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Effective Approaches For Obesity Prevention And Management

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Abstract
Being overweight and obese is characterized by abnormal or excessive fat accumulation that leads to a health risk. The difficulty has grown to epidemic proportions, with over four million human beings dying each year as a result of being overweight or obese. According to present trends, 1 in 5 adults worldwide will be affected by Obesity by 2025. It is estimated that half of the world could be overweight by 2035. Obesity has turned out to be a primary challenge for the entire society. Currently, the most widely used statistical index used to diagnose Obesity is body mass index or BMI. It is calculated by taking a person's weight, in kilograms, divided by their height, in meters squared, or BMI = weight (in kg)/ height^2 (in m^2). While lifestyle changes are essential for obesity treatment, many individuals struggle to adhere to weight loss and physical activity programs. Other options for patients requiring additional interferences include bariatric surgery, medical devices, and pharmacotherapy. Bariatric surgery, which modifies the digestive system to promote weight loss, includes several procedures: sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion with or without duodenal switch (BPD/DS), and laparoscopic adjustable gastric banding (LAGB). Pharmacotherapy currently has orlistat, phentermine-topiramate, naltrexone-bupropion, Liraglutide, semaglutide, and tirzepatide, six FDA-approved long-term use drugs. However, the current therapeutic options face limitations due to poor tolerability and compliance issues resulting from side effects, significantly hindering their broader application. Consequently, there is growing interest in developing alternative therapies with fewer side effects, including research into herbal compounds, traditional Chinese medicine(TCM), and noncoding RNA(ncRNA). However, the results of these studies are yet to be determined.

Keywords: *Obesity, Pathophysiology, Management, Bariatric surgery, Antiobesity Pharmacotherapy*

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I. Introduction

The World Health Organization (WHO) states that Obesity is a condition with a body mass index (BMI) greater than or equal to 30. [1] Obesity is the cause of leading to many diseases and health conditions that have a lower life expectancy rate and poor quality of life. Obesity, in the broader sense, is defined as the excess of body fat or adipose tissue (AT) resulting from excessive intake of nutrients and decreased energy expenditure and remains a universal health concern. Body mass index (BMI), calculated as (weight in kg/height in m2), is the widely accepted formula to define overweight (BMI 25 to29.9 kg/m2) and Obesity (BMI 30 kg/m2), while not being an authentic measure of adiposity, is simple to use in health screenings and epidemiological surveys. [2] According to the World Health Organization (WHO), the prevalence of Obesity has nearly tripled between 1975 and 2016. [3] In June 2013, the American Medical Association officially considered Obesity as a disease. The World Obesity Federation estimates that through 2020, around 770 million adults globally have been affected by Obesity. The Lancet study revealed that, in 2022, more than 1 billion people in the world are now living with

Obesity. Worldwide, Obesity among adults has more than doubled since 1990 and has quadrupled among children and adolescents (5 to 19 years of age). The data also show that 43% of adults were overweight in 2022. [4] It has been stated that Obesity decreases life expectancy by 7 years at the age of 40 years. [5] It is projected that the number of adults living with Obesity will rise from 0.81 billion in 2020 to 1.53 billion in 2035. [6] The increase in the risk of death with each unit increase in BMI drops gradually with age but remains considerable until the age group of 75 years and older. Obesity is associated with an increased risk of numerous chronic diseases, including but not limited to diabetes, hypertension, coronary artery disease, strokes, Atrial fibrillation, cancer, arthritis, and psychological. [7,8]

