Review Article

Physiologic and pharmacologic considerations in morbid obesity and bariatric anesthesia

ABSTRACT

Obesity is a growing worldwide health hazard that is characterized by excess malnutrition. Excess food intake leads to dysregulated energy homeostasis and increased adiposity, activating pro-inflammatory physiologic pathways that can contribute to the chronic inflammatory state associated with many chronic illnesses. Obesity is a preventable illness, but its multifaceted etiology, including genetic, behavioral, and environmental variables, is critical to understanding its epidemiology and pathophysiology. Obesity is a critical predisposing factor for illnesses including type II diabetes, cardiovascular disease, and cancer, with higher morbidity and death. Obesity rates are rising, and so will the need for perioperative anesthesia for subjects with obesity. Obesity epidemiology, biochemistry, and pathophysiology are significant concepts in perioperative anesthesia management for subjects with obesity. To provide optimal intraoperative care for subjects with obesity, preoperative cardiovascular assessment for coronary artery disease and drug monitoring is required. Individuals suffering from obesity have significantly higher oxygen consumption rates and a higher risk of desaturation and surgical complications. Individuals suffering from obesity require specialized perioperative treatment related to higher prevalence of perioperative complications.

Key words: Anesthesiology, bariatrics, bariatric anesthesia, morbid obesity, obesity

Introduction

Obesity is a complex chronic health condition in which a surplus of adipose tissue mass leads to excess body weight for a given height.[1,2] Although obesity is viewed as a preventable disease, a multifactorial etiology incorporates environmental, behavioral, socioeconomic, genetic, and physiologic mechanisms.[3] Obesity leads to a state of chronic energy imbalance in which increased adiposity can alter metabolic activity. This dysfunctional metabolic activity yields a chronic inflammatory condition marked by an imbalance between pro-inflammatory and anti-inflammatory adipokines.[3] This state of chronic inflammation is believed to predispose obese individuals to various chronic diseases and metabolic disorders.

Obesity is typically measured utilizing body mass index (BMI) as a parameter, defined by the ratio of your height to your

Access this article online

Website: www.saudija.org

DOI: 10.4103/sja.sja_185_22

Quick Response Code

How to cite this article: Brondeel KC, Lakatta AC, Torres GB, Hurley JJ, Kunik IL, Haney KF, *et al.* Physiologic and pharmacologic considerations in morbid obesity and bariatric anesthesia. Saudi J Anaesth 2022;16:306-13.

Kimberley C. Brondeel, Alexis C. Lakatta, Grant B. Torres, Joshua J. Hurley[1], Illan L. Kunik, Kaley F. Haney, Elyse M. Cornett[2], Alan D. Kaye[3]

Department of Medicine, University of Texas Medical Branch, 301 University Blvd, Galveston, TX, [1]Anesthesiology Resident, LSU Health New Orleans, 433 Bolivar St, New Orleans, LA, [2]Department of Anesthesiology, LSU Health Shreveport, 1501 Kings Highway, Shreveport, LA, [3]Department of Anesthesiology, Louisiana State University Health Sciences Center, Shreveport, LA, USA

Address for correspondence: Dr. Elyse M. Cornett, Assistant Professor, Department of Anesthesiology, LSU Health Shreveport, Shreveport, LA, USA.
E-mail: elyse.bradley@lsuhs.edu

Submitted: 25-Feb-2022, **Accepted:** 26-Feb-2022, **Published:** 20-Jun-2022

weight and expressed in units of kg/m^2. It is universally accepted as an indication of the relative amount of body fat relative to an individual's frame, correlates with various disease pathophysiology, and assists in stratified treatment guidelines and public health policies.[4,5] The World Health Organization (WHO) defines obesity as a BMI ≥30 kg/m^2, and further classifies obesity into Class I (30–34.9 kg/m^2), Class II (35–39.9 kg/m^2), and Class III (≥40 kg/m^2) obesity.[6] BMI ≥40 kg/m^2 has been historically referred to as morbid, severe, or extreme obesity. Still, given the negative connotation towards patients, it is clinically referred to as Class III obesity. The Center for Disease Control (CDC) states that the prevalence of obesity in the United States has increased significantly since 2000, with greater than 40% of the national adult population categorized as obese per BMI parameters.[7] Obesity is also an increasing global concern, as the World Health Organization (WHO) estimates nearly 13% of the world's adult population (age 18 years or older) was categorized as obese in 2016 and has nearly tripled since 1975.[8]

With the continued rise in prevalence among adults and various associated disease states, obesity can become challenging to manage from a pharmacologic and perioperative standpoint. Perioperative obesity management incorporates screening for associated health concerns such as coronary artery disease (CAD), altering current medication regimens, managing difficult airways with regards to intubation, increased risk of desaturation, and significant risk of postoperative complications.[9–11]

The present investigation provides a broad overview of the epidemiology, biochemistry, pathophysiology, pharmacological interventions, and perioperative management of obesity.

