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Obesity in Women: Insights for the Clinician

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Abstract

As a leading cause of morbidity and mortality in the United States and worldwide, obesity is a disease that is frequently encountered in clinical practice today and requires a range of medical interventions. While obesity affects both men and women across all ages, multiple issues are particularly germane to women's health, particularly as obesity is more prevalent among women than men in the United States and obesity among women of reproductive health relates to the growing issue of childhood obesity. Discussed herein are the epidemiology and pathophysiology of obesity along with the impact of perinatal obesity on fetal programming. Guidance on screening and management of obesity through lifestyle intervention, pharmacologic therapy, and bariatric surgery, as well as avoidance of weight-promoting medications wherever possible, is elaborated. Particular attention is paid to the contribution of these modalities to weight loss as well as their impact on obesity-related comorbidities that affect a woman's overall health, such as type 2 diabetes and hypertension, and her reproductive and gynecologic health. With modest weight loss, women with obesity can achieve notable improvements in chronic medical conditions, fertility, pregnancy outcomes, and symptoms of pelvic floor disorders. Moreover, as children born to women after bariatric surgery-induced weight loss show improved metabolic outcomes, this demonstrates a role for maternal weight loss in reducing risk of development of metabolic disturbances in children. In light of the immense cost burden and mortality from obesity, it is important to emphasize the role of lifestyle intervention, pharmacologic management, and bariatric surgery for weight loss in clinical practice to mitigate the impact of obesity on women's health.

Keywords: obesity, women, treatment of obesity, weight loss, bariatric surgery, weight loss medications

Epidemiology/Prevalence

Obesity has reached epidemic proportions in the United States, and it is a leading cause of morbidity and mortality. Obesity may be measured and categorized in various ways, which include body mass index (BMI), waist size, waist-to-hip ratio (WHR), and percent body fat. The most commonly used measure of obesity is BMI, which is a surrogate marker for a person's body fat composition, based on a person's weight in kilograms and height in meters. A BMI of 18.5 to 24.9 is normal weight. Overweight is defined as a BMI of 25 to 29.9, and BMI of 30 or greater is considered obese. Data obtained from the U.S. National Health and Nutrition Examination Survey (NHANES) show that the overall prevalence of obesity among adults in 2013–2014 was 37.7%.[1] Among women, the prevalence was 40.4% compared with 35.0% among men. The prevalence of class 3 obesity, defined as BMI ≥40, is also noted to be significantly higher in women than men, at 9.9% compared with 5.5%. The prevalence of overall obesity and the prevalence of class 3 obesity in women have both increased in a linear manner over the decade from 2005 to 2014, even adjusted for age, race, smoking status, and education.

Among U.S. adults seeking care in federally funded health centers in 2009, 76% have been found to be overweight or obese (BMI ≥25 kg/m^2).[2] In this population, women are more likely to have obesity compared to men, and also more likely to receive referrals to a nutritionist or weight-loss prescriptions.

The epidemic of obesity has also worsened in children and adolescents aged 2 to 19 years, with NHANES data showing

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the prevalence of overall obesity to be 17.0% in 2011–2014.[3] In children and adolescents, the prevalence of extreme obesity, defined as a BMI ≥120% of the sex-specific 95th percentile on the U.S. Centers for Disease Control (CDC) BMI-for-age growth charts, was found to be 5.8% over the same period.[3]

Obesity among women of reproductive age plays a role in the intergenerational transmission of obesity from mother to child. Therefore, it is worth noting that the prevalence of obesity in the prepregnant population appears to have increased consistently by an average of 0.5 percentage points every year from 2003 to 2009 in women across most age groups and racial/ethnic backgrounds based on data from the Pregnancy Risk Assessment Monitoring System in 20 U.S. states.[4]

Cost Burden

Obesity is one of the leading causes of preventable death in the United States and leads to an enormous amount of annual healthcare expenditures.[5] In 2005, obesity was responsible for ~1 in 10 deaths among U.S. adults. In 2009, the cost of obesity was ~$300 billion, which includes $173 billion in lost productivity and $130 billion in medical expenditures. Over a 14-year period, persons with obesity contributed on average an additional $1,809/person spending on healthcare services compared with those without obesity.

Obesity also contributes to increased out-of-pocket healthcare expenses, hospital inpatient expenses, hospital outpatient expenses, emergency room service expenses, and office-based medical provider expenses. Data show that the incremental cost due to obesity is higher among women than men resulting in total healthcare expenses being 31% higher in women. The two major sources of costs are inpatient care and prescription drugs, which led to 62% of healthcare expenditures due to obesity.

Federal, state, and local governments and elected officials recognize obesity as an astronomical public health problem.[6] National initiatives from former First Lady Michelle Obama's *Let's Move Campaign* to Healthy People 2010 and 2020, the Institute of Medicine's plan to measure progress in obesity prevention, have brought the problem of obesity firmly into the arena of public policy. Nevertheless, national strategies to tackle this disease have not been given priority, despite its imperativeness.

Mortality

The years of life lost due to obesity have now surpassed the years of life lost due to smoking.[7] The risk from obesity increases with exposure, and a woman's mortality risk due to obesity increases as she ages. For those born in more recent birth cohorts, obesity contributes to a greater extent to their all-cause mortality risk than those born in earlier cohorts.[8]

Among black women, the relationship between BMI and mortality risk is significantly weaker compared with white women. One reason may be that BMI is not a perfect surrogate for adiposity. Also, black women and white women at the same BMI may have different associated levels of dyslipidemia.[9] Waist circumference (WC) is a better surrogate for central adiposity.[10]

Age is an important factor as the burden of obesity is greatest in those aged 40–64 years.[5] In women ≥65 years old, obesity and elevated WC are associated with a higher risk of death, rates of major chronic disease, and disability before reaching 85 years.[10] Maximum BMI over the course of a woman's life has been shown to be a better predictor of mortality than just BMI at a given snapshot in her life.[11]

Pathophysiology

Genetics

There is a strong genetic component to the likelihood of having obesity. A landmark study by Stunkard et al. followed 540 adult Danish adoptees. It found that while there was no relationship between the adoptees' BMI and the BMI of their adoptee parents, there was a strong correlation to the BMI of their biological parents.[12] In another study with 1,974 monozygotic and 2,097 dizygotic twins, Stunkard et al. found that the concordance rate for excess weight was twice as high in monozygotic twins compared with dizygotic twins.[13] While the strong genetic component of obesity is clear, there is not yet a consensus about which theory/hypothesis explains obesity, likely because there is no simple Mendelian inheritance in polygenic common obesity.[14]

Fetal programming and early life

Perinatal influences on fetal development have a significant impact on the subsequent development of childhood obesity.[15] Obesity and pregnancy are both associated with greater insulin resistance and inflammation that cause increased adipose tissue lipolysis.[16] Increases in maternal circulating lipids due to obesity create a favorable concentration gradient across the placenta leading to excess lipid transport to the developing fetus, creating an increased risk for metabolic disease in childhood.[16]