Diabetes mellitus is held to be a major trait of Obesity. Sims and co-workers coined the term "diabesity" for the correlation between obesity and type 2 diabetes in the 1970s. Dyslipidemia gradually develops as BMI increases from 21 kg/m 2 with a rise in proatheromatous, dense, small-particle-sized LDL (low-density lipoprotein). This change increases the risk of coronary heart disease by 3·6 times. [9] Researchers found about 10% of all cancer deaths among non-smokers are related to Obesity. The WHO International Agency for Research on Cancer estimated that overweight and inactivity reason for a quarter to a third of cancers of the breast, colon, endometrium, kidney, and esophagus. [10] Hyperuricemia and gouty arthritis are increased in the obese and decline with weight loss. In US women, Obesity increases the risk of being diagnosed with major depression by 37%, whereas obese men have a 37% lower risk of depression than men of normal weight. [11] A recent study explains fatty hepatitis, fatty fibrosis, and fatty cirrhosis in 29 overweight patients referred for a study of hepatomegaly or abnormal liver functions. Nephrotic syndrome has been reported in four patients with massive Obesity. It is estimated that more than 2 billion human beings will be obese by the year 2030 worldwide if they do not act soon. Obesity is preventable. Reducing body weight with the aid of lifestyle alteration is advisable, but every so often drug intervention is necessary. [12,13,14]

In this article, based on an intensive literature search (PubMed, Google Scholar, and Research for Life) mentioning the key words “Obesity”, “Pathophysiology of obesity”, “Bariatric surgery”, “Antiobesity medication” in peer-reviewed, open-access articles, published from 2000 to 2024 is included in the study. we discuss Obesity, medical evaluation and measurement of Obesity, prevalence and complications of Obesity, etiology, pathophysiology, and its management with currently available medications.

Obesity as disease

Obesity is the most common chronic relapsing disorder worldwide. Obesity, which is the excess of body fat or adipose tissue (AT) resulting from excessive intake of nutrients and decreased energy expenditure, remains a continuing global health concern. Overweight and Obesity are aberrant or excessive fat accumulation that causes a health risk. [14] Obesity has emerged as one of the prime public health problems facing the world today. Therefore, Obesity has to turn out to be a primary challenge for the entire society. There is an awful need for a new treatment as it is associated with an increased risk of numerous chronic diseases, including type 2 diabetes (T2D), hypertension, and cardiovascular disease (CVD). [15] Obesity is a medical condition in which the accumulation of excess body fat causes adverse health effects. [16] The 1998 WHO report on global Obesity was arguably the first major public document to use the term "epidemic" referring to Obesity. In recognizing primary Obesity as a disease, milestones were the declarations of the National Institute of Health in 1998, the American Obesity Society in 2008, and the American Medical Association (AMA) in 2013. [14,17] Since 2013, "obesity as a disease" has grown, and the American Medical Association completed the recognition of Obesity as a disease, leading to a growing scientific, social, and political interest. Currently, overweight and Obesity are the fifth leading risk for global deaths. At least 2.8 million adults die each year as a result of being overweight or obese. [18]

Medical evaluation and measurement of Obesity

Genetic studies and Image diagnostics, supported by technological innovation, are able to provide an accurate body composition. For overall body fat quantification for genetic and epigenetic studies, underwater weighing and dual-energy X-ray absorption (DXA) have proven reliable, whereas computer tomography and Magnetic resonance imaging (MRI) are used for regional measurements of body fat distribution. Despite their technical accuracy, they are too costly and time-consuming for routine care or large-scale genetic studies. Alternative measures such as waist-to-hip ratio (WHR) or skin-fold thickness are used in clinical settings, regardless of their relative inaccuracy in estimating adiposity. [19] In anthropometric measurement, Obesity can be assessed through BMI, waist circumference (WC), body fat percentage (BFP), and skin fold thickness (SFT). [20,21] Currently, the most widely used statistical index used to provide an estimate of body fat is body mass index or BMI. It is calculated by taking a person's weight, in kilograms, divided by their height, in meters squared, or BMI = weight (in kg)/ height^2 (in m^2). [23] The National Institute of Health (NIH) and World Health Organization (WHO) now use BMI to define a person as underweight, normal weight, overweight, or obese. [24,25]

Table 1: BMI to define a person as underweight, normal weight, overweight, or obese.