Epidemiology

The prevalence of obesity has continued to rise in both the United States and globally since the 1980s despite the view that it is a preventable disease.[7,8] The WHO estimated that 1.9 billion adults over the age of 18 are considered overweight (BMI greater than 25 and less than 30), with approximately 650 million adults categorized as obese.[8] Obesity is not just affecting adults; as the WHO reported that in 2019, over 39 million children under the age of 5 could be categorized as either overweight or obese, as well as approximately 340 million children and adolescents between the ages of 5 and 19, worldwide.[8]

In the United States specifically, obesity has continued to rise significantly. Obesity prevalence among adults over the age of 20 in the United States has increased from 30.5% in 1999–2000 to 42.4% in the most recent national data collected in 2017–2018.[12] The age-adjusted prevalence of severe obesity among adults in the United States was 9.2% per the 2017–2018, a significant increase from a prevalence of 4.7% in 1999–2000.[7] The WHO projects that the increasing prevalence of obesity will continue trending upward.[13,14] It is estimated that by 2030, nearly 1 in 2 adults will be obese, and 86.3% of adults will be overweight.[14,15] It is also estimated that by 2030, 1 in 4 US adults will be categorized as severely obese per BMI, with severe obesity becoming the most common BMI category among women, low-income adults, and non-Hispanic black adults.[14]

The rising prevalence of obesity is concerning due to high correlations between obesity and chronic diseases, increasing morbidity and mortality. A raised BMI has been shown to significantly increase the risk for cardiovascular disease (CAD being a leading cause of death), hypertension, diabetes, musculoskeletal disorders like osteoarthritis, and cancers such as breast, liver, and kidney.[3,8] In children, obesity has been linked to disabilities and premature death.[8,16] Due to the increasing prevalence of obesity and the associated diseases, it is estimated that by 2030 18% of total healthcare costs in the US will be attributable to obesity, with an estimated 956.9 billion dollars spent on obesity and obesity-related diseases.[15]

Related to the complex etiology of obesity and varying factors that play a role, continued efforts are being made to understand the clinical significance of disease progression, morbidity, and mortality, and factors that can be done to help combat the increasing prevalence of obesity. Improved screening mechanisms among children and lifestyle modifications such as diet and exercise regimens have been shown to improve health outcomes among subjects suffering from obesity. Additionally, research continues to advance other mechanisms to combat this growing global health problem.[3,16]

Biochemistry

Obesity is a biochemically complex condition that can be summarized as a dysfunction of energy homeostasis. There is excessive energy intake in comparison to energy expenditure, resulting in the accumulation of surplus adipose tissue.[2] As an energy reserve, adipose tissue reacts to alterations in energy status; during energy intake surplus, 60%–80% of the excess calories are stored as lipids, and during nutrient-deficient conditions, adipose tissue undergoes lipolysis to supply other tissues with energy.[2,17] During chronic excess energy intake conditions like obesity, there is an increased expansion

of adipose tissue by either hypertrophy or hyperplasia.[17] The energy imbalance in obesity is due to a wide variety of factors related to chemical signaling, genetics, environment, and behavior.

Within the central nervous system (CNS), the critical regulator of energy homeostasis is the arcuate nucleus (ARC) of the hypothalamus. It signals the body's energy state through orexigenic and anorexigenic neurons via the melanocortin system.[18] Additionally, the ARC receives and interprets peripheral metabolic hormonal signals via ghrelin and leptin, which are considered biomarkers of obesity.[19] Leptin is a cytokine produced and secreted into the bloodstream by adipose tissue whose concentration in the serum is directly proportional to the amount of energy reserves that exist in the form of adipose tissue. It functions as a neurohumoral communicator between modulators of energy homeostasis.[20] After crossing the blood-brain barrier, leptin binds to the leptin receptor (LepR), conveying satiety and inducing anorexigenic effects via the proopiomelanocortin (POMC)-associated neurons in the ARC, resulting in reduced food intake and increased energy expenditure.[21] In obesity, serum leptin levels are chronically elevated, resulting in selective leptin resistance.[22] This creates a paradoxical increase in extra calories and prevention of sustained weight loss.[23–25]

In contrast, ghrelin is an endogenous hormone secreted by the fundus of the stomach. Levels of ghrelin increase in settings of low nutrient availability and decrease during sets of sufficient or surplus nutrient availability.[26] It exerts orexigenic effects via neuropeptide Y (NPY) and agouti-related peptide (AgRP) associated neurons in the ARC, resulting in the sensation of hunger and increased food intake.[20] Research has suggested the high success rate of bariatric surgeries, such as Roux-en-Y gastric bypass, is due to the procedure disrupting normal secretion of ghrelin.[27]