Maternal macronutrient intake in the prenatal period correlates well with offspring macronutrient intake at 10 years of age, and maternal fat intake is a strong predictor of offspring fat mass.[17] Postnatal feeding practices can also have a significant impact on infant metabolic regulation, including breastfeeding, which is associated with a lower risk for developing overweight and obesity later in life. A 2001 study by Hediger et al. used NHANES data to find inconsistent association between breastfeeding and its duration and the risk of being overweight in children.[18] However, Arenz et al. in a 2004 meta-analysis using nine studies with more than 69,000 participants showed that breastfeeding reduced the risk of obesity in childhood significantly, with adjusted odds ratio of 0.78 (95% confidence interval [CI] 0.71, 0.85), thus pointing to a small but consistent protective effect against obesity in children.[19] Horta et al. in a 2015 systematic review and meta-analysis reached a similar conclusion, finding that breastfeeding was inversely associated with overweight and obesity with a pooled odds ratio of 0.74 (95% CI 0.70, 0.78).[20]

The PROBIT randomized control trial saw no protective effect against overweight and obesity from increased duration of exclusive breastfeeding at 3 months when evaluating differences in BMI among children at 6.5 years of age.[21] By contrast, a meta-analysis conducted by Yan et al. of 25 studies with a total of 226,508 participants found a dose/response effect from breastfeeding duration on childhood obesity, specifically noting that breastfeeding for more than 7 months significantly decreased the risk of obesity in childhood.[22]

The mechanism by which breastfeeding might exert a protective effect against obesity is not well understood. There are several hypotheses that McCrory and Layte explore in their 2012 article on breastfeeding and risk of overweight and obesity, including the lower energy density of breast milk compared with infant formula, the lower concentration of protein in breast milk compared with infant formula, the delayed introduction of complementary foods with breastfeeding, which may be protective against the development of obesity in later life, and the occurrence of bioactive compounds such as leptin or ghrelin in human breast milk, which have a role in satiety and regulation of hunger.[23] Indeed, serum levels of appetite-regulating hormone such as leptin, ghrelin, and insulin in infants at 1, 3, and 6 months of age have been shown to be lower in breastfed children compared with formula-fed children.[24] Further research is still needed to elucidate the mechanism by which breastfeeding exerts an effect on child health and metabolism.

Reducing fetal exposure to an obesogenic intrauterine environment can lessen risk of development of metabolic disturbances in children. Smith et al. studied women undergoing biliopancreatic diversion (BPD) surgery, a type of bariatric weight-loss surgery, and compared outcomes in children born to these women before and after surgery.[25] The authors noted sustained improvements in insulin, glucose, and lipid profile in women of reproductive age with obesity to levels seen in healthy lean individuals. In their study, weight-loss surgery was also associated with fewer pregnancy complications, including gestational diabetes mellitus (GDM), hypertension (HTN), and pre-eclampsia.

Even more remarkably, the same study showed that BPD produced persistent differences in metabolic outcomes among children born to women after BPD surgery compared with children born to these women before surgery.[25] Children born after surgery had decreased incidence of macrosomia, had lower BMI-for-age, improved lipid profile, reduction in markers of insulin resistance, and improvements in levels of satiety-related hormones. There was a threefold reduction in prevalence of severe obesity among children born after surgery.

Recent evidence also indicates that father's BMI is also predictive of obesity. Fathers with obesity have children who are at higher risk of developing metabolic disease later in life, independent of the body weight of the mother.[26] Comprehensive profiling of sperm epigenome from lean men and men with obesity in a study by Donkin et al. showed markedly different small noncoding RNA expression and DNA methylation patterns. Surgery-induced weight loss was associated with dramatic remodeling of sperm DNA methylation at genetic locations implicated in central control of appetite. The impact of these gametic epigenetic changes on metabolic profile of offspring remains to be seen.

Hormonal adaptations to weight loss

A multitude of hormones, peptides, and nutrients help regulate body weight. Their perturbations after weight loss may represent transient compensatory changes to energy deficit, suggesting a physiological basis for high rate of relapse among people with obesity attempting to lose weight.[27] These compensatory mechanisms, which include changes in leptin, ghrelin, peptide YY, and cholecystokinin, persist for 12 months in persons with obesity who have lost weight, and must be overcome to maintain weight loss.

Research on animal and human models examining possible mechanisms of action for the development of obesity indicates excess accumulation of lipids in adipose tissue, as well as ectopic fat deposition in the liver, muscle, and pancreas, is associated with development of a lipotoxic environment that blocks correct glucose transport and causes adipocytes to overcome healthy size limit and subsequently release inflammatory cytokines, causing insulin resistance in the body.[28]

Unlike inflammation in peripheral tissues that develops as a consequence of obesity, Thaler et al. have found that hypothalamic inflammatory signaling is evident in rats and mice within 1 to 3 days of high-fat diet consumption, before substantial weight gain.[29] At first, the responses temporarily subsided, but with continued feeding, there was permanent inflammation and gliosis in the mediobasal hypothalamus. The authors also found evidence of increased gliosis in the mediobasal hypothalamus when evaluating humans with obesity. MRI assessment demonstrated neuronal injury to the hypothalamus as a cause of persistent hormonal signal dysregulation affecting both appetite and satiety signals. This signal dysregulation likely makes weight loss and weight-loss maintenance a challenge.

Gut microbiome

In reviewing the contribution of intestinal microbiota to metabolic dysfunction in women and children, Tilg and Adolph find that diet as well as early-life antibiotic use may contribute to childhood obesity, while major gut microbial shifts during pregnancy have been seen to affect maternal metabolism.[30] The authors note that high rates of obesity may be partly attributable to functional alterations in the gut biome. A study by Collado et al. found that the gut of pregnant women with overweight and obesity had higher levels of *Bacteroides*, *Clostridium*, and *Staphylococcus* and lower levels of *Bifidobacterium* than the gut of women of normal weight.[31] Notably, these differences were passed on to offspring, as noted in a subsequent study which demonstrated that the prevalence of *Bacteroides* and *Staphylococcus* was higher in the gut of babies of mothers with overweight.[32]

Likewise, in evaluating specific associations between gut biome and weight status in children, Kalliomaki et al. noted that early-age differences in fecal microbiota were potentially predictive of childhood weight, as children who maintained healthy weight tended to have higher *Bifidobacterium* counts, whereas other microbes such as *Staphylococcus* were elevated in children who became overweight.[33] The authors hypothesized that *Bifidobacterium* plays an anti-inflammatory role. In contrast, *Staphylococcus* may be implicated in triggering low-grade inflammation leading to the development of overweight and obesity.

Circadian rhythm

It is important to understand that circadian rhythmicity likely plays a role in response to weight-loss interventions. To determine the best tool to assess chronodisruption in obesity and metabolic syndrome (MetS), Corbalan-Tutau et al. tested several circadian rhythm variables (*i.e.*, anthropometric measurements and markers of circadian rhythms, such as sleep and feeding diary, Horne–Ostberg questionnaire,

melatonin and cortisol measurements, and wrist temperature measurements) in 70 women.[34] Their study demonstrates that wrist temperature recordings, together with two questions of sleep onset and offset, and one morning salivary cortisol determination could be enough to characterize the chronobiology of obesity and MetS.

