Obesity: Definition, Comorbidities, Causes, and Burden

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Abstract

Body mass index of 30 kg/m^2 or higher is used to identify individuals with obesity. In the last 3 decades, the worldwide prevalence of obesity has increased 27.5% for adults and 47.1% for children. Obesity is the result of complex relationships between genetic, socioeconomic, and cultural influences. Consumption patterns, urban development, and lifestyle habits influence the prevalence of obesity. The condition may be the result of disease or pharmacologic treatment. It may also be a risk factor for the development of comorbid conditions. Persons who are obese have less school attendance, reduced earning potential, and higher healthcare costs that may result in an economic burden on society. A review of the prevalence and economic consequences of obesity is provided. Potential causes and comorbidities associated with obesity are also discussed.

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For author information and disclosures, see end of text.

Definition and Incidence of Obesity

Body mass index (BMI), which is weight in kilograms divided by height in meters squared, is used to identify obesity. For adults, a BMI of 25.0 to 29.9 kg/m^2 is defined as overweight and a BMI of 30 kg/m^2 or higher is defined as obese.[1] BMI is not used for children and adolescents age 2 to 18 years; instead, it is recommended that a percentile scale based on the child's sex and age be used.[2] In this population, overweight is defined as a BMI in the 85th to 94th percentile, and obesity is a BMI at or above the 95th percentile.

For every 5-unit increase in BMI above 25 kg/m^2, overall mortality increases by 29%, vascular mortality by 41%, and diabetes-related mortality by 210%.[3] Measures of central adiposity, such as increased waist circumference, predict cardiometabolic risk, which cannot be directly determined by elevated BMI.[4] The Edmonton obesity staging system ranks excess adiposity on a 5-point ordinal scale and incorporates the person's obesity-related comorbidities and functional status. The system is intended to complement current measures and has been found to be a strong, independent predictor of increasing mortality; however, it is still unclear how to best incorporate the system into clinical practice.[5]

Worldwide, the prevalence rate for being overweight or obese between 1980 and 2013 increased 27.5% for adults and 47.1% for children, for a total of 2.1 billion individuals considered overweight or obese.[6] These increases were seen in both developed and developing countries. However, the prevalence of overweight and obesity is higher in developed countries than in developing countries at all ages (data from 2013). In developed countries, more men were considered overweight or obese than women; the opposite was seen in developing countries. (**Figure**[6]). In the United States, obesity rates are 12.4% for boys younger than 20 years, 31.7% for men 20 years or older, 13.4% for girls younger than 20 years, and 33.9%

for women 20 years or older. Prevalence rates increased between 1992 and 2002, but have since leveled off.[6]