Understanding the genetic basis of obesity is necessary to understanding the disease. Studies have revealed over 600 genes and chromosomal regions linked to obesity. The wide variation in phenotypic obesity suggests that many genes with minor effects accumulate to result in the varying phenotype of obesity.[28] Some of the proposed genetic contributors to obesity include CpG methylation, variations in receptors such as neuropeptide Y and melanocortin 4, as well as hyper-methylation of the promoter of serotonin transporter SLC64A.[29] People with different genetic alterations respond differently to treatment for obesity, suggesting there may be potential to treat obesity in a more targeted way in the future.[21]

Although genetics play a significant role in the etiology of obesity, other factors concurrently contribute to a person's predisposition to obesity, including behavior and environment.[2] In particular, there has been increased interest in epigenetic influences that occur due to fetal programming and intrauterine environments.[29] Preliminary evidence shows that increases in energy intake in pre-and post-natal life may have long-term programming effects on the hypothalamic satiety centers.[20,28] One study, in particular, showed that siblings of the same mother born after maternal bariatric surgery had a significantly lower prevalence of pediatric obesity than their siblings born before maternal bariatric surgery.[30,31] Additionally, in studies examining addiction-like behaviors about the mesolimbic dopaminergic pathway, over-eating can be seen in animal models after unrestricted access to specific diets.[32] Literature also suggests that visual cues for food increase brain response in individuals suffering from.[33,34] These findings reiterate the multifactorial etiology associated with obesity.

Pathophysiology

The pathophysiology of obesity primarily originates with physical inactivity and excessive caloric intake.[35] The excessive fat deposition—or adiposity, influences metabolic activity and results in the release of specific inflammatory markers by adipose tissue.[36] These inflammatory markers have influenced chronic diseases such as dyslipidemia, type II diabetes (T2D), and hypertension. Hormonal influences and immune abnormalities constitute new avenues in obesity-related pathophysiology as well.[37]

Research into the morbidity of obesity in past decades revealed that the distribution of fat plays the most significant role in obesity pathophysiology instead of body weight or total fat composition.[38] This notion is supported by the fact that multiple-organ-specific pathologies seen in morbid obesity are particularly notable with increased tendencies for intra-abdominal fat accumulation.[39] Intra-abdominal fat deposition or "central obesity" correlates strongly with excess visceral fat, considered the most metabolically active type of fat.[40] Excess intra-abdominal fat is accompanied by hormonal, inflammatory, and endothelial alterations often associated with obesity-related risks, such as insulin resistance, hypertriglyceridemia, and proatherogenic features.[41] This is further reinforced considering abdominal obesity is the most predominant manifestation of metabolic syndrome. Although metabolic syndrome also involves blood lipid disorders, inflammation, insulin resistance, and risks for CVD and T2D, the dysfunctionality of adipose tissue, particularly with intra-abdominal obesity, is paramount in the clinical diagnosis.[42]

Obesity has recently been referred to as a state of chronic low-grade inflammation, central to the pathogenesis of diseases such as CAD, atherosclerosis, and insulin resistance.[43,44] This derives from adipose tissue acting as a secretory organ that influences metabolism through modulation of energy expenditures, appetite, insulin sensitivity, immunity, and inflammation.[36] Adipocytes in white adipose tissue secrete "adipokines" that influence inflammatory conditions.[44] In obesity—namely in excessive visceral fat accumulation, the adipokines released are predominantly pro-inflammatory, creating an imbalance between pro-inflammatory (TNF-α, IL-6, ATII, resistin, visfatin) and anti-inflammatory (TGF-B, adiponectin) adipokines.[45] The inflammatory conditions established in dysfunctional adipose tissue depend upon and are exacerbated by immune dysfunction related to obesity-related abnormalities held.[2,46]

Adipose tissue macrophages are considered the chief source of cytokine production within adipose tissue. This is supported by studies revealing that macrophages in adipose tissue increase cytokine production with increased visceral fat deposits.[47] The two types of macrophages described in obesity are classified as M1 or M2 phenotypes, pro-inflammatory or anti-inflammatory, respectively. In individuals suffering from obesity, macrophages disproportionally shift from the anti-inflammatory M2 phenotype to the pro-inflammatory M1 phenotype; moreover, recent studies have noted that the decreased levels of the M2 phenotype correlate with obesity and inflammation.[48,49] Adipose tissue macrophages are inherently interconnected with lipid metabolism and insulin homeostasis as well.[50] For instance, saturated fatty acids and cholesterol have been shown to stimulate pro-inflammatory signaling cascades in both cultured macrophages and *in vivo* studies.[37] Additionally, the inflammatory state induced by macrophages and their chemokine secretion induces NF-KB, which inhibits the GLUT4 transporter and causes insulin resistance.[51]