A study by Bandin et al. examined 85 women with overweight and obesity and their circadian rhythms using wrist temperature, motor activity, and position, using different sensors. They found that lesser weight loss was related to more flattened pattern of rhythms measured as amplitude from cosinor ($r=0.235$, $p=0.032$), a higher fragmentation of rhythms determined by higher intradaily variability ($r=-0.339$, $p=0.002$), and an impaired wrist temperature circadian rhythm determined by the means of Circadian Function Index ($r=0.228$, $p=0.038$).[35] Circadian rhythm at the beginning of the treatment was a good predictor of weight loss during dietary intervention.

Koo et al. investigated the role of outdoor artificial light at night (ALAN) in sleep and obesity.[36] Their cross-sectional survey included 8,526 adults, 39–70 years of age, who participated in the Korean Genome and Epidemiology Study (KoGES). Multivariate logistic regression analyses showed that high outdoor ALAN was significantly associated with obesity after adjusting for age and sex (OR 1.25, 95% CI 1.14, 1.37, $p<0.001$) and even after controlling for other confounding factors, including age, sex, educational level, type of residential building, monthly household income, alcohol consumption, smoking, consumption of caffeine or alcohol before sleep, delayed sleep pattern, short sleep duration, and habitual snoring (OR 1.20, 95% CI 1.06, 1.36, $p=0.003$).

Rotating night shift work disrupts circadian rhythm and has been associated with obesity. Ramin et al. evaluated night shift work history and its relationship to obesity in 54,724 women in the Nurse's Health Study (NHS) II.[37] They found that night shift workers had increased odds of having obesity (BMI $\geq 30\,kg/m^2$, OR 1.37, 95% CI 1.31, 1.43). This relationship was more prominent in older age ranges.

Sleep health

Several epidemiologic studies have demonstrated the role of sleep in obesity. To evaluate the role of sleep duration in BMI and WC in U.S. adults, Ford et al. evaluated NHANES data from 2005 to 2010 for 13,742 participants aged ≥20 years to categorize sleep duration as ≤6 (short sleepers), 7–9, and ≥10 hours (long sleepers).[38] In this nationally representative sample of U.S. adults, the relationship between sleep duration and BMI and WC was consistently an inverse linear association.

In a 14-year follow-up of the National Institutes of Health-AARP Diet and Health Study (1995–1996), Xiao et al. examined associations between sleep duration and total mortality, cardiovascular disease (CVD) mortality, and cancer mortality among 239,896 U.S. men and women aged 51–72 years who were free of cancer, CVD, and respiratory disease.[39] Compared with 7–8 hours of sleep per day, both shorter and longer sleep durations were associated with higher total and CVD mortality in the study population. Among those participants who reported overweight or obesity, sleep durations shorter than and longer than 7–8 hours were also associated with higher all-cause mortality.

Obesity comorbidities

Obesity is associated with a number of chronic medical conditions such as HTN and type 2 diabetes (T2D). A woman's risk of obesity can be estimated using BMI, abdominal WC, or WHR.[40,41] Women undergo physiologic changes with aging that can lead to abdominal/central obesity, defined as WC ≥88 cm in women (≥102 cm in men) or WHR of >0.8–0.85 in women, with a normal BMI.[40] Hu et al. analyzed data from the Nurses' Health Study (1984–2008) to find that the duration of a woman's exposure to overweight and obesity is independently associated with an increased risk for T2D.[42] Specifically, they found that each two extra years of being overweight was associated with 9% (relative risk [RR] 1.09, 95% CI 1.08, 1.09) increased risk of developing T2D, whereas for each two extra years of having obesity, the risk of T2D was increased by 14% (RR 1.14, 95% CI 1.14, 1.15).

Overweight and obesity are also associated with menstrual cycle irregularity, anovulation, and disruption of the hypothalamic–pituitary–ovarian axis affecting hormonal regulation of oocyte growth and maturation.[43] These decrease the likelihood of conceiving through natural conception or assisted reproductive technologies. Women with polycystic ovarian syndrome (PCOS) who also have obesity represent a more severe phenotype of the disease and consequently have increased levels of androgens, increased insulin resistance, oligo/anovulation, and reduced chances of natural conception.

Pelvic floor disorders in women, which include urinary incontinence (UI), fecal incontinence (FI), and pelvic organ prolapse (POP), are also affected by obesity.[41,44] Both BMI and WC or WHR are independent risk factors for HTN and UI.[40,41] Modest weight loss of 5%–10% of initial body weight can reduce UI frequency up to 50%.[41,45] For women with obesity and stress UI, surgical interventions are a safe and effective option if weight loss is unsuccessful. Neither surgical nor behavioral treatment for FI has proven to be superior and the role of surgery for FI in women with obesity is unclear.[44] Evidence regarding treatment of POP in women with obesity and their outcomes compared with women without obesity is lacking.

Obesity is a significant risk factor for knee osteoarthritis (OA) and also increases risk of OA in nonweight-bearing joints, leading Hussein and Sharara to suggest that mechanical factors alone may not explain the impact of obesity on knee OA.[46] Their study of 84 patients with obesity and knee OA implicates the hormone leptin, which was not only significantly correlated with BMI but was also shown to be significantly correlated with levels of specific cytokines (IL1β and TNFα) and certain metalloproteinases (MMP13), which enhance cartilage degradation.

Treatment

Comprehensive

The American Heart Association (AHA), American College of Cardiology (ACC), and The Obesity Society (TOS) have released evidence-based recommendations for screening and management of overweight and obesity.[47] As per their guidelines, weight-loss treatment is indicated in individuals with BMI $\geq 30\,kg/m^2$ as well as individuals with an

overweight BMI between 25 and 29.9 kg/m^2 who have an indicator of increased cardiovascular risk, for example, T2D, HTN, or elevated WC. The bedrock of their recommendations is ongoing screening by primary care providers of patient BMI and obesity-related comorbidities to identify patients in whom weight-loss treatment is indicated. A detailed workup to help guide treatment would entail gathering information on weight and lifestyle histories to determine contributory factors, including previous weight-loss attempts, dietary habits, physical activity, family history of obesity, and medical conditions and medications that can affect weight.

In patients who express readiness to make lifestyle change, the first step is devising goals for weight loss. The AHA/ACC/TOS Expert Panel has recommended an initial loss goal of 5% to 10% of baseline weight within 6 months. Patients should first be offered comprehensive lifestyle intervention, as outlined by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) ''Clinical Practice Guidelines.''[48]

In this respect, both the quantity and quality of nutrition and physical activity are important factors in the development of overweight and obesity. While the main dietary strategy for women has been to reduce caloric intake reduction by >500 kcal/day for a total dietary intake of 1,200–1,500 kcal/day,[48] Lindberg et al. have used data from the U.S. Department of Agriculture to find that increased BMI is best predicted by a combination of fat and sugar additives in food, accounting for 96% of variance in BMI in women, while fats and sweeteners were found to have direct effect on BMI.[49] This highlights the impact of particular foods in increasing risk for compulsive eating and obesity.