Diagnosis	Body mass index (BMI) (kg/m^2)	Clinical Component (Complication)
Severely underweight	<16	No complication
Underweight	<18	No complication
Normal weight	≥24.9 -18.5	No complication
Overweight	>25-29.9	No complication
Obesity	>30	No complication
Obesity Class 1	30-34.9	One or more mild complication
Obesity Class II	35-39.9	One or more mild to moderate complication
Obesity Class III (severe obesity)	≥40	One or more severe complication
• Asian and South Asian population • Overweight - BMI between 23 and 24.9 kg/m^2 • Obesity - BMI greater than 25 kg/m^2		

Prevalence of Obesity

The occurrence of Obesity is increasing hastily worldwide. The International Obesity Task Force (IOTF) regarded Obesity as the "Millennium Disease". The overall upsurge in Obesity has reached nearly three times that in 1971. According to the World Health Organization (WHO), the prevalence of Obesity has increased more than twofold since 1980. [26] Although Obesity has been officially recognized as a disease since 1985, it has not received the attention it deserves from the medical society. In June 2013, the American Medical Association officially considered Obesity as a disease. It was once mentioned that in 2014, more than 1.9 billion adults had been overweight, along with 600 million obese people. 39% of adults aged 18 years and over were overweight in 2016, and 13% were obese. [27] More than 340 million children and adolescents aged 5-19 were overweight or obese in 2016. [28] Most of the world's population stays in nations where overweight and Obesity kill a more significant number of human beings than underweight. The issue has grown to epidemic proportions, with over 4 million people dying each year as a result of being overweight or obese in 2017, according to the global burden of disease. [29] Obesity-related ill-health accounted for over 5.0 million deaths globally in 2019, with more than half of these deaths occurring among people under 70 years old. [30] Rates of overweight and Obesity continue to grow in adults and children. From 1975 to 2016, the prevalence of overweight or obese children and adolescents aged 5–19 years increased more than four-fold from 4% to 18% globally. [31] Thirty-eight million children below the age of 5 were obese or overweight in 2019. On current trends, 1 in 5 adults worldwide is expected to be affected by Obesity by 2025. One-third of these will be living with severe Obesity (BMI ≥35 kg/m2) and at high risk of requiring medical intervention. [32] It is estimated that 1 in 5 women and 1 in 7 men will be living with Obesity (BMI ≥30kg/m 2), equating to more than 1 billion being inclined to be obese by the year 2030 worldwide. [33] Further, as per a recent BBC report, half of the world could be overweight by 2035.

Etiology of Obesity

In recent years, the etiology of the obesity epidemic has been hotly debated.

Regardless, it is widely accepted that changes in body weight and overall adiposity, at the most fundamental level, are the result of chronic positive energy balance, meaning energy expenditure is less than energy intake (or calories burned < calories consumed). [34] Although it is very complicated to identify the explanations for the rapid growth of Obesity, the leading causes are enhanced consumption of energy and food rich in saturated fats and sugars and reduced physical activity. Factors such as economic growth, geography, political and social modernization, urbanization, and globalization also drive the increase in Obesity in society. [35] Among the many predisposing factors, human behavior (lifestyle and feeding habits) and genetics are major for Obesity. Recent research has made insight into leptin, gut microbiota, and some non-codon RNA as emerging causes of Obesity.

Pathophysiology of Obesity

Monitoring energy intake and expenditure are the main mechanisms by which energy balance is achieved. [36] A proper explanation of the pathophysiology of Obesity includes two parallel discussions: one from an energetic and another from a nutritional standpoint. A widely held outlook is that obesity results from an interaction between environment/lifestyle and genetic susceptibility. [37] Genome-wide association study–based data suggest a genetic predisposition for Obesity with identification of more than 140 genetic chromosomal regions related to Obesity. Gene expression related to BMI and general adiposity is highly enhanced in the central nervous system. However, only a few genes with a large effect size on BMI have yet been identified. These are the genes encoding constituents of leptin and melanocortin signaling, as well as paternally expressed genes along a specific region of chromosome 15 responsible for Prader-Willi syndrome. Several hypotheses have been put forward to explain the subsistence of obesity susceptibility genes. The "thrifty" gene hypothesis posits that genes

