Obesity as a Disease

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KEYWORDS

- Obesity • Metabolically healthy • Causes and mechanism
- Cardiovascular disease and metabolic syndrome

KEY POINTS

- Obesity is a complex disease with many causal factors.
- Obesity is associated with multiple comorbidities contributing to significant morbidity and mortality.
- Various peripheral and central mechanisms play a role in the development of obesity.

INTRODUCTION

Obesity is a complex, chronic medical condition with a major negative impact on human health.[1] Over the last 30 years, there has been an exponential growth in the prevalence of obesity worldwide with doubling rates for adult and childhood obesity (6–11 years) and tripling rates of adolescent obesity (12–19 years).[1,2] Obesity has become a public health burden with significant and profound impact on morbidity, mortality, and cost of health care.[1]

Obesity is often stigmatized and carries with it a false perception that it is caused mostly by lack of will leading to inappropriate dietary choices and physical inactivity. However, there is a rich evidence-based literature that presents obesity as a complicated chronic medical condition caused by the interplay of multiple genetic, environmental, metabolic, and behavioral factors. In 2008, an expert panel from the Obesity Society concluded "obesity is a complex condition with many causal contributors, including many factors that are largely beyond individuals' control; that obesity causes much suffering; that obesity causally contributes to ill health, functional impairment, reduced quality of life, serious disease, and greater mortality; that successful

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treatment, although difficult to achieve, produces many benefits." Obesity was thus recognized as a disease state. Acknowledging obesity as a serious public health threat, the American Medical Association also voted for obesity as a disease in June 2013. Several other societies have now recognized obesity as a disease (**Box 1**).[3,4] This recognition led the medical community and pharmaceutical companies to tackle this rising epidemic that affects 1 in 3 United States Americans.[5] Recently, the American Association of Clinical Endocrinologists and American College of Endocrinology concluded that a "more medically meaningful and actionable definition of obesity" was needed and hence published a position statement advocating for use of the word "adiposity based chronic disease or ABCD" for obesity to better describe the disease condition. Given such high prevalence of obesity and more than 30 medical conditions related to obesity, the disease has a significant impact on morbidity, mortality, and cost of health care. Obesity is a medical condition, a disease state, and should be treated as such.

Body mass index (BMI), calculated as kg/m^2, reflects body mass, in most but not all cases correlates well with the degree of obesity, and is a significant predictor of overall mortality with a reduction in median survival by approximately 2 to 4 years for persons with a BMI of 30 to 35 kg/m^2 and 8 to 10 years at a BMI of 40 to 45 kg/m^2,[6] even more with higher BMIs of longer duration. The increase in the prevalence of obesity has

Box 1
Associations or organizations that have declared obesity is a disease

- National Institutes of Health
- US Food and Drug Administration
- Federal Trade Commission
- American Medical Association
- World Health Organization
- American College of Physicians
- American Association of Clinical Endocrinologists
- American College of Cardiology
- The Endocrine Society
- American Academy of Family Physicians
- Institute of Medicine
- The Obesity Society
- World Obesity Federation
- American Heart Association
- American Diabetes Association
- American Academy of Family Physicians
- American Society for Reproductive Medicine
- American Urologic Association
- American College of Surgeons

Data from Kahan S, Zvenyach T. Obesity as a disease: current policies and implications for the future. Curr Obes Rep 2016;5(2):291–7; and Bray GA, Kim KK, Wilding JPH. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev 2017;18(7):715–23.

occurred in parallel with the increase in prevalence of other medical conditions considered as comorbidities, including diabetes, stroke, cardiovascular disease, hyperlipidemia, cancers, nonalcoholic fatty liver disease, pulmonary disease, polycystic ovarian syndrome (PCOS), and osteoarthritis. As expected, the increase in morbidity and mortality from these diseases, mainly due to obesity, has led to an increasing financial burden. The cost of extra medications for a man or woman with obesity is estimated to be an additional US$1152 per year and US$3613 per year, respectively.[7] Extrapolation of these costs at the national level shows an estimated US$190 billion per year (21% of total US health care expenditure) in costs for the treatment of obesity and obesity-related morbidities.[7] In summary, obesity is a highly prevalent disease and poses an enormous health and economic burden to society. This article reviews the mechanisms of obesity and its related comorbidities.