With regard to physical activity, the U.S. Department of Health and Human Services (HHS) ''2008 Physical Activity Guidelines'' for the general public recommend 150 minutes of moderate-to-vigorous activity (MVPA) per week ($\sim$21 minutes per day) for preventing unhealthy weight gain.[50] Maher et al. have used NHANES data on accelerometer-recorded intensity of certain physical activities such as walking and jogging to study the relationship between obesity and time spent in activities considered MVPA—those who met a threshold of motion-induced acceleration defined as ≥2,020 counts per minute.[51] By dividing MVPA times into tertiles, they found a significantly increased risk of obesity in women with moderate MVPA (OR 1.94, 95% CI 1.50, 2.52) and low MVPA (OR 2.84, 95% CI 2.16, 3.73) compared with the highest MVPA tertile. They also noted that MVPA at the vicinity of $\sim$20 minutes per day may be protective against obesity. However, these findings pertain largely to those who are normal weight and have always maintained normal weight.

Data from the National Weight Control Registry (NWCR), using a cohort of more than 10,000 individuals—80% of them women—who have successfully lost at least 13.6 kg (30 lbs) of weight and kept it off for at least 1 year, paint a different picture for those attempting to lose weight.[52] The average weekly amount of exercise activity reported by NWCR participants translates to $\sim$60–75 minutes per day (5–6.5 kcal/min) of moderate-intensity activity such as brisk walking or $\sim$35–45 minutes (8–10 kcal/min) of vigorous activity such as jogging per day.[53] This has resulted in the separate recommendation by HHS of 60–90 minutes of MVPA per day for those attempting to lose weight or maintain weight loss.[50]

As per the American Medical Association and the American College of Sports Medicine's ''Exercise is Medicine'' initiative, physicians can provide an office physical activity assessment and a prescription and referral for physical activity.[54] An effective exercise prescription requires that frequency, intensity, type of exercise, time required, and periodic progress protocol be defined for the patient to ensure a sufficient dose of exercise to improve health and weight outcomes. It should also take into account pre-existing level of activity and presence of comorbid medical conditions such as CVD, metabolic diseases such as diabetes, and renal disease with or without symptoms—these should prompt medical clearance before adopting a structured exercise program.[55]

In terms of defining the days per week of moderate-to-vigorous exercise and the average number of minutes per day of exercise at that level, there are several studies that have attempted to clarify optimal levels. While the average weekly amount of self-reported physical activity of individuals in the NWCR cohort was $\sim$60–75 minutes of moderate-intensity activity or $\sim$35–45 minutes of vigorous activity, it is important to note that the standard deviation of the average weekly kilocalories of physical activity as reported by NWCR members was quite high, suggesting a sizeable degree of variance in the range of weekly kilocalories of physical activity.[53]

Given the potential for bias in self-reported data on physical activity, it is helpful to analyze the findings of Phelan et al. who used accelerometry to provide an objective assessment of the amount and intensity of physical activity undertaken of individuals who had lost and maintained weight and those who have always had normal BMI with stable weight.[56,57] The weight-loss-maintainer group spent significantly more minutes per day than the always-normal-weight group in physical activity (58.6 vs. 52.1; $p = 0.0001$), with more minutes spent in higher intensity activities (24.4 vs. 16.9; $p = 0.02$). The majority of individuals in the always-normal-weight group engaged in 30–60 minutes per day of physical activity, whereas a greater proportion of individuals in the weight-loss-maintainer group engaged in >60 minutes per day of physical activity ($p = 0.002$).

Thus, it is important to advise patients that substantial weight loss requires levels of physical activity that are well above the minimum recommended levels for the general population. However, physical activity even without concomitant weight loss is still beneficial in those with overweight and obesity, who are at risk for CVDs.[58]

Mental health factors

The potential for lifestyle interventions in weight regulation is great, however, this necessitates better characterization of behavioral characteristics in each patient. One notable model is the lifestyle pattern questionnaire developed by Kushner et al. The questionnaire attempts to collect meaningful information on patient's dietary and physical activity profile in addition to associated attitudinal, emotional, and social factors that are correlated with increasing BMI.[59] The usual pattern of weight loss in patients undergoing a lifestyle intervention, such as a structured program with support from a nutritionist or trained exercise specialist, is that the

maximum weight loss is achieved at 6 months, followed by a plateau and gradual regain over time.[47] However, sustainable behavior change requires time and support in order for it to become automatic. Behavioral interventions, although they vary in their scope, can help through provision of strategies for self-monitoring, individualized or group meetings, stress reduction, cognitive restructuring, behavioral contracting, and mobilization of social support.[48]

It is also important to address psychological risk factors that may be associated with weight gain in patients. Carpenter et al. surveyed a sample of 40,086 African Americans and white Americans, and found that relative to average-weight women, obese women had increased odds of past-year major depression (OR 1.37; 95% CI 1.09, 1.73). Also, increasing BMI was associated with increased odds of suicide ideation (OR 1.22; 95% CI 1.13, 1.32).[60] Greenberg et al. noted a high incidence of depression, negative body image, eating disorders, and low quality of life among weight-loss surgery candidates with BMI >40 or BMI >35 with an obesity-related comorbidity in their systemic review of articles related to weight-loss surgery and mental health.[61]

Moreover, the psychological influences promoting weight gain can date back to childhood. In a prospective study of 496 adolescent girls, Stice et al. found that self-reported dietary restraint, radical weight-control behaviors, depressive symptoms, and perceived parental obesity—but not high-fat food consumption, binge eating, or exercise frequency—predicted obesity onset.[62]

A cross-sectional analysis by Heerman et al. reviewed caregiver reports of nine types of adverse family experiences (AFEs), including socioeconomic hardship, parental separation or death or incarceration, racial/ethnic discrimination, exposure to neighborhood and domestic violence, and presence of an individual with mental illness or with drug/alcohol use in the home, using the 2011–2012 National Survey of Children's Health of children aged 10–17 years.[63] Nearly one-third (30.5%) of children had experienced ≥2 AFEs. The prevalence of obesity among children experiencing ≥2 AFEs was 20.4%, compared with 12.5% among children with 0 AFEs. Children with ≥2 AFEs in childhood were more likely to have obesity (adjusted OR 1.8; 95% CI 1.47, 2.17; $p < 0.001$) than those with 0 AFEs.

Another study by Williamson et al. evaluated 13,177 members of a California health maintenance organization aged 19–92 years. Physical abuse and verbal abuse were found to be strongly associated with body weight and obesity.[64] Compared with those experiencing no physical abuse (55%), a person being ''often hit and injured'' (2.5%) had a 4.0 kg (95% CI 2.4, 5.6 kg) higher weight and an RR of 1.4 (95% CI 1.2, 1.6) for a BMI ≥30. Study group members who were ''often verbally abused'' (9.5%) had an RR of 1.9 (95% CI 1.3, 2.7) for BMI ≥40 compared with those experiencing no verbal abuse (53%).