promoting energy intake and high fuel efficiency were selected over genes promoting energy-guzzling during human evolution. The "drifty" gene hypothesis argues that the evolutionary selection pressure for genes keeping body weight/adiposity to a minimum relaxed when humans invented weapons and fire about 2 million years ago, and thus was no longer threatened by predators with the consequence of random drift of gene swallowing increased adiposity. The early origins of the adult disease hypothesis suggest that Obesity can be fostered in offspring from mothers exposed to metabolic hardship such as undernutrition, Obesity, and diabetes. [38] One of the molecular mechanisms responsible for early-life metabolic programming is epigenetic modification of genes through methylation, histone modifications, chromatin remodeling, and noncoding RNA alterations. Prominently, such epigenetically determined increased risk for adult obesity can be transmitted to future generations, further accelerating the obesity epidemic. Thus, finding the tools and therapies to break the vicious circle of epigenetic programming is an important target of obesity research. Attempts at understanding the genetic basis of Obesity have identified numerous genes associated with syndromic monogenic, non-syndromic monogenic, oligogenic, and polygenic Obesity. [39] Eleven monogenic obesity genes have been identified to date, and their role in energy maintenance is part of the leptin-melanocortin pathway. [40] With the emergence of genome-wide association studies over the last decade, 227 genetic variants immersed in different biological pathways (central nervous system, food sense, and digestion, adipocyte differentiation, insulin signaling, lipid metabolism, muscle and liver biology, gut microbiota) have been associated with polygenic Obesity. [39,40]

Several organs are affected by genes associated with a predisposition to Obesity. The CNS is the main regulator of energy expenditure and feeding behavior, and mutations in genes in this region increase body weight. [41] In the digestive tract, mutations in taste receptor genes and digestive enzymes in the mouth are associated with higher BMI as well. [42] Furthermore, mutations in genes involved in the digestion of lactose in the Stomach, disruption of gut microbiota equilibrium, and lipid and glucose metabolism could result in Obesity. The genes involved in the musculoskeletal system's growth and glucose transport are associated with Obesity. Genes involved in fat distribution and adipogenesis can result in Obesity through a cascade of events that affect the body's energy homeostasis. [40,41]

Lee and Shin accentuate the important roles played by insulin in the pathogenesis of Obesity and carbohydrate-rich diets in the management of this condition. South Korea, the home country of Lee and Shin, has a long history of a high carbohydrate intake from vegetables and fresh fruits, even though obesity rates are low. It was established that excess intake of "added" sugars, particularly those in sweetened beverages, contributes to the pathogenesis of Obesity and that reducing the intake of these "free" carbohydrates should be a component of efforts to control weight. [42,43]