CAUSES OR MECHANISMS OF OBESITY

Obesity is a disease that has rapidly escalated over the past several decades and is caused by environmental, humoral, and genetic factors, likely working in combination. The environmental factors contributing to the increase in obesity include but are not limited to decreased physical activity; increased television watching times and sedentary lifestyle[8]; increased food consumption, particularly of energy-dense, high-calorie, palatable food served in increasing portion sizes[9,10]; and the use of medications with weight gain as a side effect.[11] However, despite most individuals being exposed to these environmental factors, not all of people become obese, suggesting differing genetic mechanisms that predispose certain individuals to developing obesity.

Many genes have been identified as potentially contributing to obesity, possibly acting in combination; studies with twins have shown relatively high heritability for eating behaviors (53%–84%).[12,13] One of the most well-studied is the fat mass and obesity-associated (FTO) gene, which exerts modest effects on its own and seems to be modified by lifestyle.[14] Relatively few individuals have monogenic forms of obesity, although up to 200 types of single gene mutations have been found to cause obesity.[15] There are relatively few well-known monogenic mutations that explain no more than 10% of extreme obesity cases, such as mutations in leptin or the leptin receptor[16] and the melanocortin-4 receptor.[17] Syndromic forms of obesity also make up a relatively small amount of clinical cases and are related to genetic disorders that include a distinct set of clinical phenotypes and also demonstrate obesity. For instance, some of the most common forms include WAGR (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation), Prader-Willi, Bardet Biedl, and Cohen syndromes.[18] Apart from genetics, certain other neuroendocrine causal factors for obesity include but are not limited to hypothyroidism, Cushing disease, pseudohypoparathyroidism, growth hormone deficiency, hypothalamic causes, and PCOS. Early referral to an endocrinologist and intervention is useful in patients suspected to have an underlying neuroendocrine or genetic cause for obesity.

More recently, studies have also implicated epigenetic factors, such as changes in DNA methylation, microRNA expression, and noncoding microRNAs, as contributing to obesity.[19–21] Unlike with genetics, epigenetics are susceptible to change throughout the lifespan and with lifestyle modifications through diet and physical activity. As research continues to grow in these areas, one begins to understand the complex gene-environment interactions that contribute to obesity and how these may be targeted as treatment.

To understand obesity further, one must examine the central nervous system (CNS) circuitry that controls appetite and how this may become dysregulated through the

gene-environment changes previously discussed. Although the oldest research focuses on changes in the homeostatic CNS control of eating in the hypothalamus, more recent research points to other networks, such as reward, emotion or memory, attention, and cognitive control as playing a more potent role in the control of appetite in humans.[22] The hypothalamus regulates homeostatic energy intake and expenditure, integrating hormonal signals from the periphery and communicating them to the rest of the CNS. For instance, leptin is secreted by adipose tissue and circulates proportionally to the amount of body fat mass, also responding to acute changes in energy deprivation.[23–25] At low levels of body fat, leptin circulates at lower levels and communicates with neurons in the hypothalamus to increase energy intake and decrease energy expenditure.[24] In obesity, the opposite occurs and leptin circulates at high levels; however, leptin does not decrease energy intake and increase energy expenditure due to leptin resistance or tolerance, demonstrating a resistance to the homeostatic control of eating.[26–28] Thus, homeostatic control of energy intake is more critical in states of starvation. Increasing evidence demonstrates that other peripheral molecules may act on several areas in the brain, such as glucagon-like peptide 1 (GLP-1) and its analogues, which have been shown to act on the attention and reward networks.[29,30] Other molecules that are secreted by the periphery and may act in the brain have not yet been studied in humans, including amylin, pancreatic hormones, myokines such as irisin, and others. These may prove to be potential targets for therapy.

Aside from the homeostatic system, other neural systems may be more potent in terms of regulating appetite and obesity. The reward system, in particular, has been suggested to be at the root of obesity.[31–51] Food is naturally rewarding and this system may be altered in patients with obesity, leading to and/or exacerbating weight gain. The 2 primary theories are that either a hyporesponsivity to rewards leads individuals to seek highly rewarding, high-fat or high-calorie foods, or there is a hyperresponsivity to food cues that leads individuals to increasingly eat highly palatable foods. These theories are supported by the observed lower availability of rewarding dopamine D2 receptors in individuals with obesity[52–56] and the heightened activity of brain areas responding to reward, such as the orbitofrontal cortex and nucleus accumbens, to visual food cues.[57–61] Emotions are also potent regulators of appetite because depressed mood and anxiety are comorbidities of obesity and related to central obesity in particular.[62–66] Indeed, stress is also known to cause changes in appetite that can lead to the development of obesity.[67] Memory, regulated by the hippocampus, may also influence eating, and impaired functioning of the hippocampus leads to increased food intake and obesity, which in turn leads to further impairment of the hippocampus.[68,69] Thus, reward, emotion, and memory all may influence eating and the development of obesity.