In attempting to find a mechanism for how chronic stress may increase comfort food intake and body weight gain, Dallman et al. found that comfort food ingestion produced abdominal obesity and decreased CRF mRNA in the hypothalamus of rats. They also noted that in depressed humans who overeat, there are decreased levels of cerebrospinal corticotropin-releasing factor, catecholamine concentrations, and hypothalamic–pituitary–adrenal activity.[65] They hypothesized that people eat comfort food in an attempt to reduce the activity in the chronic stress/response network with its attendant anxiety. These findings signify the importance of evaluation by a licensed mental healthcare provider of patients with overweight and obesity in the context of their multidisciplinary care.[61]

Pharmacotherapy and bariatric surgery

If weight loss is not achieved or sustained with comprehensive lifestyle intervention, then adjunctive therapies such as obesity drug treatment and bariatric surgery ought to be considered. Pharmacotherapy is considered in individuals with obesity, or individuals who fall in the overweight category with a BMI >27 kg/m^2 and one obesity-related comorbidity.[47] Pharmacotherapy may generally not be used alone or as first line, but its addition as a chronic treatment produces greater weight loss and weight-loss maintenance than lifestyle intervention alone through effects on appetite and/or fat absorption.[48]

As noted in the AACE/ACE guidelines, medications to promote weight loss include naltrexone and bupropion, liraglutide, lorcaserin, orlistat, and phentermine/topiramate. These medications have been studied in large randomized clinical trials that generally include a larger proportion of females to males.[48] Both orlistat and liraglutide have been effective in modifying eating behaviors, inducing weight loss, improving metabolic parameters, and regulating ovulation in women with polycystic ovary syndrome. Meanwhile, for patients who are postbariatric surgery but who have regained over 25% of their lost weight, liraglutide or phentermine/topiramate may be appropriate.

For women of reproductive potential, it is important to note that weight-loss medications may not be used in pregnancy or when breastfeeding, therefore appropriate contraception should be used.

With bariatric surgery, it may take much longer for weight to plateau. Bariatric surgery may be considered in adults with a BMI ≥40 kg/m^2 or a BMI ≥35 kg/m^2 with obesity-related comorbidities who are unable to achieve weight-loss goals from lifestyle intervention and pharmacotherapy.[47]

In obesity, such as in other chronic diseases, a combination of tailored strategies is devised and frequent follow-up visits are used to monitor the effectiveness of the plan. In addition to the role of the physician/surgeon, the behavior intervention is effectively executed by a multidisciplinary team that includes dietitians, nurses, educators, pharmacists, clinical exercise physiologists, occupational and physical therapists, and clinical psychologists. Psychologists and psychiatrists should participate in the treatment of eating disorders, depression, anxiety, psychoses, and other psychological problems that can impair the effectiveness of lifestyle intervention programs.

Bariatric surgery

Bariatric surgery has been shown to produce effective weight loss. The most common bariatric surgery procedures in 2015 were, in order, laparoscopic sleeve gastrectomy (LSG), Roux-en-Y gastric bypass (RYGB), and gastric banding.[66] A 2004 systematic review of bariatric surgery in the *Journal of the American Medical Association* found the mean percentage of excess weight loss achieved from all types of bariatric surgery interventions to be 61.2% (95% CI

58.1%, 64.4%); 47.5% (95% CI 40.7%, 54.2%) for patients who underwent gastric banding; 61.6% for RYGB (95% CI 56.7%, 66.5%); 68.2% for gastroplasty (95% CI 61.5%, 74.8%); and 70.1% for biliary pancreatic diversion (BPD) (95% CI 66.3%, 73.9%).[67] A substantial majority of patients with T2D, hyperlipidemia, HTN, and obstructive sleep apnea achieved complete resolution or improvement of these conditions after surgery, with T2D completely resolved in 76.8% of patients. In a meta-analysis of 492 patients with mean BMI of 49.2 kg/m^2 undergoing LSG with at least 5-year follow-up, the mean percentage excess weight lost was 62.3%, 53.8%, 43%, and 54.8% at 5, 6, 7, and 8 or more years after LSG, respectively, demonstrating sustained weight loss.[68]

A study by Mingrone et al. randomized 60 patients in 2009 to either medical treatment ($n=20$) or RYGB ($n=20$) or BPD ($n=20$) with a 5-year follow-up.[69] With respect to the study group's comorbidities, at 5 years, 0% of the medical group achieved remission of T2D compared with 37% of the RYGB group and 63% of the BPD group ($p=0\cdot0007$). After 2 years of achieving remission of T2D, 53% of the RYGB group relapsed, while 37% of the BPD group and 100% of the medical group relapsed. Regarding complications, medical patients had more T2D-related complications than the RYGB and BPD patients, while nutritional deficiencies happened only in the BPD group.

Similarly, a study by Ikramuddin et al. randomized 120 patients with moderate obesity (BMI 30–40) and diabetes to intensive lifestyle medical management or RYGB.[70] Lifestyle intervention consisted of participants recording weight, diet, and exercise daily, increasing level of MVPA to a total of 325 minutes per week, using meal replacements, structured menus and calorie counting, meeting regularly with a trained interventionist, and participating in counseling sessions. After 12 months, 28 participants in the RYGB group and 11 in the lifestyle medical management group had achieved the combined goal of HbA1c less than 7.0%, low-density lipoprotein cholesterol less than 100 mg/dL, and systolic blood pressure less than 130 mm Hg (OR 4.8; 95% CI 1.9, 11.7). Participants in the RYGB group required 3.0 fewer medications (mean 1.7 vs. 4.8; 95% CI for the difference, 2.3, 3.6) and lost 26.1% of their initial body weight compared with 7.9% in the lifestyle medical management group (difference, 17.5%; 95% CI 14.2%, 20.7%).

With women forming 84% of the bariatric surgery patient population and female adolescents forming an increasing proportion of this group, the impact of bariatric surgery on fertility and obstetric outcomes has gained importance.[71] Most case–control studies demonstrate increased fertility after bariatric surgery.[72] Pooling together data from 589 infertile obese women, Milone et al. have found that 58% of infertile women become pregnant after bariatric interventions, although they note great variability in reported results, with pregnancy rates ranging from 22% to 92%.[73] The authors note differences in pregnancy rate between different procedures, in this case gastric bypass versus gastric balloon (29% vs. 70%), possibly explained by difference in the baseline BMIs of patients undergoing gastrointestinal bypass versus those undergoing gastric balloon positioning (gastrointestinal bypass patients having a significant higher BMI at baseline than those undergoing gastric balloon [40.8 kg/m^2 vs. 50.1 kg/m^2, $p=0.001$]).