Increasing adiposity results in altered macrophage aggregation that induces a pro-inflammatory state promoting hyperglycemia, hyperinsulinemia, and thus insulin resistance, which poise the development of T2D. Clinically, this pathogenetic mechanism will manifest with endothelial damage, progression of atherosclerosis, development of atherosclerotic plaques, and eventually hypertension and thrombosis.[38] These clinical findings describe cardiovascular complications and precursors to CVD. Along with the synergy found between T2D, CVD, and obesity, other comorbidities include obstructive sleep apnea, GERD, gallstones, and osteoarthritis and increased risks for certain cancers (colorectal, breast, esophageal, etc.). Obese pathophysiology and its clinical manifestations are summarized in Figure 1.

Pharmacologic and perioperative considerations

Preoperative considerations

Subjects suffering from morbid obesity are at higher risk for perioperative surgical and anesthetic complications and require a thorough preoperative evaluation to identify potential risks and prepare for their management during surgery. Attention during the preoperative evaluation should be focused on evaluating patients for evidence of obstructive sleep apnea, systemic and pulmonary hypertension, signs of right or left heart failure, and symptoms of ischemic heart disease. Patients with symptoms suspicious of CAD should be referred to a cardiologist and undergo an exercise stress test or dobutamine stress echocardiogram to evaluate cardiac function further. Once a patient with CAD has been thoroughly

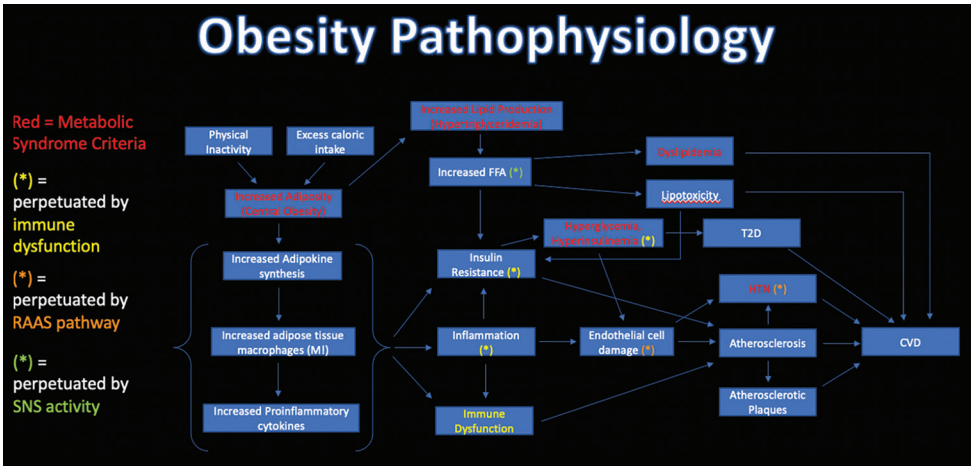

Figure 1: Obesity and pathophysiology schematic. *Adapted from:* Redinger RN. The pathophysiology of obesity and its clinical manifestations. Gastroenterol Hepatol (N Y). 2007 Nov; 3(11):856-63. PMID: 21960798; PMCID: PMC3104148(52). Heymsfield SB, Wadden TA. Mechanisms, Pathophysiology, and Management of Obesity. N Engl J Med. 2017 Jan 19;376 (3):254-266. doi: 10.1056/NEJMra1514009. PMID: 28099824(53)

assessed and appropriately managed, it is safe to proceed with surgery.[9] Patients with risk factors for obstructive sleep apnea should undergo polysomnography and be treated with continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) preoperatively.[52]

Subjects suffering from obesity are far more likely to have a difficult airway, and a thorough airway exam should be performed to identify risk factors.[10] Subjects with obesity are also more likely to have a Mallampati score of 3 or 4 and a neck circumference of >43 cm, both of which are associated with an increased risk of difficult intubation. The excess adipose tissue surrounding the neck of subjects with obesity may hide a decreased thyromental distance; care should be taken to evaluate this by making sure the thyromental distance is greater than three finger breadths, which is roughly 50–60 mm.[10,53,54]

The patient's usual medication regimen should be continued, except insulin and oral hypoglycemic agents.[55] Subjects suffering from obesity are at higher risk for aspiration, given their increased intra-abdominal pressure and increased incidence of gastroesophageal reflux disease. Aspiration prophylaxis can be given to high-risk patients using a combination of metoclopramide and either a proton pump inhibitor or an H2 blocker.[56] Subjects with obesity are also at higher risk for venous thromboembolism; thus, deep vein thrombosis prophylaxis with subcutaneous heparin 5000 IU or enoxaparin along with intraoperative use of sequential compression devices can be considered.[55]

Intraoperative considerations

There are many necessary intraoperative considerations in subjects suffering from obesity, including patient positioning, airway management, and ventilation, and increased adiposity affects anesthetic drugs' pharmacology.

