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Weight Regulation in Menopause

Michael G. Knight, MD, MSHP¹, Chika Anekwe, MD, MPH², Krystilyn Washington, MD³, Eftitan Y. Akam, MD⁴, Emily Wang⁵, Fatima Cody Stanford, MD, MPH, MPA⁶

¹Division of General Internal Medicine, Department of Medicine, The George Washington University School of Medicine and Health Sciences, Washington, DC, USA

²Department of Internal Medicine, Endocrine Division, Harvard Medical School, Boston, MA, USA

³Kaiser Permanente - Mid-Atlantic Permanente Medical Group, Washington, DC, USA

⁴Departments of Internal Medicine and Pediatrics, Massachusetts General Hospital and Harvard Medical School. Boston, MA, USA

⁵Emory College- Emory University, Atlanta, GA, USA

⁶Department of Internal Medicine- Neuroendocrine Unit and Department of Pediatrics- Pediatric Endocrinology, MGH Weight Center, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Abstract

Importance and Objective: Obesity is a chronic disease of epidemic proportions that continues to affect millions of Americans each year. Post-menopausal women are particularly affected by obesity and have higher rates of severe obesity when compared to their male counterparts. The prevalence of obesity in this population is linked to increased morbidity and mortality and promotes the development and progression of numerous obesity related health conditions. This review examines the epidemiology, pathophysiology, clinical assessment and treatment of postmenopausal women with obesity.

Methods: We have reviewed relevant and up to date literature in the MEDLINE database to represent the current understanding of obesity and its effects in this patient population. Articles published between the year 2000 and 2020 were selected for review to represent the most up to date evidence on the topic. Search terms used in the PubMed search included women, obesity, menopause, aging, mid-age women, metabolism, weight gain, treatment of obesity, weight loss, bariatric surgery, weight loss medications, diet, physical activity, and behavior modification.

Discussion and Conclusion: Obesity is a complex, chronic, relapsing disease that requires comprehensive assessment and treatment. Obesity is linked to hormonal, lifestyle, and environmental changes that occur during the menopausal transition, and it increases the risk for cardiometabolic disease. The utilization of appropriate clinical evaluation methods to identify obesity in post-menopausal women, and the implementation of effective lifestyle,

pharmacotherapeutic, and surgical interventions, have the propensity to reduce the deleterious effects of obesity in this population.

Keywords

women; obesity; menopause; weight gain; treatment of obesity; weight loss

Introduction

Obesity is one of the largest epidemics in the world and is the most prevalent chronic disease that continues to grow at an exponential rate within the United States (U.S.). With age adjusted prevalence of obesity in U.S. adults surpassing 40% in data obtained from the U.S. National Health and Nutrition Examination Survey (NHANES) for the first time in 2018, the efforts of public health initiatives and health care professionals have thus far been unsuccessful in reversing the course of this epidemic [1].

As a leading cause of mortality and morbidity, obesity is associated with numerous health conditions including cardiovascular disease, diabetes, and several cancers [2]. This epidemic continues to strain the American healthcare system, with costs in the United States at an estimated 113.9 billion dollars in the year 2008 alone [3]. Although there is no significant difference in the prevalence of obesity between women and men, severe obesity, which is highly correlated with poor health outcomes, is more prevalent in women [1]. Pathophysiology because obesity is a major risk factor for cardiovascular disease, sleep apnea, metabolic syndrome, gallbladder disease, musculoskeletal disorders, several cancers, and all-cause mortality [4].

Over 43% of menopausal women have obesity, and the challenges that promote these staggering rates, and barriers to effective treatment, are multifactorial [1]. During menopause, there is an increase in fat mass and a decrease in lean muscle mass [5]. Additionally, medications used to combat the hormonal and physical changes of menopause in women, such as antidepressants and hormone treatments, have been shown to promote considerable weight gain [4, 6, 7]. Currently, the treatment of obesity in menopausal women mainly centers around lifestyle and diet changes. However, the long term effectiveness of these approaches continues to be a challenge, and the integration of pharmacotherapy and bariatric surgery is on the rise [8]. The objective of this review is to compile and describe relevant literature on the prevalence, pathophysiology, and clinical management of obesity in postmenopausal women.

Methods

In order to identify pertinent literature on the prevalence, pathophysiology, diagnosis, management, and prognosis of obesity in postmenopausal women, a search was conducted via PubMed of articles on life science and biomedical topics in the MEDLINE database. Articles published between the year 2000 and 2020 were selected for review to represent the most up to date evidence on the topic. Search terms used in the PubMed search included women, obesity, menopause, aging, mid-age women, metabolism, weight gain, treatment of obesity, weight loss, bariatric surgery, weight loss medications, diet, physical activity, and

behavior modification. Publications from the initial search were further refined to include those describing studies that included postmenopausal women and addressed overweight and obesity. Publications describing the pathophysiology, clinical presentation, assessment, diagnosis, treatment, or prognosis of obesity in postmenopausal women were included. Publications that did not describe these factors related to obesity in postmenopausal women were excluded.