In a retrospective cohort analysis by Edison et al. in the United Kingdom, details on bariatric surgery procedures and comorbidities for women aged 18–45 years were extracted from the National Bariatric Surgery Registry (NBSR).[74] A comparison was made with nonoperative cases (aged 18–45 and BMI ≥40 kg/m^2) from the Health Survey for England, 2007–2013. Almost one-third of women in NBSR had menstrual dysfunction at baseline. BMI fell in the first year postoperatively from 48.2 ± 8.3 to 37.4 ± 7.5 kg/m^2 ($p<0.001$). In the postoperative period, the prevalence in the NBSR group of T2D fell by 54%, PCOS by 15%, and any menstrual dysfunction by 12%. However, further randomized controlled trials are needed to validate the effectiveness of bariatric surgery on reproductive function.[73]

Attempts have also been made to understand the impact of bariatric surgery on obstetric outcomes. A systematic review of case–control and cohort studies on pregnancy and bariatric surgery by Guelinckx et al. notes a linear association between maternal prepregnancy BMI and mean birthweight.[71] In a study comparing pre- and postoperative pregnancies of women who underwent BPD, a decreased incidence of macrosomic infants as well as an increased incidence of healthy maternal weight gain was found.[75] In a retrospective study of all women who delivered after bariatric surgery in a tertiary unit in Israel between 1988 and 2006, encompassing 301 deliveries preceding bariatric surgery and 507 following surgery, Weintraub et al. found decreased rates of GDM in pregnancy after surgery, at 17.3% versus 11.0%, as well as decreased rates of hypertensive disorders in pregnancy, at 23.6% versus 11.2%.[76]

A study from Sweden compared 596 singleton pregnancies in women who had previously undergone bariatric surgery with 2,356 control pregnancies in women matched for presurgery BMI, age, parity, smoking history, educational level, and delivery year; this study reported lower incidences of GDM and large for gestational age babies in the postbariatric surgery women.[77] However, rates of small for gestational age births and shorter gestation periods were higher in the postbariatric surgery women than in controls. A recent meta-analysis of 11 cohort studies compared maternal and fetal outcomes in obese women who had undergone bariatric surgery with obese women who had not had surgery.[78] The findings included lower likelihood of GDM, HTN, and macrosomia following bariatric surgery but increased odds of offspring being small for gestational age; rates of cesarean section, postpartum hemorrhage, and preterm delivery were not significantly different.

Narayanan and Syed also note that the first 12 months after bariatric surgery represent an active catabolic state due to rapid weight loss, with gradual stabilization of the body's nutritional state in the following months. Thus, women should generally be advised to avoid pregnancy for 12–24 months after bariatric surgery.[79]

Operative complications are not uncommon with bariatric surgery and several cases have pointed to the increased risk for nutritional deficiencies in a subsequent pregnancy.[71,79,80] Nutrient deficiencies may be minimal after gastric banding, whereas gastric bypass may be associated with deficiencies of iron, vitamin B12, calcium, vitamin D, other fat-soluble vitamins, and trace elements.[79] Sleeve gastrectomy is associated with the same deficiencies but less severe. BPD procedures are associated with malabsorption of protein, fat, and micronutrients such as vitamins A, D, and B12, calcium, iron, selenium, zinc, and copper. Women of childbearing age should have regular monitoring for deficiencies, with care

being taken to ensure that supplements are safe in pregnancy. Physiological increase in insulin secretion and insulin sensitivity that occurs in early gestation increases the risk of hypoglycemia in women who conceive following bariatric surgery. The standard oral glucose tolerance test is frequently poorly tolerated in women who have had the above procedures causing significantly distressing symptoms from early dumping as well as profound reactive hypoglycemia from late dumping. Dumping refers to when food, especially sugar, moves too fast from the stomach to the duodenum. Continuous glucose monitoring over 1–2 weeks around 24–28 weeks of gestational age may be better tolerated.

The mainstay to management of postprandial hypoglycemia is dietary modifications, namely, a diet high in dietary quality and fiber and low in processed carbohydrates. The increased abdominal pressure, anatomical repositioning of the intra-abdominal organs during pregnancy, and frequent occurrence of emesis during pregnancy can predispose to technical problems with gastric banding.[71] Band adjustability can permit adaptation to the altered requirements of pregnancy and thus allows for healthy maternal weight gain and normal birthweight babies.[80]

The management of postbariatric surgery pregnancies can benefit from a team approach, including a maternal/fetal medicine specialist, bariatric surgeon, and nutritionist.[81] We can look forward to continuing insights on this topic, as evidenced by the ongoing AURORA trial, a prospective cohort study extensively monitoring women who undergo bariatric surgery up until a subsequent pregnancy and their postpartum period.[82]

There are also alternatives to conventional bariatric surgery, with one example being intra-abdominal vagal nerve blockade. The ReCharge randomized clinical trial, involving 239 participants with BMI 40–45 kg/m^2 or with a BMI of 35–40 kg/m^2 with 1 or more obesity-related conditions, had 162 patients receive an active vagal nerve block device and 77 receive a sham device.[83] The objective was to determine if vagal nerve block was superior to sham by a 10-point margin with at least 55% of patients in the vagal block group achieving a 20% loss and 45% achieving a 25% loss. The vagal nerve block group had a mean 24.4% excess weight loss versus 15.9% excess weight loss in the sham group. The mean difference in the percentage of the excess weight loss between groups was 8.5 percentage points (95% CI 3.1, 13.9). At 12 months, 52% of patients in the vagal nerve block group achieved 20% or more excess weight loss and 38% achieved 25% or more excess weight loss versus 32% in the sham group who achieved 20% or more loss and 23% who achieved 25% or more loss. The adverse event rate in the vagal nerve block group was 3.7% (95% CI, 1.4%, 7.9%), which consisted mainly of heartburn, dyspepsia, and abdominal pain.

Lifestyle

Tailored lifestyle modification helps patients develop strategies to manage the external food environment. Higher autonomous motivation, self-efficacy, and self-regulation skills have emerged through research as the best predictors of beneficial weight and physical activity outcomes.[84] In this respect, pregnancy, perhaps unlike any other time in a woman's life, presents a period of increased contact with healthcare providers and pregnant women may be especially motivated to make lifestyle changes out of concern for the health of their offspring.[85,86] In the NIH-sponsored Diabetes Prevention Program study of 3,000 prediabetic patients with obesity, almost 70% of whom were women, patients were randomized into a control group, a medication group (metformin 850 mg twice a day), and a lifestyle intervention group.[87] It was found that intensive lifestyle intervention using diet, exercise, and behavior modification with support from individual counseling resulted in increased sustained weight loss compared with taking metformin alone. After 6 months of intervention, subjects in the lifestyle group lost significantly more weight compared with the other groups, with half of them reaching the 7% loss of initial body weight goal. At 4 years from enrollment, compared with placebo, the lifestyle group achieved a 58% reduction in progression to diabetes, whereas the metformin group attained a 31% reduction.