Economic Consequences of Obesity

Direct Healthcare Costs

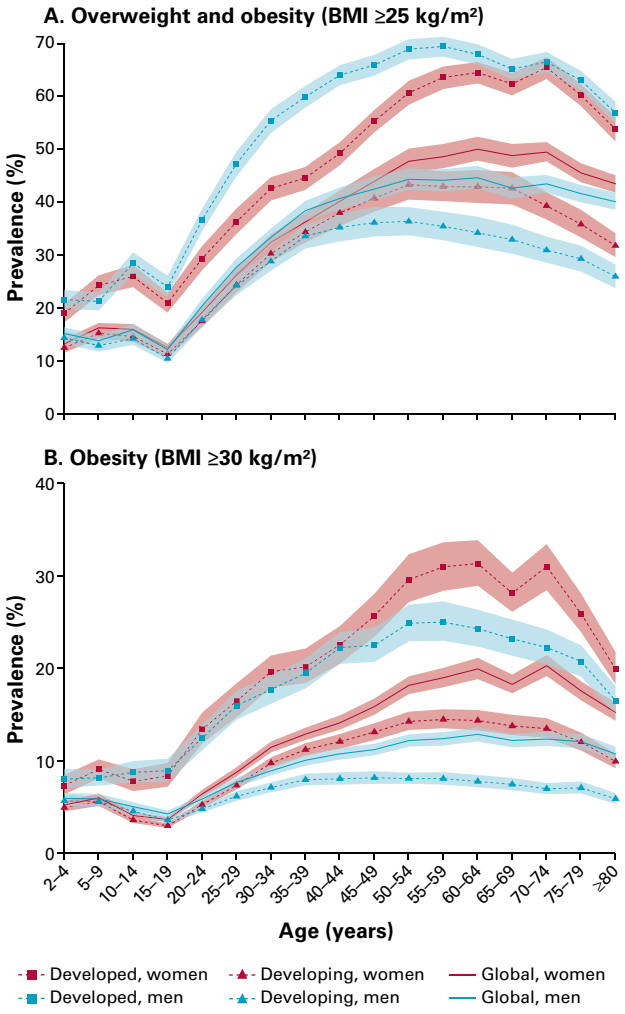
Obesity is associated with increases in annual healthcare costs of 36% and medication costs of 77% compared with being of average weight.[7] Data from the Medical Expenditure Panel Surveys (MEPS), a large national survey of civilian, noninstitutionalized individuals (N = 21,877), reported 2006 costs across all payers (eg, Medicare, Medicaid, and private insurers). Results showed that patients who were obese had annual medical spending that was on average $1429 (42%) higher than patients who were of normal weight, and obesity was attributed to about $40 billion in increased medical spending. For Medicare patients, the main contributors to healthcare costs were non-inpatient services and medications, which were attributed to the introduction of prescription drug coverage at that time. The costs for Medicare patients who were obese were $600 higher per year than for patients who were of normal weight.[8]

Long-term Economic Consequences of Obesity on the Individual

Obesity is associated with long-term negative economic consequences. Children with obesity were absent from school significantly more (12.2 ± 11.7 days) than children who were considered to be of normal weight (10.1 ± 10.5 days).[9] Obesity was associated with 1.9 more days absent after controlling for age, gender, race/ethnicity, and school. A higher BMI in the late-teen years was associated with a lower level of accumulated education, and data from the National Longitudinal Survey of Youth found that a 1-unit increase in BMI is directly associated with 1.83% lower hourly wages.[10] In addition, children who are obese or overweight are at increased risk for being the target of aggressive behavior from their peers. A study looking at the relationship between bullying and BMI found that adolescents who were overweight or obese were more often the victims of rumors/lies, name-calling, teasing, physical abuse, and isolation.[11]

If obesity could be addressed early in life, it could have a substantial impact on healthcare costs. It is estimated that if the number of individuals ages 16 and 17 who are overweight or obese could be reduced by 1%, then the number of adults with obesity in the future could be reduced by 52,812; this would result in a decrease in lifetime medical costs of $586 million.[12] Obesity appears to influence school attendance, level of education, earning ability, and social interactions.

Figure. Prevalence of Overweight and Obesity and Obesity Alone, by Age and Sex, 2013[6]



BMI indicates body mass index.
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Factors Associated With the Development of Obesity

The exact cause of obesity is unknown; however, there appears to be a complex relationship among biologic, psychosocial, and behavioral factors, which include genetic makeup, socioeconomic status, and cultural influences.[13] Obesity has been linked to microorganisms, epigenetics, increasing maternal age, greater fecundity, lack of sleep, endocrine disruptors, pharmaceutical iatrogenesis, and intrauterine and intergenerational effects.[14] Comorbid conditions and their treatments may also be a factor

in developing obesity. A list of causes of obesity can be found in the Table.[15] The pathophysiology of obesity is well understood; however, treatment and prevention have focused on the psychological and social components of the disease. To date, the best noninvasive interventions have been in dietary management and behavioral change. The best outcomes are associated with bariatric surgery. Drug therapy has limited effectiveness, particularly in children. Genetic testing is applicable for a small group of these patients. Researchers are still in the process of integrating basic science data with clinical research and learning how to apply the results to patient care.[16]