Subjects suffering from obesity are more prone to developing intraoperative nerve injuries and ischemic pressure injuries; thus, care must be taken to ensure proper patient positioning with appropriate padding of pressure points and avoidance of limb hyperextension, which can cause brachial plexus or sciatic nerve palsies.[11,57]

To optimize the view for direct laryngoscopy and facilitate intubation, subjects with obesity should be placed in a "ramped" position in which a series of folded blankets or towels are placed under the shoulders, head, and neck so that the patient is in a 30 degree back up position with the external auditory meatus is at the same level as the sternal notch.[58] To ensure an optimal oxygen reserve, it is also crucial to pre-oxygenate subjects with obesity for several minutes with a goal end-tidal O_2 of >80%. When subjects with obesity are in the supine position, their intra-abdominal contents press against their diaphragm, decreasing lung expansion and reducing functional residual capacity (FRC). Additionally, reduced FRC in subjects with obesity translates to limited O_2 reserves, placing them at high risk for rapid oxygen desaturation during the apneic period during direct laryngoscopy and intubation.[59] This risk can be minimized by pre-oxygenating patients in the reverse Trendelenburg position (RTP), allowing for improvement in FRC.

Atelectasis is common in morbidly subjects with obesity following induction of anesthesia and intubation. To improve atelectasis and improve oxygenation and ventilation, proper patient positioning and alveolar recruitment maneuvers and judicious use of positive end-expiratory pressure (PEEP) are recommended. If possible, patients should be positioned in the RTP for the duration of the surgery. Alveolar recruitment maneuvers in which a sustained inspiratory pressure of at least 40 cm H20 for 10 s can be used to re-expand areas of the atelectatic lung. To maintain the patency of these newly recruited alveoli, recruitment maneuvers need to be followed by adequate levels (i.e., 12 cm H20) of PEEP.[60-62]

Obesity causes physiologic changes that can alter the pharmacokinetics and pharmacodynamics of many anesthetic medications. Most induction agents, benzodiazepines, and opioids are highly lipophilic, and subjects with obesity have a significantly increased volume of distribution compared to non-subjects with obesity. A common approach to medication dosing in subjects with obesity is to dose water-soluble drugs based on ideal body weight and lipid-soluble drugs based on total body weight. Because 20% to 40% of the increase in total body weight of obese individuals can be attributed to an increase in their lean body mass, adding 30% to the ideal body weight is an appropriate dose adjustment for subjects suffering from obesity.[55] Regarding people with paralysis, the intubating dose of succinylcholine should be based on total body weight as subjects with obesity have an increased fluid compartment and pseudocholinesterase levels, which require higher doses to ensure adequate paralysis. The non-depolarizing neuromuscular blockers are all dosed according to ideal body weight as they are hydrophilic drugs.[63]

Postoperative considerations

Following surgery, the most important postoperative considerations in subjects with obesity are adequate recovery from anesthesia, pain control, and deep venous thrombosis (DVT) prophylaxis. Following surgery and before

extubating, patients should be placed in the RTP to increase FRC, which will maximize oxygenation. Delayed recovery from anesthesia can be seen in subjects with obesity due to the build-up of lipophilic drugs in adipose tissue. Thus, care should ensure that these patients have adequate respirations, complete muscle strength, and fully recovered airway reflexes before tracheal extubation. Once the trachea is extubated, patients should be placed in a semi-recumbent position with continuous pulse oximetry and supplemental oxygen therapy to maintain appropriate O_2 saturations.[55,64] Patients with a history of obstructive sleep apnea (OSA) are at an increased risk for respiratory failure in the postoperative period. It is currently recommended that these patients receive CPAP or BiPAP therapy in the immediate postoperative period as long as there are no contraindications to their use.[52]

Postoperative pain control in patients with obesity is complicated because these patients experience an increased respiratory depressant response to opioids. This respiratory depressant effect is even more pronounced in patients with OSA. Therefore, a multimodal approach to pain control is preferred in these patients.[65,66]

The risk of postoperative DVT is higher in subjects suffering from obesity.[67] Sequential compression device and anticoagulation therapy with subcutaneous heparin or enoxaparin can be continued postoperatively, but one of the most critical interventions for DVT prophylaxis is early ambulation when possible.[68]

Conclusion

Obesity is a global health concern of increasing prevalence that can be defined as a state of malnutrition by excess. This excess of nutrients leads to an imbalance in energy homeostasis and increased adiposity, activating pro-inflammatory physiologic mechanisms that can lead to a chronic inflammatory state associated with the progression of many chronic diseases. Despite the view that obesity is a preventable disease, the multifactorial etiology incorporating components such as genetic, behavioral, and environmental factors play an essential role in understanding the epidemiology and pathophysiology of the disease. The continued concern regarding the increasing prevalence of obesity worldwide is linked to the understanding that obesity is a significant predisposing factor to conditions such as type II diabetes, cardiovascular disease, and cancer-related to increased morbidity and mortality.