Higher CNS centers, such as those controlling attention and cognitive control, are also altered in obesity. Individuals with obesity and even normal weight individuals who later gain weight show more attention to food cues and attentional bias toward eating when sated.[70–75] Attention, controlled primarily by the parietal and occipital visual cortices, is generally increased for items of salience and in obesity these areas demonstrate increased activation to highly palatable food cues.[76,77] Cognitive areas in the prefrontal cortex exert control inappropriate behaviors, such as eating when full or eating unhealthy foods.[78] Individuals with obesity and normal weight individuals who later gain weight have shown impaired inhibitory control toward food cues[79–92] and even when performing tasks not related to food.[85,92] Cognitive control may also suppress reward-related responses and, in the case of obesity in which cognitive control is impaired, this may enhance the activation of the reward system.[93,94] Altogether, the control of eating in the human brain is complex and involves several cortical and subcortical networks.

Inflammatory links between obesity and insulin resistance (IR) or metabolic syndrome were suggested when increased tumor necrosis factor (TNF)-α expression was found in the adipose tissue of obese humans and rodents almost 20 years ago.[95] Further research demonstrated involvement of multiple inflammatory pathways and increased cytokine levels in the mechanism of obesity and obesity-related IR.[96,97] Along the same lines, De Souza and colleagues[98] found that rats subjected to long-term high-fat diet (HFD) had increased activation of Jun N-terminal kinase (JnK) and Nuclear factor kappa B (NF-κB) inflammatory pathways resulting in increased cytokines (interleukin [IL]-6, TNFα, and IL-1β) in the mediobasal hypothalamic region. They further demonstrated that this inflammation led to significant impairment in insulin and leptin signaling pathways.[98] These results have since been replicated by other investigators with consistent finds in mice and also other nonhuman primates.[99,100] At the cellular level, HFD-induced inflammation involves reactive gliosis of the hypothalamus in rats.[100,101] Reactive gliosis, which involves recruitment, proliferation, and morphologic transformation of astrocytes and microglia, is observed as early as 24 hours after starting an HFD diet in rats and resolves after 4 weeks of returning to a normal chow diet.[100,101] However, prolonged HFD diet has shown to result in more significant and irreversible changes in hypothalamus, including gliosis, loss of synapsis in proopiomelanocortin (POMC) neurons, and reduction of neurogenesis in the hypothalamic region, leading to structural changes in the blood brain barrier.[102]Although studies in rodents have provided some critical insights, they may not fully capture the complexity of the human CNS and obesity.

METABOLICALLY HEALTHY VERSUS UNHEALTHY

BMI is most frequently used for the classification of obesity. Mortality, morbidity, and complications increase with the grade of obesity. Grade II and III obesity (BMI equal to or greater than 35 kg/m^2 and equal to or greater than 40 kg/m^2, respectively) have been associated with increased risk of cardiovascular disease and comorbidities compared with grade I obesity (BMI 30–35 kg/m^2).[103–106] However, there is a known subset of the obese population devoid, in the short-term, of cardiometabolic complications such as diabetes mellitus, hyperlipidemia, IR, and cardiovascular disease, and hence are known as metabolically healthy obese (MHO), which has gained much interest. Although several studies have better characterized this phenotype using cutoffs for blood pressure, IR measures (eg, fasting plasma glucose, hemoglobin [Hb]A1c, homeostatic model assessment [HOMA]- insulin resistance [IR]), and cholesterol (high-density lipoprotein [HDL], low-density lipoprotein [LDL], Total cholesterol (TC), Triglyceride (TG), or TG/HDL ratios), there are no set criteria that distinguish metabolically healthy from metabolically unhealthy obese (MUO) persons.[107,108] Importantly, none of the current guidelines distinguish between these 2 phenotypes and, therefore, recommend lifestyle interventions as the first-line treatment of all patients with obesity. As opposed to the MHO phenotype, another phenotype that has gained interest is the metabolically unhealthy normal weight (MUHNW) phenotype. These patients are not obese per BMI criteria but have a dysfunctional metabolic profile as would be typically found with obesity. This is more commonly observed with patients of Asian origin, particularly the Asian Indian and Chinese subgroups, who tend to have a normal BMI but increased visceral adiposity. Data from the Korean National Health and Nutrition Examination Survey showed a 12.7% prevalence of MUHNW phenotype among normal-weight individuals (BMI <25 kg/m^2) and 47.9% prevalence of the MHO phenotype among obese population (BMI >30 mg/m^2).[109] Several studies have examined all possible transitions among MHO, MUO, and MUHNW and many have suggested