Food Choices and Influence on Weight

Food choices, which are influenced by the home, child care, school, workplace, and community environments, directly affect the type and amount of caloric intake. Over the last 100 years, because of technological advances in food processing, the types of foods consumed have changed. Foods with decreased fiber and increased fat, simple sugar, salt, and increased calories are more readily available, and they are typically cheaper than healthier alternatives. Consumption of these ultra-processed foods has led to a 205-calorie increase in an individual's average daily caloric intake since the 1960s.[17]

A school-based study conducted by the CDC reported that two-thirds of high school students drank some type of sugar-sweetened beverage (eg, soda, Hawaiian punch, lemonade, Kool-Aid, other sweetened fruit drinks, iced tea) at least once a day, and about 22% drank them at least 3 times a day. Male and non-Hispanic black students ate at a fast food restaurant at least 1 day a week, watched television more than 2 hours a day, and had a greater chance of consuming sugar-sweetened beverages at least 3 times a day than other groups studied. Students less likely to consume those drinks were non-Hispanic or those who were physically active at least 60 minutes a day for at least 5 days a week.[18] One soda a day, depending on the size (8 oz to 20 oz), could provide 270 to 690 calories a day. Consumption of sugar-sweetened beverages is associated with an increase in the risk of obesity; the risk increases 1.6 times (95% CI, 1.14-2.24; P = .02) for each additional serving of sugar-sweetened drink consumed daily.[19]

Consumption of energy-dense foods is positively associated with an increase in waist circumference and BMI.[20,21] A 6-year, longitudinal study demonstrated that women who consumed a diet made up of higher energy-dense foods, consisting of more servings from grain, meats, and fat groups, had an increase in BMI of 2.5 units, whereas women who consumed lower energy-dense diets, containing more servings of vegetables and fruit, had an increase in BMI of 0.9 units.[21]

Table. Causes of Obesity[15]

Primary causes
Genetic causes
Monogenic disorders
Melanocortin-4 receptor mutation
Leptin deficiency
Proopiomelanocortin deficiency
Syndromes
Prader-Willi
Bardet-Biedl
Cohen
Alström
Froehlich
Secondary causes
Neurologic
Brain injury
Brain tumor
Consequences of cranial irradiation
Hypothalamic obesity
Endocrine
Hypothyroidism[a]
Cushing syndrome
Growth hormone deficiency
Pseudohypoparathyroidism
Psychological
Depression[b]
Eating disorders
Drug-induced
Tricyclic antidepressants
Oral contraceptives
Antipsychotics
Anticonvulsants
Glucocorticoids
Sulfonylureas
Glitazones
Beta-blockers

[a]Controversial whether hypothyroidism causes obesity or exacerbates obesity.
[b]Depression associated with overeating or binging.
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Relationship of Socioeconomic Factors and Obesity

Racial or cultural makeup of the living environment likely influences a person's weight. In another report, racial segregation in metropolitan areas was not associated with obesity among men; however, segregation did appear to affect obesity rates among some women. For black women, living in a highly segregated area was associated with a 1.29 times higher obesity prevalence (95% CI, 1.00-1.65), and a medium-segregated area was associated with a 1.35 times higher obesity prevalence (95% CI, 1.07-1.70). Conversely, for Mexican-American women, living in a highly segregated area was associated with significantly lower obesity prevalence (prevalence ratio, 0.54; 95% CI, 0.33-0.90).[22]

It is recommended that adults engage in at least 150 minutes of moderate-intensity physical activity a week.[23] However, a reduction or lack of physical activity is attributed to neighborhood planning that discourages active transportation, such as walking or biking. Other factors contributing to lack of physical activity are decreased availability of physical education classes and a general philosophy in the work and school environment that physical activity is not a priority.[24]