As the prevalence of obesity continues to rise, perioperative anesthetic care for subjects suffering from obesity will also increase. Understanding the epidemiology, biochemistry, and pathophysiology of obesity and its related chronic diseases plays a vital role in the perioperative anesthetic care of subjects suffering from obesity. Preoperative screening of subjects suffering from obesity for cardiovascular diseases such as CAD and monitoring current medication regimens are imperative for understanding baseline physiology among subjects suffering from obesity for intraoperative care. Tracheal intubation and airway management can become complicated in subjects suffering from obesity, with increased risk of desaturation and postoperative complications. Continued understanding of the unique pathophysiology of obesity must be made to provide the best perioperative care for subjects suffering from obesity due to the increased incidence of perioperative complications within this patient population.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Gadde KM, Martin CK, Berthoud HR, Heymsfield SB. Obesity: Pathophysiology and Management. J Am Coll Cardiol 2018;71:69–84.
2. Sikaris KA. The clinical biochemistry of obesity. Clin Biochem Rev 2004;25:165–81.
3. Khanna D, Rehman A. Pathophysiology of obesity. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021. Available from: http://www.ncbi.nlm.nih.gov/books/NBK572076/. [Last accessed on 2022 Jan 04].
4. Zierle-Ghosh A, Jan A. Physiology, body mass index. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: http://www.ncbi.nlm.nih.gov/books/NBK535456/. [Last accessed on 2022 Jan 25].
5. Nuttall FQ. Body mass index. Nutr Today 2015;50:117–28.
6. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res 1998;6(Suppl 2):51S-209S.
7. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. NCHS Data Brief 2020;(360):1-8. Available from: https://www.cdc.gov/nchs/products/databriefs/db360.htm#:~:text=The%20age%2Dadjusted%20prevalence%20of%20severe%20obesity%20among%20U.S.%20adults,60%20and%20over%20(5.8%25). [Last accssed on 2022 Jan 25].
8. Obesity and overweight. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. [Last accessed on 2022 Jan 06].
9. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, *et al*. 2014 ACC/AHA Guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation 2014;130:e278–333.
10. Juvin P, Lavaut E, Dupont H, Lefevre P, Demetriou M, Dumoulin JL, *et al*. Difficult tracheal intubation is more common in obese than in lean patients. Anesth Analg 2003;97:595–600.
11. Velchuru VR, Domajnko B, deSouza A, Marecik S, Prasad LM, Park JJ,