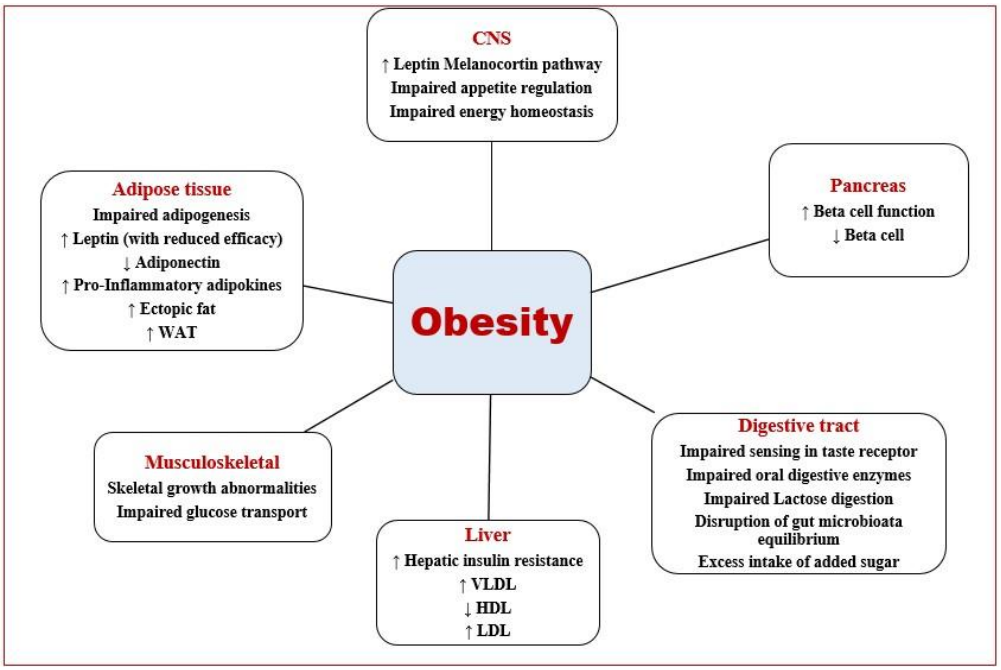

Figure-1 Pathophysiology of Obesity

Management of Obesity

Lifestyle changes remain the foundation of obesity treatment, even though adherence to weight loss and physical activity intervention programs is poor. [46] The initial goal is to achieve a 5% to 10% weight loss over the initial 6 months of treatment. [47] Weight loss is primarily dependent on reducing total calorie intake, not the proportion of carbohydrates, fat, and protein in the diet. [48] In addition to reducing calorie intake, patients are encouraged to burn more calories. There is a distinction between physical activity and exercise. [48] Physical activity consists of any bodily movement that increases energy expenditure, e.g., activities of daily living like walking, climbing stairs, gardening, etc., whereas exercise is defined as planned, structured, and repetitive movement done to improve or maintain one or more components of physical fitness. [47] Studies have validated that lifestyle activities are as powerful as based exercise applications in improving cardiorespiratory fitness and weight reduction. Although accumulating 150min/week of moderate physical activity has shown to be effective in preventing weight gain, ≥ 250min/week of moderate physical activity has been associated with clinically significant weight loss. All patients should be provided with lifestyle therapy, with consideration from pharmacotherapy and bariatric surgery when indicated. [48] Another approach gaining popularity nowadays to reduce weight is intermittent fasting, which consists of different timing schedules for temporarily avoiding food, including alternate-day fasting, other similar full-day fasting patterns, and time-restricted feeding. [49]

Pharmacotherapy, medical devices, and bariatric surgery are other treatment options for patients requiring additional interferences. [50] It is important to recognize that currently, the diagnosis of Obesity is made with BMI, not based on a specific biomarker. Hence, the contributing causes of Obesity and its pathophysiology might not be the same for all patients. Therefore, there is considerable heterogeneity in response to approved and established treatments. According to the 2013 American College of Cardiology/American Heart Association/The Obesity Society's guideline for the management of overweight and Obesity in adults and the Endocrine Society's clinical practice guidelines on the pharmacologic management of Obesity, Obesity can be considered if patients have a body mass index (BMI) of 30 kg/m 2 or greater or a BMI of 27 kg/m 2 or greater with weight-related comorbidities.[51] The common Antiobesity medications used are Phentermine, orlistat, phentermine/topiramate extended-release, lorcaserin, naltrexone sustained-release (SR)/bupropion SR, and Liraglutide. In June 2021, semaglutide was approved for the treatment of Obesity. Recently, in November 2023, tirzepatide injection was approved by FDA for chronic weight management in adults with obesity (body mass index of 30 kilograms per square meter (kg/ m2) or greater) or overweight (body mass index of 27 kg/m2 or greater) with at least one weight-related condition (such as high blood pressure, type 2 diabetes or high cholesterol) for use, in addition to a reduced calorie diet and increased physical activity. [52]

Table 2: Management of obesity

Lifestyle Therapy	Medical device	Available Pharmacotherapy	Bariatric surgery
Simple advice to lose weight in a physician's office	Intragastric balloons	Orlistat	Laparoscopic Adjustable Gastric banding (LAGB)
Internet programs or self-help books		Phentermine/Topiramate	
Advice from a registered dietitian, DASH diet	Electric stimulation system	Naltrexone-Bupropion	Laparoscopic gastric Sleeve (LSG)
Physical exercise (best if planned and directed by a certified- personal trainer)		Liraglutide	
Structured programs (Commercial program, YMCA, telecommunication)	Gastric emptying system	Semaglutide	Roux-en-Y gastric bypass (RYGB)
Physician-driven customized multidisciplinary programs		Tirzepatide	