that MHO is a state in time and that the natural progression would eventually be to the MUO state.[110,111] A recent study followed more than 3500 women for 6 years to study the progression of different metabolic phenotypes. The study concluded that highest rate of metabolic improvement was noted in MUHNW women, whereas the highest rates of metabolic deterioration was seen in MHO women.[112] A third of women with the MHO phenotype transitioned to a MUO state at the end of 6 years,[112] suggesting that, given enough time, many patients who appear to be MHO would convert to MUO. A recent study involving 15,000 participants in the third National Health and Nutrition Examination Survey (NHANES) showed that patients with normal BMI but higher waist or hip ratio (>0.85 in women and >0.90 in men) had higher mortality compared with patients with normal fat distribution irrespective of BMI.[113] A combination of central adiposity along with metabolic status seems to be the most consistent and significant predictor of morbidity and mortality. Hence, weight loss and lifestyle changes should be recommended even for MHO patients.

Obesity is associated with an increased risk of more than 20 medical conditions, such as diabetes mellitus type 2, hypertension, dyslipidemia, Cardiovascular disease (CVD), stroke, sleep apnea, urogenital issues, gall bladder disease, and multiple cancers (**Fig. 1**). Not only does obesity have significant impact on physical health but also tremendously affects patients psychologically and is associated with very poor self-esteem, increased rates of depression, and poor quality of life. Obese patients often suffer from discrimination and social stigmatization. There are multiple pathophysiological mechanisms that interplay in development of comorbidities in relation to obesity (**Fig. 2**). Next a few of the major obesity-related comorbidities and their mechanisms are discussed.

METABOLIC SYNDROME, DIABETES, AND CARDIOVASCULAR DISEASE IN RELATION TO OBESITY

Obesity is associated with increased mortality.[6] Each 5 kg/m^2 increase in BMI above 25 kg/m^2 increases overall mortality by approximately 30%; vascular mortality by

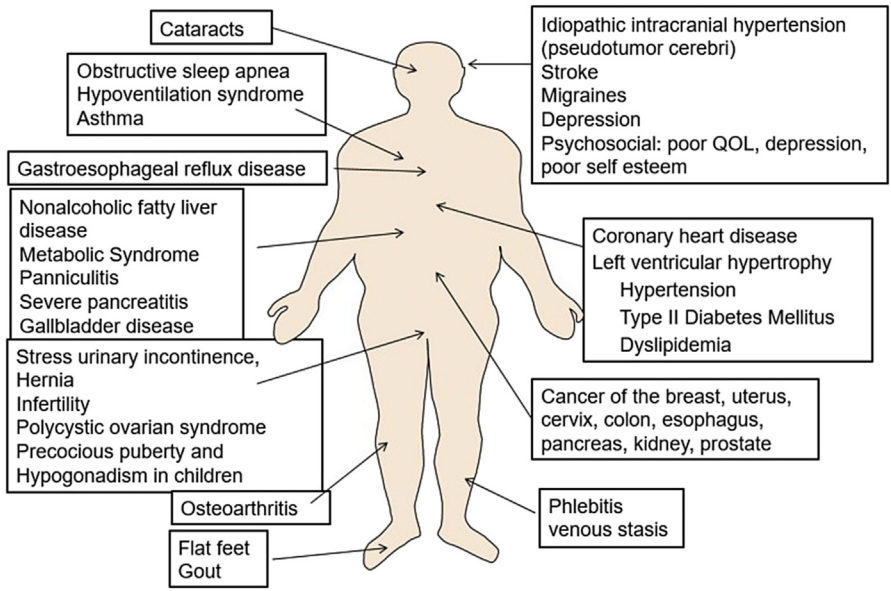

Fig. 1. Comorbidities associated with obesity. QOL, quality of life.