et al. Obesity increases the risk of postoperative peripheral neuropathy after minimally invasive colon and rectal surgery. Dis Colon Rectum 2014;57:187–93.
12. Products-Data Briefs-Number 360-February 2020. 2020. Available from: https://www.cdc.gov/nchs/products/databriefs/db360.htm. [Last accessed on 2022 Jan 25].
13. Zhang Y, Liu J, Yao J, Ji G, Qian L, Wang J, *et al*. Obesity: Pathophysiology and intervention. Nutrients 2014;6:5153–83.
14. Ward ZJ, Bleich SN, Cradock AL, Barrett JL, Giles CM, Flax C, *et al*. Projected U.S. State-level prevalence of adult obesity and severe obesity. N Engl J Med 2019;381:2440–50.
15. Wang Y, Beydoun MA, Liang L, Caballero B, Kumanyika SK. Will all Americans become overweight or obese? estimating the progression and cost of the US obesity epidemic. Obesity 2008;16:2323–30.
16. Whitlock EP, Williams SB, Gold R, Smith P, Shipman S. Screening and interventions for childhood overweight. Rockville (MD): Agency for Healthcare Research and Quality (US); 2005. (U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews). Available from: http://www.ncbi.nlm.nih.gov/books/NBK43282/. [Last accessed on 2022 Jan 6].
17. Choe SS, Huh JY, Hwang IJ, Kim JI, Kim JB. Adipose tissue remodeling: Its role in energy metabolism and metabolic disorders. Front Endocrinol (Lausanne) 2016;7:30.
18. Roh E, Song DK, Kim MS. Emerging role of the brain in the homeostatic regulation of energy and glucose metabolism. Exp Mol Med 2016;48:e216.
19. Yeung AY, Tadi P. Physiology, obesity neurohormonal appetite and satiety control. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: http://www.ncbi.nlm.nih.gov/books/NBK555906/. [Last accessed on 2022 Jan 23].
20. Cui H, López M, Rahmouni K. The cellular and molecular bases of leptin and ghrelin resistance in obesity. Nat Rev Endocrinol 2017;13:338–51.
21. Vohra MS, Benchoula K, Serpell CJ, Hwa WE. AgRP/NPY and POMC neurons in the arcuate nucleus and their potential role in treatment of obesity. Eur J Pharmacol 2022;915:174611.
22. Mark AL. Selective leptin resistance revisited. Am J Physiol Regul Integr Comp Physiol 2013;305:R566-81.
23. Izquierdo AG, Crujeiras AB, Casanueva FF, Carreira MC. Leptin, obesity, and leptin resistance: Where are we 25 years later? Nutrients 2019;11:2704.
24. Woods SC, Schwartz MW, Baskin DG, Seeley RJ. Food intake and the regulation of body weight. Annu Rev Psychol 2000;51:255–77.
25. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, *et al*. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996;334:292–5.
26. Briggs DI, Andrews ZB. Metabolic status regulates ghrelin function on energy homeostasis. Neuroendocrinology 2011;93:48–57.
27. Sala PC, Torrinhas RS, Giannella-Neto D, Waitzberg DL. Relationship between gut hormones and glucose homeostasis after bariatric surgery. Diabetol Metab Syndr 2014;6:87.
28. Harvey J, Withers DJ. Neurobiology of Obesity. Cambridge, United Kingdom: Cambridge University Press; 2008. Available from: http://ebookcentral.proquest.com/lib/utmb-ebooks/detail.action?docID=377906. [Last accessed on 2022 Jan 23].
29. From genetics and epigenetics to the future of precision treatment for obesity. Available from: https://www-ncbi-nlm-nih-gov.libux.utmb.edu/pmc/articles/PMC5691547/. [Last accessed on 2022 Jan 23].
30. Kral JG, Biron S, Simard S, Hould FS, Lebel S, Marceau S, *et al*. Large maternal weight loss from obesity surgery prevents transmission of obesity to children who were followed for 2 to 18 years. Pediatrics 2006;118:e1644-9.
31. Smith J, Cianflone K, Biron S, Hould FS, Lebel S, Marceau S, *et al*. Effects of maternal surgical weight loss in mothers on intergenerational transmission of obesity. J Clin Endocrinol Metab 2009;94:4275–83.
32. The role of reward circuitry and food addiction in the obesity epidemic: An update-ScienceDirect. Available from: https://www-sciencedirect-com.libux.utmb.edu/science/article/pii/S0301051116303763?via%3Dihub. [Last accessed on 2022 Jan 23].
33. Carnell S, Gibson C, Benson L, Ochner CN, Geliebter A. Neuroimaging and obesity: Current knowledge and future directions. Obes Rev 2012;13:43–56.
34. Shott ME, Cornier MA, Mittal VA, Pryor TL, Orr JM, Brown MS, *et al*. Orbitofrontal cortex volume and brain reward response in obesity. Int J Obes (Lond) 2015;39:214–21.
35. Diagnosis of obesity based on body composition-associated health risks—Time for a change in paradigm-Bosy-Westphal-2021-Obesity Reviews-Wiley Online Library. Available from: https://onlinelibrary-wiley-com.libux.utmb.edu/doi/10.1111/obr0.13190. [Last accessed on 2022 Jan 23].
36. Rivera CA. Pathophysiology of obesity. Pathophysiology 2008;15:69–70.
37. Khanna D, Rehman A. Pathophysiology of obesity. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: http://www.ncbi.nlm.nih.gov/books/NBK572076/. [Last accessed on 2022 Jan 23].
38. Kral JG. Morbidity of severe obesity. Surg Clin North Am 2001;81:1039–61.
39. Lean ME. Pathophysiology of obesity. Proc Nutr Soc 2000;59:331–6.
40. Lopez-Jimenez F, Miranda WR. Diagnosing obesity: Beyond BMI. Virtual Mentor 2010;12:292–8.
41. Seravalle G, Grassi G. Obesity and hypertension. Pharmacol Res 2017;122:1–7.
42. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006;444:881–7.
43. Latorre J, Lluch A, Ortega FJ, Gavaldà-Navarro A, Comas F, Morón-Ros S, *et al*. Adipose tissue knockdown of lysozyme reduces local inflammation and improves adipogenesis in high-fat diet-fed mice. Pharmacol Res 2021;166:105486.
44. Xu J, Kitada M, Ogura Y, Koya D. Relationship between autophagy and metabolic syndrome characteristics in the pathogenesis of atherosclerosis. Front Cell Dev Biol 2021;9:641852.
45. Chugh PK, Sharma S. Recent advances in the pathophysiology and pharmacological treatment of obesity. J Clin Pharm Ther 2012;37:525–35.
46. Zhang L, Losin EA, Ashar YK, Koban L, Wager TD. Gender biases in estimation of others' pain. J Pain 2021;22:1048–59.
47. Martinez FO, Sica A, Mantovani A, Locati M. Macrophage activation and polarization. Front Biosci 2008;13:453–61.
48. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007;117:175–84.
49. Odegaard JI, Ricardo-Gonzalez RR, Goforth MH, Morel CR, Subramanian V, Mukundan L, *et al*. Macrophage-specific PPARγ controls alternative activation and improves insulin resistance. Nature 2007;447:1116–20.
50. Odegaard JI, Chawla A. Alternative macrophage activation and metabolism. Annu Rev Pathol 2011;6:275–97.
51. Redinger RN. The Pathophysiology of obesity and its clinical manifestations. Gastroenterol Hepatol (N Y) 2007;3:856–63.
52. Practice guidelines for the perioperative management of patients with obstructive sleep apnea: An updated report by the American society of anesthesiologists task force on perioperative management of patients with obstructive sleep apnea. Anesthesiology 2014;120:268–86.
53. Samsoon GL, Young JR. Difficult tracheal intubation: A retrospective study. Anaesthesia 1987;42:487–90.
54. Mallampati SR, Gatt SP, Gugino LD, Desai SP, Waraksa B, Freiberger D, *et al*. A clinical sign to predict difficult tracheal intubation: A prospective study. Can Anaesth Soc J 1985;32:429–34.
55. Ogunnaike BO, Jones SB, Jones DB, Provost D, Whitten CW. Anesthetic considerations for bariatric surgery. Anesth Analg 2002;95:1793–805.