A person's urban environment impacts the amount and type of physical activity. One study examined proximity of physical activity facilities to the residential locations of the 20,745 adolescents who participated in wave I of the National Longitudinal Study of Adolescent Health.[25] Higher socioeconomic areas had a greater number of physical activity facilities, which, in turn, were associated with increased relative odds of adolescents participating in at least 5 sessions of physical activity a week and decreased rates of adolescents being overweight. Increased physical activity is important in management of excess weight; clinical guidelines recommend that all obesity management programs consist of a reduced-calorie diet, increased physical activity, and behavior modification.[1,15]

Genetics and Obesity

Numerous polymorphic gene products may also be a cause of obesity. Li and colleagues reported that 12 obesity-susceptible loci have been identified. Investigators examined the association between those loci and BMI, waist circumference, weight, and height, as well as the predictive value for obesity risk. Variants had a cumulative effect on obesity measures, with each additional allele associated with an increase in weight of 444 g and increased risk of obesity of 10.8%. However, the alleles combined had limited predictive value for obesity risk.[26]

Genetic influences on BMI appear to be strongly correlated.[27] Researchers assessed identical twins reared together and apart, as well as fraternal twins reared together and apart. Intrapair correlations for BMI of identical twins reared apart were 0.70 for men and 0.66 for women, demonstrating that genetic influences were independent of environmental influences.[27] A comparison of body fat in a cohort of adult twins who were reared apart versus a control group of twins reared together showed that body fat is strongly associated with genetic factors.[28] About 60% of individual differences in body fat were attributed to genetics, but because the correlation is less than 100%, the environment must also influence body fat percentage. A study of monozygotic and dizygotic twins examined the heritability estimates for fat measures and found that these measures were about the same for both sexes, although slightly higher in men.[29] The genetic variance range for BMI and body fat percentage was 0.58 to 0.63; for total skin folds, 0.48 to 0.69; and for waist circumference, 0.61 for men and 0.48 for women. Therefore, genetics appear to determine who will become obese, and the environment appears to determine the extent of obesity.[28,29]

Gut Microbiome

The body's microbiome—the bacteria, viruses, archaea, and eukaryotic microbes residing in and on the body—have the potential to impact our physiology in several ways, including contributing to metabolic function.[30] Studies have demonstrated that the gut microbiome can increase dietary energy harvest, and an "obese microbiome" results in greater total body fat than a "lean microbiome."[31] Clinical trials are needed to assess replacing or altering the gut microbiome to treat obesity and its complications.

Chronodisruption

Chronodisruption is associated with the development of obesity, prediabetes, diabetes, and lipid disorders.[32,33] Chronodisruption can be induced by shift work, sleep deprivation, or shifting the normal eating time to night hours.

Relationship Between Hormones and Weight

The regulation of food intake is managed by neural and hormonal signals between the gut and central nervous system (CNS). Hormones, such as glucagon-like peptide (GLP), oxyntomodulin (OXM), leptin, peptide tyrosine-tyrosine (PYY), and cholecystokinin (CCK), signal to important areas in the CNS involved in appetite control.[34,35] Blood concentrations of these hormones increase after a meal; the concentrations are proportional to the caloric intake and composition of a meal.[34]

Glucagon-like Peptide

Several biologically active peptides are produced from proglucagon.[35] These include GLP and OXM. GLP stimulates insulin release and inhibits glucagon release in a glucose-dependent manner. Nonglycemic effects include weight loss. Independent of weight loss, potential effects include cardiovascular, neurologic, and renal benefits, along with changes in taste perception. Currently, a GLP-1 receptor agonist is approved for the treatment of obesity.[36]

Oxyntomodulin

OXM regulates the secretion of gastric acid and intestinal hydro-minerals. It is also needed for the control of food intake and energy expenditure. In the CNS, OXM suppresses hunger and reduces food intake. In addition, it increases energy expenditure and inhibits the orexigenic signal carried by ghrelin. In all, these features make OXM a good target for the development of an anti-obesity drug.[35]

Peptide Tyrosine-Tyrosine

PYY regulates food intake in lean and obese persons. The exact mechanism of its anorectic effects are unclear. High concentrations of circulating PYY are found in patients with anorexia nervosa, and low concentrations are observed in those with obesity. In addition, PYY may increase energy expenditure by increasing postprandial thermogenesis, resting metabolic rate, and 24-hour respiratory quotient.[34]