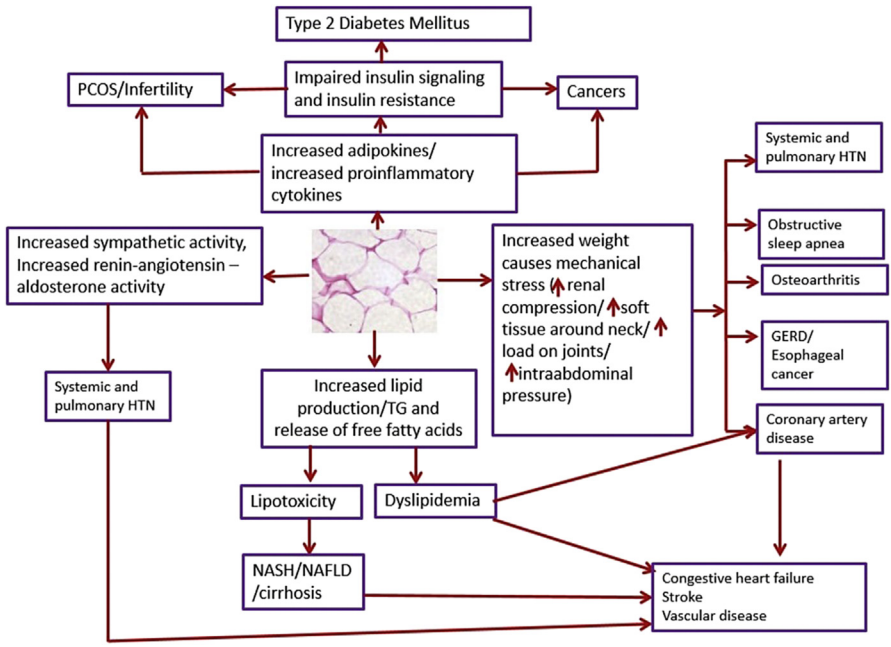

Fig. 2. Pathways through which obesity leads to comorbidities. GERD, Gastroesophageal reflux disease; HTN, Hypertension; NAFLD, Nonalcoholic fatty liver disease; NASH, Nonalcoholic steatohepatitis.

40%; and diabetic, renal, and hepatic mortality by 60% to 120%.[6] At 30 to 35 kg/m^2, median survival is reduced by 2 to 4 years and at 40 to 45 kg/m^2 by 8 to 10 years.[6] The main causes of death include ischemic heart disease,[114] stroke[115] and diabetes-related complications.[6] The vicious cycle resulting in increased mortality in obesity involves IR, as well as all the components of metabolic syndrome (ie, hyperglycemia, dyslipidemia, and hypertension).

Obesity is associated with an increased risk for IR.[116] HOMA-IR correlates strongly with visceral fat mass [correlation factor (r) r = 0.570], total fat mass (r = 0.492), BMI (r = 0.482), and waist circumference (r = 0.466).[116] In contrast, lower extremity fat is not associated with HOMA-IR.[116] Adipose tissue controls metabolism by regulating the levels of nonesterified fatty acids (NEFAs), glycerol, proinflammatory cytokines, cells of immune system (macrophages, lymphocytes), and hormones such as leptin and adiponectin.[117] In obesity, the production of most of these molecules is increased and can affect insulin sensitivity through multiple pathways. Much is known about the biochemical and physiologic effects of obesity on IR. First, increased NEFA delivery and consequently elevated intracellular levels compete with glucose for substrate oxidation, resulting in inhibition of important enzymes (ie, phosphofructokinase, pyruvate dehydrogenase, hexokinase II) participating in glycolysis.[117] Additionally, fatty acid metabolites (ie, ceramides, diacylglycerol [DAG], fatty acyl-coenzyme A [acyl-CoA]) are increased, resulting in serine or threonine phosphorylation of insulin receptor substrate (IRS)-1 and IRS-2, reduced activation of phosphatidylinositol (PI)-3-kinases, and inhibition downstream of insulin-receptor signaling.[117,118] Second, increased secretion of TNFα, IL-6, and monocyte chemoattractant protein-1 activate proinflammatory signaling pathways in adipose tissue, liver, and muscle.[119] The proinflammatory signaling pathways involve activation of JNK and inhibitor of nuclear factor kappa-B kinase, leading both

to phosphorylation of IRS-1 and IRS-2, as well as to increased transcription of inflammatory genes.[119] Finally, increased levels of proteins, such as retinol-binding protein-4 and leptin, and reduced levels of adiponectin affect insulin sensitivity, by impairing PI (3) kinase signaling in muscle, inducing the expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase in the liver and stimulating fatty acid oxidation. The net outcome of all the pathophysiological changes in obesity is the development of liver and muscle IR, depicted by impaired suppression of glucose output from the liver and reduced glucose uptake from the muscle.[119–121]