56. Mahajan V, Hashmi J, Singh R, Samra T, Aneja S. Comparative evaluation of gastric pH and volume in morbidly obese and lean patients undergoing elective surgery and effect of aspiration prophylaxis. J Clin Anesth 2015;27:396–400.
57. Sawyer RJ, Richmond MN, Hickey JD, Jarrratt JA. Peripheral nerve injuries associated with anaesthesia. Anaesthesia 2000;55:980–91.
58. Collins JS, Lemmens HJ, Brodsky JB, Brock-Utne JG, Levitan RM. Laryngoscopy and morbid obesity: A comparison of the "sniff" and "ramped" positions. Obes Surg 2004;14:1171–5.
59. Jense HG, Dubin SA, Silverstein PI, O'Leary-Escolas U. Effect of obesity on safe duration of apnea in anesthetized humans. Anesth Analg 1991;72:89–93.
60. Tusman G, Böhm SH, Vazquez de Anda GF, do Campo JL, Lachmann B. "Alveolar recruitment strategy" improves arterial oxygenation during general anaesthesia. Br J Anaesth 1999;82:8–13.
61. Whalen FX, Gajic O, Thompson GB, Kendrick ML, Que FL, Williams BA, *et al*. The effects of the alveolar recruitment maneuver and positive end-expiratory pressure on arterial oxygenation during laparoscopic bariatric surgery. Anesth Analg 2006;102:298–305.
62. Perilli V, Sollazzi L, Modesti C, Annetta MG, Sacco T, Bocci MG, *et al*. Comparison of positive end-expiratory pressure with reverse Trendelenburg position in morbidly obese patients undergoing bariatric surgery: Effects on hemodynamics and pulmonary gas exchange. Obes Surg 2003;13:605–9.
63. Thompson J, Bordi S, Boytim M, Elisha S, Heiner J, Nagelhout J. Anesthesia case management for bariatric surgery. AANA J 2011;79:147–60.
64. Kuruba R, Koche LS, Murr MM. Preoperative assessment and perioperative care of patients undergoing bariatric surgery. Med Clin North Am 2007;91:339–51.
65. Soleimanpour H, Safari S, Sanaie S, Nazari M, Alavian SM. Anesthetic considerations in patients undergoing bariatric surgery: A review article. Anesth Pain Med 2017;7:e57568.
66. Tufanogullari B, White PF, Peixoto MP, Kianpour D, Lacour T, Griffin J, *et al*. Dexmedetomidine infusion during laparoscopic bariatric surgery: The effect on recovery outcome variables. Anesth Analg 2008;106:1741–8.
67. Eriksson S, Backman L, Ljungström KG. The incidence of clinical postoperative thrombosis after gastric surgery for obesity during 16 years. Obes Surg 1997;7:332–5; discussion 336.
68. Lau BD, Murphy P, Nastasi AJ, Seal S, Kraus PS, Hobson DB, *et al*. Effectiveness of ambulation to prevent venous thromboembolism in patients admitted to hospital: A systematic review. CMAJ Open 2020;8:E832–43.