Pathophysiology

The menopausal state is associated with several hormonal changes. The most notable is the decreased levels of circulating estrogen that leads to several physiologic changes such as genital atrophy, loss of urogenital tissue support, and bone loss. These changes are promoted by a significant decrease in estradiol (E_2) and estrone (E_1). Estrone continues to be produced by peripheral aromatization while levels of estradiol, produced by the ovary, decline. The ovary, however, continues to produce androstenedione and testosterone. This, in conjunction with a decrease in levels of sex hormone binding globulin (SHBG), leads to higher levels of free androgens [9].

A decrease in SHBG is implicated in the increase in prevalence of type 2 diabetes and cardiovascular disease in postmenopausal women. Low SHBG and increased central adiposity are risk factors for metabolic disease. In this population, there is an accelerated increase in total cholesterol, which is explained by an increase in low-density lipoprotein cholesterol (LDL-C) [9]. During this time period the levels of high-density lipoprotein (HDL) cholesterol trend downwards also [9]. These changes lead to deleterious cardiovascular effects in postmenopausal women [9].

The postmenopausal state is also associated with increases in total body weight. It has been documented that during the menopausal transition, women gain an average of 1 pound per year. However, average weight gain varies widely with 20% of women gaining 10 pounds or more during this transition period [10]. This overall increase in body weight has not been proven to have a direct correlation to changes in hormonal status, but it appears to be related to increasing age and decreased energy expenditure [11, 12]. However, menopause is associated with increased abdominal subcutaneous and visceral adipose tissue deposition [13].

In pre-menopausal women, estrogens are responsible for the accumulation of subcutaneous adipose tissue deposition in the gluteal and femoral regions. This gynoid distribution has been linked to positive cardiometabolic effects such as decreased insulin resistance. Androgens, in contrast, are responsible for the accumulation of subcutaneous fat in the abdominal region, a metabolically unfavorable location. This central adiposity is associated with increased cardiovascular and metabolic diseases, as well as decreased physical activity and poorer quality of life [11]. During menopause, an increase in follicle stimulating hormone (FSH) and decrease in circulating estradiol while androgen levels are maintained leads to relative hyperandrogenemia [14]. The decrease in the production of sex-hormone binding globulin during the menopausal transition also increase the levels of bioavailable androgens [15]. This leads to a change in body composition that is characterized by an

android fat distribution, with adipose tissue accumulating mostly in the abdominal area. There is also an increase in total visceral adipose tissue [16].

The relationship of estrogens and central adiposity in postmenopausal women has been shown to be bidirectional, suggesting that increased central adiposity may also lead to increased levels of estrogens. This occurs as a result of the production of estrogens from the peripheral conversion of androgens in adipose tissue (aromatization). Postmenopausal women with obesity have been shown to have higher levels of estrogens when compared to nonobese women, though lower overall than pre-menopausal women. However, these estrogens derived through peripheral aromatization have not been shown to be associated with positive cardiometabolic effects such as reductions in insulin resistance and risk for diabetes and cardiovascular disease [14, 16]. This relationship also varies through the menopausal transition, with highest future estradiol levels seen in later stages of menopause compared to lower levels in early menopause [17].

In addition to these physiological hormonal changes, medications used to combat the hormonal and physical changes of menopause in women, such as antidepressants like selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), and hormone treatments, have been shown to promote considerable weight gain [4, 6, 7].

Clinical Presentation

The prevalence of overweight and obesity has increased significantly in the United States over the past decades, with greater than 70% of adults over the age of 20 meeting criteria for overweight or obesity in 2016 compared to 56% in 1988 [18]. Rates are disproportionately higher in Black (76%) and Hispanic (80%) communities compared to White (71%), and there is higher prevalence in those making less than 400% of the federal poverty level (FPL) [18]. Rates of overweight and obesity are high with age for women 20 years and older, with 70% of women of perimenopausal age with overweight or obesity. The incidence reaches a peak of 76% then declines after the age of 75 [18].