Cholecystokinin

CCK-induced hunger suppression mainly occurs via the CCK 1 receptor. CCK does not appear to impact gastric emptying; CCK likely acts peripherally because it is unable to cross into the CNS. It appears to reduce food intake via the vagus nerve; however, the mechanism is unclear. CCK and leptin may have a synergistic effect on food intake inhibition.[34]

Leptin

Leptin is responsible for the communication in the brain of energy availability and storage; the hypothalamus responds to these signals by controlling behavior and metabolic responses. Leptin can suppress appetite and increase energy expenditure, resulting in weight loss.[37] However, when leptin signaling is not functioning properly, it can result in weight gain. Leptin resistance was associated with obesity (odds ratio [OR]: 4.12; 95% CI, 3.29-5.16), while normal weight was associated with the absence of leptin resistance (OR: 0.13; 95% CI, 0.01-0.20). Leptin resistance and obesity are possibly heritable traits. One hypothesis is that people who are obese are resistant to endogenous leptin signaling. Patients who were obese were reported to have significantly higher serum leptin concentrations than patients who were considered to be of normal weight (mean serum leptin concentration 31.3 ± 24.1 ng/mL in participants who were obese vs 7.5 ± 9.3 ng/mL in participants who were considered of normal weight, P <.001).[38] In addition, there was a strong correlation between serum leptin concentration and body fat percentage (r = 0.85, P <.001), BMI (r = 0.66, P <.001), fasting serum insulin concentration (r = 0.57, P <.001), and age (r = 0.26, P <.001).[39]

Adiponectin

Adiponectin appears to assist in the modulation of glucose and lipid metabolism in insulin-sensitive tissues. It increases sensitivity to insulin, reduces hepatic glucose production, and stimulates fatty acid oxidation. Plasma adiponectin concentrations are decreased with insulin resistance (such as in type 2 diabetes [T2D]). Obesity is associated with adiponectin deficiency, which makes this hormone a possible target for therapeutic interventions.[40]

Ghrelin

Ghrelin is a potent orexigenic hormone that stimulates food intake. Its levels are elevated 1 to 2 hours before a meal and are decreased soon after. Exogenous ghrelin is associated with increased food intake, reduced resting energy expenditure, and catabolism in adipose tissue.[40]

Obesity and Associated Conditions

Conditions Associated With Weight Gain

Hypothyroidism, Cushing's syndrome, polycystic ovary syndrome (PCOS), and certain neurologic problems are associated with excessive weight.[41]

Hypothyroidism

With hypothyroidism affecting weight and obesity affecting thyroid function, the interrelationship between hypothyroidism and obesity is a complex one.[42] Thyroid hormones are linked to body composition because they are integral in basal metabolism and thermogenesis; they also affect glucose and lipid metabolism, fat oxidation, and food intake.[43] As stated above, an increase in thyroid-stimulating hormone (TSH) levels has been seen with an increase in BMI, suggesting that obesity has an impact on the hypothalamic-pituitary–thyroid axis,

leading to changes in thyroid function tests similar to the abnormalities seen in primary hypothyroidism.[44-46] However, weight gain associated with hypothyroidism is often a result of fluid retention; studies of body composition before and after treatment for hypothyroidism have shown that weight loss was the result of a decrease in lean body mass and not in fat mass.[47]

Cushing's Syndrome

Cushing's syndrome, which is a condition caused by long-term exposure to excessive glucocorticoids, is a rare disease that affects an estimated 10 to 15 people per million in the United States.[48] Patients with obesity who experience mild hypercortisolism, diabetes, and hypertension may have Cushing's syndrome.[49] Clinical features include sudden weight gain and central obesity.[50] A screening of patients who were obese (N = 150) showed that 9.33% had Cushing's syndrome. Unless the patient exhibits other clinical features such as poorly controlled hypertension, hypokalemia unresponsive to treatment, diabetes, or rapidly progressing osteoporosis, clinicians often do not screen patients with obesity for Cushing's syndrome. Tiryakioglu and colleagues reported that a screening program for patients with obesity resulted in the identification of 14 cases of Cushing's syndrome in 150 patients with obesity, suggesting that patients with obesity should routinely be screened for Cushing's.[51]