Bariatric surgery

Bariatric surgery, or weight loss surgeries, involves changes to the digestive system for weight loss. It is indicated if diet and exercise haven't worked or there are some serious health issues due to being overweight. As per the BMI, it is recommended for patients with more than 40kg/m2 or 35kg/m2 with comorbidities. Due to the increasing load of Obesity and the limitations of its treatment, surgery has become a popular option, with about a half million procedures worldwide. Research has reported that its benefits are more than just weight loss; they depend on an individual's metabolic profile. Studies reported a reduction in chronic inflammation due to Obesity, alteration of biomarkers, increase in gut microbiota, and long-term remission of T2DM after the bariatric surgery.

Further, a decrease in serum leptin level, associated with lean BMI, was found after bariatric surgery. In addition, there are no reports of deaths associated with any primary bariatric procedure or any subsequent revisional procedure. [53-56] The most common types of surgeries include SG (sleeve gastrectomy) (58%), RYGB (Roux-en-Y gastric bypass) (38%), BPD/DS (Biliopancreatic diversion with or without duodenal switch) (1%), and LAGB (Laparoscopic adjustable gastric banding). [59] Weight losses for RYGB, SG, and LABG were found to be 27%, 18%, and 11%, respectively, in 4 years' follow-up study in 2,410 patients. [56,57]

RYGB (Roux-en-Y gastric bypass)

The Roux-en-Y Gastric Bypass, often called the "gastric bypass," has been performed for over 50 years, and the laparoscopic approach has been refined since 1993. [58] It is one of the most common operations and is very effective in treating Obesity and obesity-related diseases. The name is a French term meaning "in the form of a Y." [59] In RYGB surgery, the Stomach is divided into a small remnant pouch, and anastomosis of the gastrojejunal is performed along the jejunum. This reconstruction of the upper gastrointestinal tract diverts the ingested nutrients bypassing most of the Stomach, the duodenum, and the first part of the jejunum. RYGB causes significant changes in gut-brain neuronal and hormonal signaling mechanisms, a primary mechanism for weight loss. [60-62] Researchers have also found an increase in white adipose tissue gene after RYGB surgery. Further analysis revealed an increase in the post-prandial circulating level of satiety hormones peptide –YY (PYY) and glucagon-like peptide-1 (GLP-1), secreted by distal bowel L cells after RYGB surgeries. [62-64] Gastric bypass restricts food intake, and results in partial malabsorption, changes in appetite-regulating hormones (such as ghrelin), and changes in bile acids and gut microbiota, all of which are believed to contribute to weight loss.

SG (sleeve gastrectomy)

In sleeve gastrectomy, approximately 80% of the larger part of the Stomach on its greater curvature size is removed using a linear cutting stapler. The smaller Stomach and remainder of the intestinal tract stay intact. Weight loss is found due to food restriction, changes in gut-brain neuronal and hormonal mechanisms, and, to some extent, the removal of endocrine-rich gastric tissue. At present, SG and RYGB are the most popular weight loss surgeries. SG avoids many surgical complications such as marginal ulceration, anastomotic leakage, dumping syndrome, internal herniation, and nutritional deficiencies and is considered safe in comparison to RYGB. As per the American Society for Metabolic and Bariatric Surgery (ASMBS) Estimate of Bariatric Surgery Numbers, 2011-2020, published in June 2022, SG solely accounted for 122,056 of the bariatric procedures among a total of 198,651 patients in 2020. [65] Due to its advantages, safety, and comfort, SG is gaining popularity these days. However, studies have reported some shortcomings of SG as well, such as staple line leakage, worsening of Gastroesophageal reflux disease(GERD) symptoms, and the possibility of weight gain after SG. To overcome these shortcomings, bariatric surgeons developed SG plus procedures with simplified procedures, reduced risk, and maintained good outcomes, which emerged as promising alternatives. These SG plus procedures include banded SG, sleeve gastrectomy plus duodenal – jejunal bypass (SG + DJB), sleeve gastrectomy with jejunal – jejunal bypass (SG + JJB), Stomach intestinal pylorus – sparing surgery (SIPS) and single anastomosis duodenal – ileal switch (SADI-S). [66-70]

