestyle changes, and physicians should not withhold such counseling from patients because of advanced age alone. The obesity guidelines from the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society[26] recommend 150 to 175 minutes of PA (brisk walking or similar aerobic exercise) per week for weight loss.[25] However, the patients should be counseled that increased physical activity alone, in the absence of caloric restriction, is unlikely to lead to substantial weight loss initially. Conversely, dietary restriction alone is unlikely to provide sustained results in the absence of a regular exercise program or increase in PA. Sustained caloric deprivation leads to a decrease in the basal metabolic rate and energy expenditure, thereby negating the effect of reduced caloric intake. Therefore, an intensive exercise program is required for weight maintenance (see subsequent discussion). Resistance exercises are particularly beneficial because they improve lean body mass, thereby increasing the basal metabolic rate and energy expenditure.

Independent of its effect on weight loss, resistance exercise improves body composition by decreasing abdominal fat and preserving lean body mass.[34] Moreover, regular physical activity in general helps ameliorate weight-related problems even in the absence of actual weight loss. For example, regular exercise improves insulin sensitivity and glycemic control, lowers cholesterol levels and blood pressure, and decreases cardiovascular and all-cause death.[35]

Behavioral Support

Weight management is about changing behaviors, with the goal of a lifelong commitment to healthy lifestyle habits. Therefore, psychological support geared toward identifying barriers to change, monitoring behaviors, problem solving, strategizing, and reinforcement is an important component of weight loss programs. Such counseling can be pursued in individual or group sessions on the basis of the patient's needs, preferences, and available resources.

It is also important to manage psychological issues including depression and anxiety, which can compromise a patient's adherence to a healthy lifestyle. Along these same lines, women should be screened for sleep disturbances and stress, and appropriate treatment strategies should be offered to manage these issues.

Weight Regain After Weight Loss

Although initial weight loss with intensive lifestyle interventions occurs with relative ease,

TABLE. US Food and Drug Administration–Approved Medications for Weight Loss

Drug	Mechanism of action	Common adverse effects	Dosage
Liraglutide	GLP-1 receptor agonist; delayed gastric emptying and decreased appetite, resulting in reduced calorie intake	Nausea, vomiting, constipation, diarrhea, fatigue, headache	Initial: 0.6 mg SC once daily; increase weekly in increments of 0.6 mg/d until maintenance dosage of 3 mg once daily is reached
Lorcaserin	Selective serotonin 2C receptor agonist; promotes satiety and decreases food intake by activating hypothalamic neurons	Nausea, fatigue, headache, dizziness	20 mg/d orally, given as single dose or twice- daily dosing
Naltrexone/bupropion SR	Regulates food intake by unclear mechanisms	Nausea, vomiting, constipation, diarrhea, headache, insomnia, dizziness, anxiety	Naltrexone 8 mg/bupropion 90 mg (1 tablet) orally once daily, gradually increased to maintenance dose of 2 tablets twice daily
Phentermine	Appetite suppressant	Insomnia, central nervous system stimulation	15-37.5 mg/d given as single dose or twice-daily dosing
Phentermine/topiramate ER	Phentermine: appetite suppressant Topiramate: suppresses appetite and increases satiety	Nausea, constipation, altered taste, xerostomia, paresthesia, dizziness, insomnia	Low-dose: 7.5 mg/46 mg once daily (starting dose: 3.75 mg/23 mg once daily) High-dose: 15 mg/92 mg once daily (starting dose: 11.25 mg/69 mg once daily)

ER = extended release; GLP = glucagonlike peptide; SC = subcutaneously; SR = sustained release.

most patients find it difficult to maintain their weight, even in the presence of sustained efforts at lifestyle improvement.[25] Half the patients are back to their baseline weight within 3 to 5 years of weight loss.[25] This result remains a major problem in obesity management. Patients should be prepared and counseled about weight plateau and potential regain after initial weight loss, which may result from several compensatory changes in appetite and the energy regulation pathways that promote weight gain.[36]

Weight loss leads to a prolonged decrease in total energy expenditure beyond that predicted on the basis of change in body weight and composition. The decrease in total energy expenditure may persist, potentially for years, which therefore requires even more intensive efforts at lifestyle changes for weight maintenance.[36] Other predictors of weight maintenance include adherence to a meal plan, a good social support system, and problem-solving abilities, whereas behaviors like emotional eating, limited PA, and lack of support predict weight regain.[25] Consistent behavioral counseling and intensive PA (200-300 min/wk) can help prevent weight regain.[25,37]

Menopausal Hormone Therapy

In the absence of a contraindication to its use, menopausal hormone therapy (MHT) is recommended to manage bothersome menopausal symptoms in recently menopausal women. Although MHT has not been found to result in any weight changes in women, it has consistently been reported to favorably alter body composition.[38] Women receiving MHT tend to have improvements in lean body mass, insulin resistance, and lipid levels and a decrease in central adiposity.[39] These changes might partly explain the lower cardiovascular mortality in young, recently menopausal women receiving MHT compared with those who are not.[40] However, MHT use is not recommended for prevention of chronic disease or prevention or management of weight gain. Women who are receiving MHT for management of bothersome vasomotor symptoms can, nonetheless, be counseled regarding its favorable effects on body fat distribution.

Weight Loss Medications

Weight loss medications can be offered to women with a BMI greater than 30 kg/m^2 or with a BMI greater than 27 kg/m^2 in the

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presence of at least one weight-related comorbid condition.[26,41] Their use should be considered as an adjunct to lifestyle changes and not intended to replace them. Several US Food and Drug Administration–approved medications are available to choose from, with some recent additions (Table).[25] However, it is important to recognize the challenges of pharmacotherapy, including modest efficacy (about 5%-10% weight loss), expense, potential adverse effects, and possibility of weight plateau and regain despite continued use. Therefore, medication use should be considered to maximize weight loss for women who are motivated to pursue lifestyle changes but may be unable to achieve the amount of weight loss desired despite their best attempts at lifestyle interventions, if they are able to afford the medication and if their goal is modest weight loss.[25] A detailed review of pharmacotherapy for weight loss is outside the scope of this concise review.

Bariatric Surgery and Endoscopic Bariatric Therapies

Bariatric surgery is indicated for patients with a BMI greater than 40 kg/m^2 or with a BMI greater than 35 kg/m^2 in the presence of weight-related complications. Candidacy for bariatric surgery is complex and is assessed by a team of experts including a medical practitioner (usually an endocrinologist), psychologist, and bariatric surgeon.

Endoscopic bariatric therapies are an emerging line of treatment for obesity. These treatments include intragastric balloons, endoscopic gastroplasty, and the recently approved percutaneous endoscopic gastrostomy tube for aspiration of gastric contents (AspireAssist; Aspire Bariatrics).[42] These techniques are less invasive than bariatric surgery and offer greater efficacy than pharmacotherapy (about 20%-25% weight loss). However, current challenges include lack of insurance coverage and short-term results (in the case of the gastric balloon).[42]

CONCLUSION

Weight gain and increased visceral fat are common problems in midlife women. These changes considerably affect the physical, emotional, and psychosocial health of women. We recommend that medical practitioners actively screen for overweight/obesity in midlife women and offer appropriate education, treatment, and support. This includes management of issues unique to midlife women, including vasomotor symptoms, mood disorders, and sleep disturbances, that interfere with adoption of healthy lifestyle measures.

Abbreviations and Acronyms: **BMI** = body mass index; **MHT** = menopausal hormone therapy; **PA** = physical activity

Potential Competing Interests: Dr Faubion in on the advisory board for Mithra Pharmaceuticals.

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