In a study by Huseinovic et al. of 110 postpartum women with a self-reported BMI ≥27 at 6–15 weeks postpartum who were randomly assigned to a group receiving a structured 12-week diet behavior modification treatment by a dietitian based on the Nordic Nutrition Recommendations or a control group, it was found that a low-intensity diet treatment delivered by a dietitian produced clinically relevant and sustainable weight loss, with 6.1 kg lost in the treatment group versus 1.6 kg lost in the control group at 12 weeks, and 10 kg versus 4.3 kg lost, respectively, at 1 year.[88] Studies comparing treatment groups using pharmacotherapy alone versus pharmacotherapy plus lifestyle and dietary modification show greater ability to achieve expected weight loss when using both modalities and show greater patient satisfaction with the medication and with one's health, appearance, and self-esteem.[89]

Here the findings from the NWCR are particularly germane. Klem et al. noted that approximately one-half of NWCR participants lost weight without any formal assistance and an equal number used commercial or self-help programs.[90] While there was immense diversity of dietary strategies and physical activities used by registry members, some common factors were observed, with nearly every member of the registry using a combination of diet plus exercise to both lose weight and maintain weight loss. Their strategies, however, varied and appeared to produce energy intakes well below national averages in addition to a high quantity of MVPA that resulted in an average weekly energy expenditure that met or exceeded recommended levels. It is worth noting that this was self-reported data subject to bias.

Physicians should help patients set realistic weight reduction goals and encourage them to begin with keeping a daily food record and increasing daily physical activity.[40,89] Recommendations for patients to aim for a ''normal BMI'' should be discouraged as they are often unrealistic.[87,91] They also noted that women and those with higher BMI had greater weight-loss expectations and goals. Kyle and colleagues have found that the belief that exercise is a very effective way to lose weight is stronger in individuals with higher weight status, even though this idea is contrary to evidence. This belief is also a strong predictor of discouragement with exercise.[92] Women who exercise for appearance or weight-related reasons have been observed to be less persistent with exercise and have a poorer body image when compared with peers. Therefore, patients may need to be counseled about realistic weight-loss patterns and the importance of dietary modification as a cornerstone of weight loss.

Providing ongoing support structures for behavioral change (including family, community, and medical resources) can increase the likelihood of behavior change and success. Furthermore, it is important to appreciate that exercise and physical activity can improve body composition profile through increased muscle mass as well as decreased total and visceral fat—thereby reducing comorbidities and medications—even when no weight change is apparent.[93] In addition, decreased sedentary time may itself be an independent factor in improved body composition profile. Maher et al. find that total sedentary time is not associated with increased risk of obesity, whereas Healy et al. have found significant positive associations between sedentary time and WC using NHANES 2003–2006 data.[51,94]

In terms of more small-scale interventions that may have clinical benefits, healthy adults can take anywhere between ~4,000 and 18,000 steps/day, and 10,000 steps/day is a reasonable target for healthy adults. In the AusDiab study, of 1,126 men and women in Tasmania, Australia, who wore a pedometer, the authors found that increasing daily steps was associated with a decline in the obesity measures, with a sharper decline for those with lower baseline daily steps. An additional 2,000 steps for those taking only 2,000 steps per day at baseline was associated with a reduction of 2.2 cm in WC among women (95% CI 0.6, 3.9 cm) compared with a 0.6 cm in reduction in women (95% CI 0.2, 1.0) already walking 10,000 steps daily.[95] In a review of studies on pedometer use and the association with increased activity and resultant change in BMI, Bravata et al. used 26 studies with a total of 2,767 participants with mean intervention duration of 18 weeks.[96] An important predictor of increased physical activity among participants was having a step goal such as 10,000 steps per day ($p = 0.001$). Pedometer users significantly decreased their BMI by 0.38 (95% CI, 0.05, 0.72; $p = 0.03$). They also significantly decreased their systolic blood pressure by 3.8 mm Hg (95% CI, 1.7, 5.9 mm Hg, $p < 0.001$). This decrease was associated with greater baseline systolic blood pressure ($p = 0.009$) and greater change in steps per day from baseline ($p = 0.08$).

Gender variation in response

A systematic review by Williams et al. found small differences in weight loss favoring men for lifestyle interventions.[97] The authors noted that weight loss in men occurs against a backdrop of a greater muscle mass percentage compared with fat mass, contributing to higher resting and total energy expenditure and a greater potential impact of exercise on weight loss. They also report that women have higher concentrations of leptin, an appetite regulation hormone that reduces energy intake. There is, however, little consensus on whether these physiological mechanisms have practical implications for difference in weight-loss success between the two genders. The authors note that current evidence supports moderate energy restriction (limiting caloric intake to 1,200 kcal/day for women and 1,500–1,800 kcal/day for men) in combination with physical activity in both men and women.

Medical management

Certain issues associated with obesity are particularly germane to women, specifically reduced fertility, maternal/fetal complications, and postmenopausal changes in body composition and metabolic rate. Furthermore, certain risks of obesity treatment are more relevant to women, most notably decreasing bone mineral density and potential teratogenicity of some pharmacotherapies.[87]

The percentage of women of reproductive age who suffer from PCOS is 6%–21%, of whom 30%–75% have obesity.[48] Lifestyle modification is the first-line treatment in PCOS, even though it is associated with low adherence and sustainability. A systematic review by Naderpoor et al. of 12 randomized clinical trials with 608 women with PCOS demonstrated that lifestyle intervention plus metformin is associated with lower BMI, decreased amount of subcutaneous adipose tissue, and also associated with improved menstruation and lower testosterone.[98] Patients with overweight or obesity and PCOS should be considered for treatment with orlistat, metformin, or liraglutide, alone or in combination, because these medications can be effective in decreasing weight or improving PCOS manifestations.[48]

With respect to menopause, perimenopausal weight gain is common due to biological and environmental factors as well as use of certain drugs, for example, steroids, insulin, and glitazones.[99] In patients who gain weight due to age or medication use, lifestyle interventions and pharmacologic options can be used to induce weight loss. In those patients with obesity at risk of developing diabetes or those who have already developed diabetes, metformin and/or exenatide can be used as adjunctive medications. As Samat et al. note, while neither metformin nor exenatide is licensed for weight loss, treatment with metformin and with exenatide has been shown in separate trials to produce weight loss in addition to helping achieve glycemic control.

Weight-promoting medications

An important consideration for clinical practice is the role of medications in inducing weight gain. Certain pharmacotherapies that are aimed at obesity-related comorbidities, such as diabetes and HTN, can actually cause weight gain, which in turn exerts a deleterious effect on glucose control, blood pressure, lipid profile, and CVD risk.[100]

Medicines that promote glycemic control, including insulin, insulin-secretagogues, and peripheral insulin sensitizers such as thiazolidinedione, are culprits in drug-induced weight gain.[100] Combination therapy of insulin and metformin has been shown to promote less weight gain compared with insulin therapy alone. Clinical studies also report less weight gain with peakless long-acting insulin glargine and basal insulin detemir than with neutral protamine Hagedorn insulin.