Polycystic Ovary Syndrome

PCOS is characterized by irregular menstrual periods, excess hair growth, infertility, severe acne, oily skin, ovarian cysts, patches of thickened dark skin, and obesity.[52] According to the American College of Obstetrics and Gynecology, approximately 80% of women with PCOS are obese, with prevalence rates 6- to 7-fold higher in morbidly obese women than in controls.[52,53] Increased body fat is associated with increased androgen levels and increased metabolic risk, so it is recommended that women with PCOS be screened for increased adiposity.[54] Losing weight can have a positive effect on hormone balance in these women. A small study evaluated the response of PCOS symptoms and hormone levels to weight loss in women who were morbidly obese. Premenopausal women undergoing bariatric surgery were screened, and 17 out of 36 were found to have PCOS. At 1-year follow-up, mean weight loss was 41 ± 9 kg (95% CI, 36-47 kg; P <.001). Women had less hirsutism and normalization of total and free testosterone, androstenedione, and dehydroepiandrosterone concentrations. A restoration of insulin sensitivity and increase in circulating sex hormone-binding globulin were also observed.[53]

Comorbid Conditions With Obesity as a Risk Factor

Patients with obesity are at increased risk of morbidity from dyslipidemia, T2D, hypertension, coronary heart disease, stroke, gallbladder disease, respiratory problems, sleep apnea, osteoarthritis, and some cancers.[1] Compared with adults of normal weight, adults with a BMI of 40 kg/m^2 or higher had an increased risk of diabetes (OR, 7.37; 95% CI, 6.39-8.50), hypertension (OR, 6.38; 95% CI, 5.67-7.17), hyperlipidemia (OR, 1.88; 95% CI, 1.67-2.13), asthma (OR, 2.72; 95% CI, 2.38-3.12), arthritis (OR, 4.41; 95% CI, 3.91-4.97), and fair or poor health (OR, 4.19; 95% CI, 3.68-4.76).[55] A study (N = 300) examining the mean values and heritability of 3 global and 11 regional obesity measures in siblings with or without hypertension suggested a genetic link between hypertension and obesity.[56] On average, siblings with hypertension were more obese and had more centrally distributed body fat. A pooled analysis of 20 studies reported that heart disease was the most common underlying cause of death in patients with class III obesity (BMI 40.0-59.9 kg/m^2), followed by cancer and diabetes. There was a 2.57-fold (95% CI, 2.41-2.74) increased risk of death in people with a BMI of 40.0 to 59.9 kg/m^2 versus 18.5 to 24.9 kg/m^2. In addition, people with a BMI of 40 to 59 kg/m^2 live 6.5 to 13.7 years less than those with a BMI of 18.5 to 24.9 kg/m^2.[57]

Rheumatoid Arthritis

Obesity has been shown to increase the risk of chronic conditions such as rheumatoid arthritis (RA). A meta-analysis of 13 studies, involving 400,609 participants, found that the relative risk (RR) of RA was 1.21 (95% CI, 1.02-1.44) for patients who were obese and 1.05 (95% CI, 0.97-1.13) for patients who were overweight. A 13% increase in the risk of RA was seen for every 5 kg/m^2 increase in BMI.[58]

Nonallergic Rhinitis

Adults and children who are overweight or obese are at an increased risk of nonallergic rhinitis, with adjusted OR of 1.43 (95% CI, 1.06-1.93) for adults and 0.88 (95% CI, 0.63-1.22) for children.[59] However, being overweight or obese does not appear to increase the risk of allergic rhinitis.