LABG (Laparoscopic adjustable gastric banding)

In the surgical treatment of Obesity, laparoscopic adjustable gastric band (LAGB) surgery is a restrictive surgical procedure. It is an advantageous surgical technique as it does not involve any anastomosis or resection, it is reversible, there are very few life-threatening complications, and it is a minimally invasive intervention. LAGB is a synthetic band that is placed just below the gastroesophageal junction, creating a gastric pouch. The gastric band can be inflated or deflated to alter the degree of constriction around the Stomach, and subsequently, the patient is able to limit caloric intake and maintain satiety by delaying gastric emptying. [71]

At present, SG and RYGB are the most popular.SG has gained popularity in recent years as it is safer than RYGB and provides comparable short-term outcomes. Furthermore, SG avoids many of the surgical complications associated with RYGB, e.g., marginal ulceration, internal herniation, anastomotic leakage, dumping syndrome, nutritional deficiencies, and so on [72,73]. According to the American Society for Metabolic and Bariatric Surgery (ASMBS) estimate of Bariatric Surgery Numbers, 2011 – 2022, SG accounted for 61.4% of the bariatric procedures performed over the period. [73] However, SG is not without problems; studies have reported staple line leakage, worsening of GERD symptoms, and the possibility of weight regain after SG. [74] Bariatric surgeons are constantly attempting to develop new procedures based on SG that simplify the surgical procedure and reduce the risk of surgical and metabolic complications while maintaining a good outcome. [75] Some new SG plus procedures are considered promising alternatives to RYGB. [76]

Antiobesity drugs/Antiobesity medicine (AOM)

Antiobesity medicines are employed to enhance weight loss and decrease cardiometabolic health risks, which can be accomplished with the aid of lifestyle modification alone. They need to, in addition, reduce visceral

Obesity, improve program adherence and weight loss maintenance, enhance the quality of life, and be preferentially administered orally, devoid of serious adverse events, and distributed at affordable expenses. The reason for the low prescription rate of Antiobesity medications includes lack of training in the science of Obesity, limited familiarity with medicines, concern over their safety, lack of sufficient resources to support patients, and biased attitudes regarding Obesity. [77] A legacy effect on safety is somewhat justified since this class of drugs has been plagued by the removal of several drugs from the marketplace: Fenfluramine and Dexfenfluramine in 1997 were withdrawn from the market because of their possible detrimental effects on heart valves and Sibutramine in 2010 were also withdrawn due to an increased risk of heart attacks and strokes from the US and Rimonabant from Europe in 2009. However, four new medications were approved by the FDA in 2012 that demonstrate favorable benefits to risk ratios, thus providing more options for pharmacology treatment for patients with Obesity. [78,79,80]

Medication for Obesity has traditionally fallen into two major categories: Appetite suppressants or anorexiants and gastrointestinal fat blockers. Appetite-suppressing medication has traditionally targeted three monoamine receptor systems in the hypothalamus: Noradrenergic, dopaminergic, and serotonergic. In 1930, amphetamine was first introduced as anorexiant. However, amphetamine was addictive and had euphoric side effects, and later replaced with modifying the side chain of amphetamines β. Among the centrally acting adrenergic agents that have been marked for the treatment of Obesity, three compounds, Phentermine, Phendimetrazine, and Diethylpropion, have been most commonly used. [81,82] In 1960 all three of these sympathomimetic amines were approved as adjuncts in the management of Obesity. These medications are labeled as scheduled drugs by the Drug Enforcement Agency (DEA). [83]. Among the anorectics, Phentermine is the most commonly prescribed agent in the USA, accounting for 8 million prescriptions in 2018. Orlistat was approved by the FDA in 1999 as the first lipase inhibitor for obesity management, including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. [84,85] Based on its safety profile, the medication was approved as an over-the-counter medication in the US in 2007 at half the prescription dose. The drug is a synthetic hydrogenated derivative of naturally occurring lipase inhibitor, lipostatin, produced by the mold Streptomyces toxytricini. [86] Orlistat is a potent, slowly reversible inhibitor of pancreatic, gastric, and carboxyl ester lipase and phospholipase A2, which are required for the hydrolysis of dietary fat in the gastrointestinal tract into fatty acid and monoacylglycerols. [87-89]