Increases in body weight have also been documented with traditional beta-blockers such as propranolol, metoprolol, and atenolol, with most of the weight gain occurring within the first few months of starting therapy.[101] By contrast, carvedilol has not been associated with exacerbating weight gain in the GEMINI study of 1,164 diabetic and hypertensive patients.[102] Beta-blockade is hypothesized to reduce total energy expenditure in obese hypertensive patients and has a documented negative effect on exercise capacity.[103] Although certain beta-blockers have important absolute indications for use, alternatives include angiotensin-converting enzyme inhibitors, which are associated with less weight gain and even weight loss in some cases.[101]

Table 1. Summary of Practice Guidelines

Practice guidelines for practitioners	*Levels of evidence*
Weight-loss treatment indicated in those with BMI ≥30 kg/m^2 and those with BMI between 25 and 29.9 kg/m^2 with increased cardiovascular risk, for example, type 2 diabetes and hypertension.[47]	Level I
Initial weight-loss goal between 5% and 10% of baseline weight within 6 months is appropriate. Patients should first be offered comprehensive lifestyle intervention.[47]	Level I
Current evidence supports moderate energy restriction for those attempting to lose weight (limiting caloric intake to 1,200 kcal/day for women and 1,500).[98]	Level II
Those attempting to lose weight or maintain weight loss should undertake 60–90 minutes of moderate-intensity physical activity (such as brisk walking) or 35–45 minutes of vigorous activity (such as high-intensity interval training) per day.[50]	Level I
Having a daily step goal such as 10,000 steps/day is an important predictor of increased physical activity, and the use of pedometers and change in steps per day from baseline is associated with decreases in BMI as well as systolic blood pressure.[96]	Level I
Pharmacotherapy may generally not be used alone or as first line, but as an addition to chronic treatment. Medications to promote weight loss include naltrexone and bupropion, liraglutide, lorcaserin, orlistat, and phentermine/topiramate.[48]	Level I
Bariatric surgery may be considered in adults with a BMI ≥40 kg/m^2 or a BMI ≥35 kg/m^2 with obesity-related comorbidities who are motivated to lose weight but have not responded to lifestyle intervention with or without pharmacotherapy.[47]	Level I
Nutrient deficiencies after certain bariatric surgery procedures include deficiencies of iron, vitamin B12, calcium, vitamin D, other fat soluble vitamins, and trace elements. This is risk of hypoglycemia in women who conceive following bariatric surgery, and this can be managed with a low carbohydrate diet.[79]	Level III
Studies comparing treatment groups using pharmacotherapy alone versus pharmacotherapy plus lifestyle and dietary modification show greater ability to achieve expected weight loss when using both modalities and greater patient satisfaction.[87,89]	Level I
Menopausal or perimenopausal patients with obesity at risk of developing diabetes or those who have already developed diabetes can benefit from metformin and/or exenatide as adjunctive medications in producing weight loss and achieving glycemic control.[99]	Level I
Patients with overweight or obesity and PCOS should be considered for treatment with orlistat, metformin, or liraglutide, alone or in combination.[48]	Level I
Increases in body weight have also been documented with traditional beta-blockers such as propranolol, metoprolol, and atenolol.[101]	Level I
Atypical antipsychotics (clozapine, olanzapine, risperidone, and quetiapine) cause marked weight gain and may also exert a diabetogenic influence. SSRIs can be weight promoters, however, SNRIs and SNDRIs are weight neutral. Patients taking antipsychotics who are treated with adjunctive metformin have shown a decrease in weight gain and reduction in metabolic abnormalities.[100,104,105,107]	Level II

Levels of evidence: Level I—Evidence from systematic reviews and meta-analyses of relevant randomized controlled trials or evidence-based clinical practice guidelines based on systematic reviews of multiple randomized control trials; Level II—Evidence from at least one randomized control trial; Level III—Evidence obtained from controlled studies without randomization; Level IV—Evidence from case–control or cohort studies; Level V—Evidence from systematic reviews of qualitative studies; Level VI—Evidence from a single descriptive or qualitative study; Level VII—Evidence based on expert opinion.

BMI, body mass index; PCOS, polycystic ovarian syndrome; SNDRI, serotonin–norepinephrine–dopamine reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin receptor inhibitor.

Chronic corticosteroid use is known to cause weight gain due to increased truncal adipose tissue.[100] For women, a combination of oral contraceptives (estrogen plus progestin) has not been conclusively found to be weight promoting, however, medroxyprogesterone acetate (MPA) does induce weight gain. More well known is the role of psychotropic medications in inducing weight gain. Antipsychotics block anticholinergic, serotonergic, and histaminergic sites, all of which are related to appetite stimulation.[104] Atypical antipsychotics (clozapine, olanzapine, risperidone, and quetiapine) cause marked weight gain and may also exert a diabetogenic influence.[105] Mood stabilizers and antiepileptics such as lithium, valproic acid derivatives, carbamazepine, gabapentin, and lamotrigine are also weight-gain promoters.[106] Notably, however, topiramate is utilized as a weight-loss therapeutic.[100]

The mechanisms by which certain antidepressants cause more weight loss are unclear. Selective serotonin receptor inhibitors (SSRIs) were thought to be weight-loss promoters due to their serotonin-enhancing effect. However, in clinical practice, marked weight gain after initial weight loss is a common and well-known side effect of paroxetine, a commonly used SSRI.[100] This is less true for other SSRIs such as fluoxetine and sertraline. By contrast, venlafaxine, which is a serotonin–norepinephrine reuptake inhibitor, and nefazodone, which is a serotonin–norepinephrine–dopamine reuptake inhibitor, are both weight neutral. In addition, stimulants are a class of psychotropic drugs that have been used in treatment of obesity.[104]

While psychotropic medications are notoriously weight promoting, multiple trials of patients taking antipsychotics, who are treated with adjunctive metformin, have shown a

decrease in weight gain and reduction in metabolic abnormalities.[107] Bupropion should be considered as first-line therapy for patients with overweight and obesity and major depressive disorders.[104] In patients with overweight and obesity who desire contraception, copper uterine devices showed less potential for weight gain compared to MPA.[104] If switching medications is not feasible, consider the use of antiobesity pharmacotherapy.

Summary

Obesity is a complex disease process that requires a systematic approach to ascertain the etiology and treatment options for each patient. Table 1 summarizes the most recent research relevant to clinical practice as outlined in this review. While we do discuss several factors that play a role in weight and weight regulation, it is important to note that the scope of this topic is vast. We were unable to capture all possible causes of obesity due to its intricacy and breadth. In this review, we provide information on the increasing rates in obesity and the associated cost and mortality. We explore the pathophysiology of obesity. We evaluate the role of fetal programming and hormonal adaptations to weight loss. We present information on the gut microbiome, circadian rhythm, and sleep and the role they play not only in obesity itself but also its associated co-morbidities. We discuss the 2013 guidelines by AHA, ACC, and TOS which are helpful for clinicians who aim to treat patients who struggle with obesity. In each of the treatment modalities that include lifestyle modification, pharmacotherapy, and weight-loss surgery, we do note that there is often a gender variation in response to these treatments. Finally, we conclude with information on the cost and mortality associated with the most common chronic disease in the United States—obesity.

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