Major Depressive Disorder

Obesity is also a risk factor for major depressive disorder (MDD). For women with a baseline BMI of

30 or higher, the odds of MDD rose significantly (OR, 5.25; 95% CI, 1.41-19.58) independent of other risk factors such as age, education, prior depressive symptoms, marital status, chronic disease, low social support, and financial strain.[60] Persons with a higher BMI showed a slightly increased risk of developing depression (over a 6-year study period).[61] However, no relationship has been found between BMI and the persistence of depression. A temporal connection was also reported between obesity and general anxiety disorder (GAD). Women with a BMI of 30 or higher had a greater chance of developing GAD (OR, 6.27; 95% CI, 1.39-28.16); this was not found for women with a baseline BMI of 25 or higher (OR, 2.15; 95% CI, 0.78-5.93).[60] Similarly, a meta-analysis showed that baseline excess weight was associated with depression in people 20 years or older, but not younger.[62] People who were obese had a 55% increased risk of depression, and people who were depressed had a 58% increased risk of becoming obese.

Cancer

Additionally, patients who are obese have an increased risk of cancer. Prospectively collected data from the UK Clinical Practice Research Datalink were evaluated, including BMI values and the prevalence of 22 different cancers for 5.2 million people. The mean BMI of the population was 25.5 kg/m^2; 3.8% developed any cancer, and 3.2% developed 1 of the 22 cancers recorded in the study. Thirteen of the 22 cancers were associated with being overweight or obese; 41% of cases of uterine cancer and more than 10% of gallbladder, kidney, liver, and colon cancers were attributable to being overweight or obese. Higher BMI was positively correlated with an increased risk of uterine, gallbladder, kidney, cervical, and thyroid cancers, along with leukemia, and positive associations were seen with liver, colon, ovarian, and postmenopausal breast cancers.[63] A similar relationship between obesity and cancer was observed in cancer-related deaths in the United States. Death from cancer was attributed to being overweight, and obesity ranged from 4.2% to 14.2% for men and 14.3% to 19.8% for women. If people could potentially maintain a BMI under 25 kg/m^2, an estimated 90,000 deaths per year from cancer could be avoided.[64]

Pharmacotherapy for Other Conditions and Associated Weight Gain

Several medication classes have been associated with weight gain, including antidepressants, atypical antipsychotics, antiepileptic drugs, and beta-blockers.

Antidepressants

Common treatments of MDD may increase the risk of obesity. Grundy and colleagues reported that women who took antidepressants were more likely to be obese (OR, 1.71; 95% CI, 1.16-2.52).[65] Weight gain appears to occur in a large proportion of patients taking antidepressants. One study of 362 patients (mostly women) showed that antidepressant use promoted weight gain in 55.2% of patients, with a mean gain of 4.97 ± 6.16 kg, usually occurring in the first 3 months of treatment. Treatment with escitalopram, sertraline, or duloxetine is associated with significant weight gain; patients gain 7% or more from their baseline weight in the first 3 months of use. Mirtazapine, citalopram, venlafaxine, or paroxetine is associated with a 20% or higher weight gain.[66]

Polypharmacy, either adding a second antidepressant or an atypical antipsychotic, may become necessary for the management of MDD. Examining antidepressant plus antidepressant co-treatment (AD + AD) versus antidepressant monotherapy (AD) showed that AD + AD therapy is associated with an increased risk of weight gain (RR, 3.15; 95% CI, 1.34-7.41; P = .009). Specific classes of antidepressants are associated with greater weight gain than others. For example, the addition of noradrenergic and specific serotonergic antidepressants (NaSSAs) to selective serotonin reuptake inhibitors (SSRIs) is associated with a greater incidence of weight gain than SSRI therapy alone. The RR of 7% or higher weight gain was 3.81 (95% CI, 1.37-10.55).[67]