Obesity is strongly associated with the development of type 2 diabetes. IR in the liver, muscle, and adipose tissue demands an increase in insulin supplied by the pancreatic β cells to maintain normoglycemia.[117] Healthy pancreatic β cells can improve their function and mass to satisfy the increasing demands.[122] However, genetic and environmental factors may lead to a β cell dysfunction.[117,119] Certain mutations or single nucleotide polymorphisms in genes involved in critical β cell-pathways can directly affect beta cell function and survival.[123] Genetically susceptible β-cells will fail to satisfy the high insulin demands deriving from chronic increased caloric intake and reduced physical activity, resulting in hyperglycemia.[124] The combination of hyperglycemia and hyperlipidemia (glucolipotoxicity) will accelerate β cell death, reduce insulin secretion, and aggravate hyperglycemia.[125] The relative risk for incident diabetes is 1.87, 1.87, and 1.88 per standard deviation of body mass index, waist circumference, and waist or hip ratio, respectively.[126] The adjusted relative risk for incident type 2 diabetes is 8.93 in MUHO and 4.03 in MHO adults compared with healthy normal-weight individuals.[127] This shows that even healthy obesity is not a harmless condition. Additionally, the age of obesity onset is important. Individuals with childhood onset of obesity have approximately 24-fold risk of HbA1c greater than 7% after 45 years. This risk is lower for young (16-fold) and middle (2.99-fold) adulthood obesity onset.[128]

Obesity is associated with dyslipidemia. This is characterized by increased plasma triglycerides and apolipoprotein B (apoB), as well as by decreased HDL-cholesterol (HDL-C).[129] Accumulation of the lipolytically active visceral fat in combination with the development of IR lead to a prominent increase in the flux of free fatty acids in the portal vein and, subsequently, in the liver, resulting in high triglyceride synthesis.[129] In addition, hepatic secretion of very low density lipoprotein (VLDL)-apoB is increased and the catabolism of HDL-apoA-I is induced. A BMI greater than 30 kg/m^2 is associated with an odds ratio of approximately 6 for low HDL-C and approximately 3 for increased total cholesterol.[130] Given the high relevance between dyslipidemia and atherogenesis, the obesity-mediated changes in lipid profile significantly contribute to the increased cardiovascular mortality.

Obesity promotes hypertension.[131] Individuals with BMI greater than 30 kg/m^2 have a 9-fold increased risk for high blood pressure.[130] Several mechanisms are implicated in the pathophysiology of obesity-related hypertension. First, obesity is characterized by altered hemodynamics due to volume overload.[132] This results in high cardiac output, increased peripheral resistance, and pressure overload. Second, high salt intake due to increased food consumption impairs sodium homeostasis promoting hypertension.[131] In addition, higher sodium reabsorption combined with elevated renal blood flow and glomerular hyperfiltration lead to renal structural changes and dysfunction, contributing to elevated blood pressure.[133,134] Furthermore, hormonal changes (hyperaldosteronism, hyperinsulinemia, and hyperleptinemia) result in activation of the renin-aldosterone-angiotensin system, stimulation of sympathetic nervous system, and decrease of parasympathetic activity.[131,135] Finally, endothelial dysfunction combined with vascular stiffness, increased oxidative stress, and chronic low-grade inflammation lead to vascular injury.[131,136–138] All these hormonal and vascular changes increase blood pressure and lead to hypertension.

Altogether, obesity is associated in a causal way with IR, dyslipidemia, hypertension, hyperglycemia, and diabetes. This explains the high risk of cardiovascular events in obesity and specifically of myocardial infarction, heart failure, and stroke.[139–141] The metabolic consequences of obesity (ie, hypertension, dyslipidemia, diabetes), mediate 44% of the excess risk of obesity for coronary heart disease and 69% of stroke. Among them, hypertension seems to have the most important role, accounting for 31% of the excess risk for coronary heart disease and 65% for stroke.[140] However, even MHO individuals have a 2-fold relative risk of CVD events compared with healthy normal-weight people.[142] In addition, the risk seems to be much higher in adults with obesity who were overweight or obese as children.[143] In summary, early onset, long-duration, and excessive obesity aggravate the CVD risk and, consequently, cardiovascular-related mortality.