Four medications were approved by the FDA in 2012: Lorcaserin, Phentermine- Topiramate extended-release, Naltrexone -bupropion extended-release, and Liraglutide. These medications met the requirement of the 2007 FDA draft guidance for approval, which required conducting a prospective, randomized, double-blind study. The medications were approved with the requirement to conduct a post-marketing long-term CVD outcomes trial. [91,92] Semaglutide injection for chronic weight management in adults with Obesity or overweight got approval from the FDA in June 2021. Further, In November 2023, the FDA approved tirzepatide injection for chronic weight management in adults with Obesity. [90] Currently, there are six FDA-approved drugs—Orlistat, Phentermine-Topiramate, Naltrexone-Bupropion, Liraglutide, Semaglutide, and Tirzepatide—for long-term use. The mechanism of action with the side effects of the drugs are listed in Table 3. [78,90,91]

Table 3: Medication for weight management with the mechanism of action and side effects

Drug	Mechanism	Common Adverse effects
Phentermine	Sympathomimetic	Dry mouth Insomnia Dizziness Irritability
Orlistat	Pancreatic lipase inhibitor	Fecal urgency, oily stool, Flatus with discharge, Fecal incontinence
Phentermine/Topiramate ER	Sympathomimetic anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)	Paresthesia Dizziness Dysgeusia Insomnia, Constipation, Dry mouth
Naltrexone/Bupropion SR	Opioid receptor antagonist; dopamine and noradrenaline reuptake inhibitor	Nausea, vomiting, Constipation, Headache Dizziness, Insomnia, Dry mouth
Liraglutide	GLP-1 receptor agonist	Nausea, vomiting, Diarrhea, Constipation, Dyspepsia,

Drug	Mechanism	Common Adverse effects
		Abdominal pain
Semaglutide	GLP-1 receptor agonist	Nausea, vomiting, Diarrhea, Constipation, Dyspepsia, Abdominal pain Hypoglycemia
Tirzepatide	Glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonists	Nausea Diarrhea Decreased appetite Vomiting Constipation

II. Discussion

Obesity has elevated at an alarming rate in the world throughout the last three decades. The number of obese patients is increasing extremely in the world. Withdrawal of medicines such as Fenfluramine, Dexfenfluramine, Sibutramine, and Rimonabant from the market due to their potential adverse effects put together the reservation for the use of medicine in Obesity. Present therapeutics of Obesity are confined due to poor tolerability and low compliance owing to associated side effects restricting their potential widespread use. Therefore, the development of additional drugs from alternative sources is currently arousing considerable interest due to the fact that most, in all likelihood, have fewer side effects. With the growing attention of people's healthcare, drugs with herbal products as raw substances are progressively preferred by way of human beings all over the world for their special advantages in preventing and curing diseases, rehabilitation, and health care with minimal adverse effects. Reports of effective findings of a variety of clinical trials of traditional Chinese medicine TCM for weight issues have given insight into it as an alternative therapy modality with possible high efficacy and few harmful effects. Due to the rising prevalence, scientists are delving deeper into exploring the role of noncodon RNAs in the pathogenesis of Obesity as well. Studies have exhibited that microRNA(miRNAs), a small noncoding RNA molecule, plays an important role in adipocyte differentiation and contributes to the development of Obesity. In addition, Long noncoding RNAs (lncRNA) emerge as a critical regulator of adipose tissue since they can modulate gene expression at the epigenetic, transcriptional, and post-transcriptional levels.

III. Conclusion

There is a significant demand for effective obesity treatments that offer maximum efficacy while minimizing side effects. Ongoing research into herbal compounds, traditional Chinese medicine, and noncoding RNA may hold promising potential for addressing this issue; however, the outcomes of these investigations remain to be seen.

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