Antipsychotics

Antipsychotics used as adjunctive treatment in MDD are associated with weight gain, diabetes, and lipid disorders. A randomized study examining the effectiveness of atypical antipsychotics reported a weight gain of more than 7% from baseline in 30% of patients taking olanzapine, 16% of patients taking quetiapine, 14% of patients taking risperidone, 12% of patients taking perphenazine, and 7% of patients taking ziprasidone.[68] Long-term treatment, even at low doses, can lead to increases in blood lipids, triglycerides, and glucose, eventually leading to weight gain.[69] It is recommended that potential weight gain be considered when selecting an antipsychotic and that patients be informed of the estimated weight gain for the medications.[15] Once an antipsychotic is prescribed, clinical guidelines recommend that clinicians monitor a patient's height, weight, BMI, and waist circumference throughout treatment with antipsychotics; if the patient gains 5% or more of his/her baseline weight, the clinician should consider a different antipsychotic.[70]

Sulfonylureas, Thiazolidinediones, and Insulin

Many treatments for T2D are associated with weight gain, with the potential of patients gaining up to 10 kg within 6 months after the start of treatment.[15] Weight gain of 3.0 kg has been reported for thiazolidinediones; sulfonylureas, 1.12 kg; and insulin, 1.7 to 2.5 kg.[15,71] Other classes of medications, such as sodium-glucose cotransporter 2 (SGLT-2) inhibitors, GLP-1 receptor agonists, and dipeptidyl peptidase 4 (DDP4) inhibitors, have been shown to be weight-reducing or weight-neutral therapies. Metformin is also associated with weight loss. Patients who are obese and require treatment for T2D should be prescribed weight-loss or weight-neutral medications as first- or second-line treatment. It is recommended that patients with obesity and T2D who require insulin also be prescribed metformin, pramlintide, or GLP-1 agonists to offset insulin-associated weight gain.[15]

Antiepileptic Drugs

Valproic acid, carbamazepine, and gabapentin are antiepileptic medications that are associated with weight gain. The most significant weight gain has been reported with valproic acid, in the range of 5 to 49 kg.[72]

Corticosteroids

Steroid therapy is essential to the treatment of inflammatory disorders; however, steroids are associated with weight gain. Glucocorticosteroid therapy is associated with a 4.4% increase in weight after a year of treatment, and that weight gain is often maintained even after glucocorticosteroid therapy is stopped.[73] Treatment guidelines recommend against chronic steroid treatment to avoid weight gain in individuals who are overweight or obese.[15]

Beta-blockers

Beta-blockers, which are used for migraine and myocardial infarction prophylaxis and for the management of hypertension and heart failure, have also been associated with a mean weight gain of 1.2 kg.[72] A study examined the effects of beta-blockers on weight loss and reduction of waist circumference in 3582 patients (173 were taking beta-blockers) involved in an intensive calorie-restriction program of 900 kcal/day. Participants taking beta-blockers lost a mean 0.67 kg less than participants in the control group and had a smaller decrease in waist circumference (–24.2 vs –25.2 cm, respectively).[74] The authors recommend that alternate hypertensive treatment should be considered for patients with obesity. Treatment guidelines recommend a selective or nonselective beta-blocker (eg, carvedilol or nebivolol) because these agents have less potential of weight gain.[15]

Conclusion

The paradigm shift from thinking of obesity as a character flaw to an understanding that it is a disease is monumental. Hopefully, this will motivate healthcare professionals to be proactive and intervene sooner when individuals are identified at risk or meet the definition of obesity. Prescribers and pharmacists should be aware of the pathophysiology of obesity to understand the rationale for medication therapy. Awareness of the risk factors of obesity, especially those that are preventable, is important so that clinicians can counsel patients on how to avoid or minimize them. Obesity is a serious public health concern, and the associated financial and health consequences to Americans can be addressed by prescribers and pharmacists.

Obesity is a complex interaction between multiple genetic, socioeconomic, and cultural factors that also are associated with existing or resulting comorbidities and their treatments. The prevalence of obesity continues to be high, as are associated comorbidities and healthcare costs. Early intervention and effective treatment of obesity are needed to reduce costs and improve outcomes for these patients.

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