OTHER COMPLICATIONS AND COMORBIDITIES ASSOCIATED WITH OBESITY

Polycystic Ovarian Syndrome

There is a confirmed relationship between obesity and PCOS. The prevalence of obesity in women diagnosed with PCOS is as high as 80% in the United States.[144] PCOS is characterized by increased production of androgens, which affects the hypothalamus-hypophysis-ovarian axis (HHOA) and may affect fertility.[145] Obesity is considered a factor in the pathophysiological cascade of PCOS through 2 major pathways: IR and hyperandrogenism.[145] However, obesity can also be considered a complication of PCOS, considering the presence of increased visceral fat in PCOS.[146] Hyperinsulinemia and IR have shown to decrease sex hormone-binding globulin, leading to higher levels of free androgens in PCOS. This is indirectly conducted through downregulation of hepatic nuclear factor–4α.[145] Increased insulin levels is a key factor in the development of the disease and has shown to increase pulsatility of the HHOA, resulting in increased ovarian synthesis of androgens.[147] This correlation is further evidenced by use of metformin in the treatment of PCOS. Metformin improves IR, and at the same time improves the hyperandrogenemia in PCOS.[148] High insulin levels also stimulate the hypothalamus-hypophysis-adrenal axis (HHAA), resulting in enhanced secretion of adrenal androgens.[149]It was reported that 45% of girls with premature pubarche developed PCOS later in their lives.[150] Obesity in adolescence has been associated with hyperandrogenism due to the stimulatory effect of insulin and Insulin-like growth factor 1 (IGF-1) on steroidogenic enzymes in the adrenal glands.[151] Baptiste and colleagues[152] demonstrated another feedback mechanism in which hyperandrogenemia leads to increased free fatty acid levels and IR through serine phosphorylation of IRS-1. The third mechanism that explains the hyperandrogenism in patients with PCOS and obesity is hyperleptinemia, which leads to decreased production of the soluble leptin receptor with subsequent elevation in androgen levels.[151] Effective weight-loss measures have been reported to improve the regularity in menstruation.[153] More than 35% of women who lost greater than 5% of their body weight were reported to regain either their fertility or normal menstrual cycles in a study by Kiddy and colleagues.[154] Importantly, although much less common, PCOS is also reported in a subset of lean women, suggesting a different mechanism, such as increased androgen receptors sensitivity or the increased activity of HHAA.[149,155] However, a strong relationship exists between PCOS, hyperinsulinemia, and hyperandrogenism in relation to obesity that needs to be further explored.[156]

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) prevalence has been demonstrated to be high in patients with obesity[157] and coincides with several comorbidities, such as hypertension,

type 2 diabetes mellitus, dyslipidemia, nonalcoholic fatty liver disease, congestive heart failure, and atrial fibrillation.[158,159] The prevalence of OSA is almost double in obese compared with lean individuals.[160] With the rising rates of obesity, the prevalence of OSA is expected to increase in the next few years.[161] Obesity is thought to be a predisposing factor of OSA due to fat deposition around the upper respiratory airways, chest wall, and truncal fat, which leads to a decrease in the functional residual capacity.[162] This is further evidenced by the direct correlation that exists between the apnea hypoxia index and adiposity measures.[160] Furthermore, treatment of OSA with continuous positive airway pressure has shown to improve visceral obesity, suggesting a role of OSA in the pathogenesis of obesity.[163] In physiologic conditions, the collapsibility of the upper airway tract is determined by the critical closing pressure inside the pharynx.[164] This pressure in maintained by a balance between the mechanical and neurologic factors, which keeps it toward the positive side.[165] This means that when the pressure inside the lumen decreases in rapid eye movement sleep, a neuromuscular impulse, also called negative pressure reflex, is elicited to dilate the muscles and restore its patency.[166] In OSA, this balance seems to be disturbed, either by the increased mechanical effect of anatomic alteration due to adiposity of the neck region or a defect of the neuromuscular signaling in these cases, or the combined effect of both factors.[167] The reflex dilatation is not sufficient because it requires higher level of activity to overcome the higher tissue mass in obesity.[165] In addition, obesity increases the soft palate length, which was found to be correlated with the severity of OSA.[168] Another proposed mechanism for the pathophysiology of OSA related to obesity is snoring.[169] The inflammatory process resulting from the vibration related to snoring leads to peripheral nerve damage, especially those responsible for the negative pressure reflex.[170] Studies have shown that decrease in body weight through lifestyle modification could improve all the symptoms related to OSA.[171]