Because obesity is a major risk factor for cardiovascular disease, sleep apnea, metabolic syndrome, gallbladder disease, musculoskeletal disorders, several cancers, and all-cause mortality [19]. The United States Preventative Services Task Force (USPSTF) recommends screening for overweight and obesity in all routine primary care physical examinations and to refer individuals with obesity for appropriate management [20]. The most frequently used screening method is Body Mass Index (BMI), the weight in kilograms divided by height in meters squared), which defines overweight as $BMI \geq 25$ - 29.9 kg/m^2 and obesity as $BMI \geq 30 \text{ kg/m}^2$ [21]. There is evidence that metabolic and cardiovascular disease risk depends on the distribution of adipose tissue [22], therefore other assessments such as waist circumference, waist-to-hip ratio, skinfold thickness, bioelectric impedance, and more advanced imaging-based techniques may be better indicators of disease risk than BMI alone, particularly in patients with increased muscle mass and those of non-European descent [23, 24].

Assessment and Diagnosis

Thmedical and obstetric history, family history of obesity and associated conditions, as well as a physical exam and laboratory evaluation obstetric history, family history of obesity and associated conditions, as well as a physical exam and laboratory evaluation [25, 26]. As energy balance is vital to obesity management in postmenopausal women, dietary inventory and physical activity assessment can yield insight into a patient's freening for eating disorders is paramount, as approximately 30% of treatment-seeking individuals with obesity in the general adult population are reported to have an eating disorder [25].

Screening for eating disorders is paramount, as approximately 30% of treatment-seeking individuals with obesity in the general adult population are reported to have an eating disorder [26, 27]. While binge eating disorder (BED) and bulimia are most common in this population, identification of any abnormal eating patterns, including binging, purging, lack of satiety, food-seeking behavior, and night-eating syndrome, is crucial [26]. In postmenopausal women, disordered eating is also reported with 13% of women over age 50 years endorsing at least one eating disorder symptom. In addition, 60% reported the negative effect of personal weight concerns on their lives [28]. Weight promoting medications are also of concern. Several commonly used medications in postmenopausal women, including beta-blockers, psychotropic medications, and sleep medications, are associated with weight gain and metabolic dysfunction [29]. Identification and modification of these medications will improve obesity management.

The clinical presentation of a patient with obesity may include physical findings such as central adiposity, acanthosis nigricans, hirsutism, abdominal striae, hepatomegaly, cardiomegaly, respiratory insufficiency, coxa vara and other joint deformities [26]. Clinicians should screen patients for associated conditions with laboratory evaluation of glucose, Hemoglobin A1C, lipids, liver and thyroid function, as well as a sleep study, depression and cancer screenings and specialist referrals as clinically warranted [26]. The skilled clinician will also assess the patient's readiness to treat their obesity and will work to reconcile any obstacles to treatment [30].

Treatment

A successful obesity treatment plan incorporates a culturally competent approach to lifestyle and behavior modifications, as well as an assessment for pharmacologic and surgical candidacy. Nutrition is a key component of weight management. Despite the extensive body of research on different dietary styles, there is a lack of sound evidence to recommend any one specific dietary plan over another for the purposes of weight loss [31, 32]. Emerging evidence on the effects of intermittent fasting and time-restricted eating indicate metabolic benefits, however effects on weight loss are inconclusive [33, 34]. Regardless of the particular dietary approach, any long-term weight loss and weight maintenance plan requires a reduction in energy intake from baseline [31]. This may be achieved by reduced consumption of fat and processed food, smaller portion sizes, and increased energy density[31]. No matter the approach taken, dietary changes must be safe, tolerable,

affordable, nutritionally adequate, culturally acceptable and sustainable by the individual for weight loss and long-term weight maintenance [30, 35].

Physical activity with both aerobic and resistance training is also necessary for weight maintenance [31, 36, 37]. Adults should do at least 150 to 300 minutes a week of moderate-intensity, or 75 to 150 minutes a week of vigorous-intensity aerobic activity (or an equivalent combination), as well as full-body muscle-strengthening activities on two or more days a week [31, 38-40]. Higher doses of exercises are recommended for patients with obesity due to the metabolic and cardiopulmonary benefits, and the attenuation of lean mass often lost with concomitant caloric reduction [36, 39-43].

Patient preference, accessibility issues and physical limitations are important considerations when discussing an exercise regimen; options may include water aerobics, dance, targeted resistance training, physical therapy, cardiopulmonary rehab and non-exercise activity thermogenesis (NEAT) [31, 44].

It should be acknowledged that weight loss is often less rapid and requires sustained effort in postmenopausal women. However, there are numerous health benefits from even 5-10% total body weight loss [45, 46]. The adoption of healthier dietary and physical activity approaches may lead to this moderate weight loss and the transition to metabolically healthy obesity, where evidence of metabolic dysfunction and the risk of adverse health outcomes is reduced. This alternative goal may be employed while continuing to pursue the long-term goal of achieving normal weight in postmenopausal women with obesity [47, 48].