Cancer

Obesity is a known risk factor for many cancers including pancreatic, liver, colorectal, postmenopausal breast cancer, esophageal adenocarcinoma, endometrial, and kidney cancers.[172,173] One in 5 of all cancers are thought to be related to obesity.[174] There is growing evidence that increasing BMI is associated with a parallel increase in risk of cancer with rates as high as 70% in BMI greater than 40 kg/m^2.[175] Mortality rates are 52% higher in obese men and 62% higher in obese women compared with the normal-weight population.[174] Furthermore, weight loss after bariatric surgery is associated with a decrease in the cancer risk, suggesting importance of healthy weight in cancer prevention.[176] Several mechanisms linking cancer and adiposity have been proposed. Etiologic factors include increase in IR, elevated IGF-1 levels, low-grade chronic inflammation due to obesity, dysregulation of adipocyte-derived factors, and alteration in sex hormones.[177,178] Although hypoadiponectinemia is associated with IR, in type 2 diabetes, cancer, and atherosclerosis, adiponectin has been shown to increase insulin sensitivity and has demonstrated antiproliferative effects, making it a potential diagnostic tool and therapeutic option in cancer.[179,180] Research is underway to decipher the various other unknown mechanisms and pathways involved in obesity and cancer.[181] Similarly, in humans, high levels of cytokines, such as IL-6 and TNF, have been shown to cause hepatic inflammation, which further activates the Janus kinase–Signal Transducer and Activator of Transcription pathway that includes oncogenic transcription factor STAT3.[182,183] Mechanisms linking obesity and cancer, however, still remain unclear and much research is needed to establish these links. All in all, healthy weight has multiple health benefits and thus the obesity pandemic needs to be addressed rather urgently.

SUMMARY

Obesity has emerged as an epidemic that poses an unprecedented public health challenge. Historically known to be a rare disease of the affluent, this disease has now flipped the coin and is more prevalent among the lower socioeconomic and less-educated classes. Although multiple risk factors have been identified for obesity, a deeper understanding of how these factors interact is yet to be determined. Major determinants and contributors of the obesity epidemic are the highly processed, high-calorie food available in large portions and at a cheaper rate, along with physical inactivity and increased screen time. These environmental changes overlay genetic and epigenetic mechanisms to regulate adiposity and lead to the development of obesity in many individuals. With increasing trends, this disease is also associated with a wide variety of complications and comorbidities, adding to the socioeconomic burden. Increasing trends of diabetes, hypertension, cardiometabolic disease, cancers, and mortality are just a few of the major comorbidities associated with obesity that lead to significant economic burdens.

Significant reductions in the cost of health care could occur if the progress of the rising trends of obesity could be slowed. Although various guidelines recommend a combined approach to treatment and pharmacotherapy as only an adjunct to diet and exercise, antiobesity medications are still underused in health care. Clearly, there is a need to generate awareness, not only among the general public but also among the medical community, for proper utilization of currently available therapies. Although there is good evidence that obesity is a daunting public health challenge, there are few effective programs and strategies to combat this epidemic. Although multiple interventions at many levels and for a long period of time would be required to achieve reversal of obesity epidemic, the declaration of obesity as a disease by AMA and multiple other organizations is the first step. Using similar to criteria for other disease states, obesity has been determined to be a disease state for several reasons, including

1. It is associated with impaired body function.
2. Although precipitated by environmental factors acting on a specific genetic predisposition, the final common pathways leading to obesity (or, obesities) signifies abnormal physiology.
3. It exacerbates or accelerates hundreds of comorbid disease states.
4. It is associated with substantial morbidity and mortality or premature death.

The determination that obesity is a disease state ultimately dictates and energizes practitioners toward an appropriate approach to obesity and allows a more effective strategy to marshal resources and tools, define clinical strategies, and structure payment policies to effectively combat this twenty-first century epidemic. Ultimately, this is expected to lead to a better understanding, prevention, and treatment in the not so distant future. Consequently, recognition of the problem would certainly help to allocate more resources and increase more awareness to decelerate the epidemic of obesity. There is an urgent need to draw public and government interest to allocate more resources, awareness, education, and research to curb the obesity epidemic in large populations worldwide. Recent study of obesity and better understanding of underlying mechanisms is expected to lead to pharmacologic treatments reaching the therapeutic armamentarium in the near future. Obesity is now considered a chronic disease state that needs a chronic treatment.

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