Pharmacotherapy has emerged as an impactful component of a comprehensive approach designed to achieve sustainable weight loss in patients with obesity. It is an effective intervention to support behavioral changes and dietary intervention, which alone may achieve limited weight loss that is difficult to maintain due to adaptive physiologic responses [49]. Weight loss pharmacotherapy has been recommended for the treatment of obesity in patients with BMI ≥ 30 or in patients with overweight with a BMI ≥ 27 with associated conditions such as type 2 diabetes, hypertension, and hyperlipidemia [45].

Currently, there are four medications approved for long term use by the Food and Drug Administration (FDA) for the treatment of obesity: orlistat, phentermine/topiramate, naltrexone/bupropion, and liraglutide 3.0 mg [50]. The first medication approved for obesity in the United States was the sympathomimetic amine, phentermine, which is the medication most commonly prescribed for obesity in the United States for short term use. Phentermine is also approved as a combination medication with topiramate extended release (phentermine/topiramate ER) for the chronic treatment of obesity. Other approved medications include orlistat, which decreases intestinal fat absorption, and bupropion sustained release / naltrexone which combines a dopamine/norepinephrine reuptake inhibitor and an opioid receptor antagonist. Liraglutide 3.0mg is a glucagon-like peptide-1 (GLP-1) receptor agonist that has also emerged as a promising pharmacologic treatment for obesity [51]. The potential effect of a reduction in insulin resistance seen with liraglutide may be particularly effective for the treatment of obesity in post-menopausal women.

Despite the effectiveness of pharmacotherapy in the treatment of obesity, weight loss medications are prescribed by few clinicians. The rates of prescribing are even lower in older adults, including postmenopausal women. In this population there is often a concern about the risk of adverse effects of weight loss medications, however the continuing risk of progressive cardiometabolic disease should so be considered in patients with poorly treated obesity [52].

Bariatric surgery is as an effective and sustainable treatment for obesity and obesity related conditions such as type 2 diabetes. Growing evidence from longitudinal and prospective studies have outlined the benefits of bariatric surgery on mortality, weight loss, and obesity associated diseases in patients, from adolescents to the older adults. Criteria for the surgical treatment of obesity were established by a National Institutes of Health (NIH) consensus panel in 1991 which outlined the appropriateness of bariatric surgery for patients with BMI (> 40 kg/m²) and for patients with BMI between 35-40 with certain obesity associated conditions such as type 2 diabetes, heart disease, and obstructive sleep apnea. However, in recent years, data has supported the expansion of these criteria, including a suggested surgical indication type 2 diabetes for patients with BMI 30-35 [53].

While a number of surgical options for the treatment of obesity have emerged over the last 50 years, adjustable gastric banding (AGB), the vertical sleeve gastrectomy (VSG), and Roux-en-Y gastric bypass (RYGB), represent the majority of surgical procedures performed worldwide for the treatment of obesity [54]. These surgical treatment options have been shown to not only be effective with weight loss of up to 50-60% of excess body weight, but they also have a rate of severe perioperative complications of less than 1% [55]. In postmenopausal women, bariatric surgery has been shown to be effective with 60-70% of excess body weight loss achieved at 12-24 months with RYGB. Though some evidence has shown that the weight loss effect of AGB is reduced in postmenopausal women when compared to women of reproductive age, no differences in outcomes were seen after RYGB [56]. These findings support the use of bariatric surgery to achieve weight loss in eligible postmenopausal women.

Prognosis

Obesity in postmenopausal women is associated with increased morbidity and mortality [57]. Prospective studies have shown that a BMI ≥ 35 is associated with increased mortality in this population [58]. These findings are to be expected due to the association of obesity with a host of cardiometabolic diseases including type 2 diabetes, cardiovascular disease, and hyperlipidemia. These conditions are all associated with increased morbidity and mortality with advancing age. Comprehensive care for patients with obesity may lead to improved outcomes. Increased physical activity, including aerobic exercises, in post-menopausal women who were previously sedentary, led to decreased adiposity for some patients a lower risk for breast cancer [59, 60]. In women with normal weight status, weight gain may be mitigated in the peri- to postmenopausal period with increased physical activity and long-term dietary changes [61, 62].

Conclusion

In order to effectively impact the growing epidemic of obesity and its prevalence among post-menopausal women, a comprehensive approach is needed. We must acknowledge the obesity epidemic and the epidemiologic and physiologic factors that promote excess weight gain, understand the clinical assessment and diagnostic factors, and utilize the full breadth of treatment options across the health care spectrum to optimize weight regulation in menopause in communities across the U.S.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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