Review Article

A Global Review of Obesity

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ABSTRACT

Obesity is major health problem and are defined as abnormal or excessive amount of fat accumulation that presents a risk to health. A body mass index (BMI) over 24 is considered overweight, and over 30 is obese. obesity are main risk factors for a number of chronic diseases, like cardiovascular diseases such as heart disease and stroke, which are the leading causes of death worldwide. Over 800 million people around the world are living with obesity. The medical consequences of obesity will cost over $1 trillion by 2025.People living with obesity are twice as likely to be hospitalized if tested positive for COVID-19. The weight loss segments are one of the major contributors to the overall revenue of the dietary supplements in market. Anti-obesity drugs are used as pharmacological agents which reduce or control body weight. These drugs can change one of the fundamental processes of the human body or weight regulation by altering either appetite or absorption of calories. The treatment for obese patients is dieting and physical exercise. An anti-obesity drug have produce sustained weight loss with minimal side effects.

Keywords: Obesity, BMI, Weight Loss, Pathologies, Anti-Obesity Drugs.

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INTRODUCTION

Obesity is a complex disease involving an excessive amount of body fat. It is a medical problem that increases your risk of other diseases and health problems, such as heart disease, diabetes, high blood pressure and certain cancers. There are many reasons why some people have difficulty avoiding obesity. Usually, obesity results from a combination of inherited factors, combined with the environment and personal diet and exercise choices[1]. World obesity day takes place annually on March 4th. Worldwide obesity has nearly tripled since 1975. In 2016, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 650 million were obese. A person has traditionally been considered to be obese if they are more than 20 percent over their ideal weight. That ideal weight must take into account the person's height, age, sex, and build[2]. Obesity is characterized by increase in adipose cell size which is determined by amount of fat accumulated in the cytoplasm of adipocytes. This change in the metabolism in the adipocytes is regulated by various enzymes such as fatty acid synthase, lipoprotein lipase and adipocyte fatty acid-binding protein. Obesity results from an imbalance between energy intake and expenditure. It is caused by altered lipid metabolic processes including lipogenesis and lipolysis. Lipogenesis is the process that stores free fatty acids in the form of triglyceride (TG). Lipolysis is the process whereby the TG stored is metabolized to free fatty acids and glycerol. Obesity accompanied by hyperlipidemia which is indicated by abnormally high concentration of lipids in blood[3].

HOW TO ASSESS OBESITY?

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health. It is defined by Body Mass Index(BMI) and further evaluated in terms of fat distribution via the waist–hip ratio and total cardiovascular risk factors. BMI is closely related to both percentage body fat and total body fat. In children, a healthy weight varies with age and sex [4].

The following classes trusted Source are used for adults:

BMI	Class
18.5 or under	Underweight
18.5 to <25.0	"normal" weight
25.0 to <30.0	overweight
30.0 to <35.0	class 1 obesity
35.0 to <40.0	class 2 obesity
40.0 or over	class 3 obesity (also known as morbid, extreme, or severe obesity)[5]

Body mass index (BMI):

Body mass index is a measurement which correlates weight and height.

BMI= Mass (kg)/ Height (m).

Obesity is diagnosed when your body mass index (BMI) is 30 or high.

Waist to Hip Ratio (WHR):

WHR is used as a measurement of obesity, which in turn is a possible indicator of other more serious health conditions, WHO states that abdominal obesity is defined as a waist–hip ratio above 0.90 for males and above 0.85 for females. Women with waist–hip ratios of more than 0.8, and men with more than 1.0, are at increased health risk because of their fat distribution. WHR has been shown to be a better predictor of cardiovascular disease than Waist Circumference and body-mass index.

WHR is more recent evidence, which deals with the central distribution of body fat as an indicator of health risks. Waist distribution of fat has been assessed by calculating the waist/hip ratio[6].

WHR =Waist Circumference / Hip circumference

CAUSES

Obesity ensues when an individual's body accumulates abnormal amounts of fat. This takes place when energy intake exceeds energy expenditure over time. Many factors could contribute to the rising obesity[7].

Genetics:

Obesity has a strong genetic component. Children of obese parents are much more likely to become obese than children of lean parents. That doesn't mean that obesity is completely predetermined. What you eat can have a severe effect on which genes are expressed and which aren't. Some people have genes that make it difficult for them to lose weight[8].

Genetic causes of obesity can be divided into:

1. Monogenic obesity: these are caused by a single gene mutation, primarily located in the leptin-melanocortin pathway.
2. Syndromic obesity: severe obesity associated with other phenotypes such as neurodevelopmental abnormalities, and other organ malformations.
3. Polygenic obesity: It is caused by cumulative contribution of a large number of genes whose effect is amplified in a 'weight gain promoting' environment[9].

DIET Intake:

- **Unhealthy diet:** A diet that's high in calories, lacking in fruits and vegetables, junk food, and laden with high-calorie beverages and oversized portions contributes to body weight gain.
- **Liquid calories:** Person can drink many calories without feeling full, especially calories from alcohol. Other high-calories, such as sugared soft drinks, can increase body weight gain.
- **Sedentary lifestyle:** If you have a sedentary lifestyle, you can easily take in more calories. Looking at screens of PC, tablet and phone is a sedentary activity. The hours you spend in front of a screen is highly associated with weight gain.

Leptin Resistance:

Leptin is another hormone that plays an important part of role in obesity. Its produced by fat cells and its blood levels increase with higher fat mass. So, leptin levels are especially high in people with obesity. In healthy people, high leptin levels are linked to reduced appetite. When working properly, it should tell your brain how high your fat stores are. The problem is that leptin isn't working as because it should in many obese people, because for few reason it cannot cross the blood-brain barrier. This condition named called as leptin resistance and is believed to be a leading factor in the pathogenesis of obesity[10].

Health Conditions and Medications:

Overweight and obesity may caused by some type of hormones, such as underactive thyroid, Cushing syndrome and polycystic ovary syndrome (PCOS). Cushing syndrome, a condition caused by having high cortisol levels (the stress hormone) in your system. Polycystic ovary syndrome (PCOS), a condition that causes an imbalance of female reproductive hormones[11]. Some medicines also may cause body weight gain, including some corticosteroids, antidepressants, and seizure medicines.

Stress, Emotional Factors, and Poor Sleep

Some people eating more than usual when they are bored, angry, upset, or stressed. Studies also have found that the less sleep of people, the more likely they are to be overweight or obese. This is partly because hormones that are released during sleep control appetite and the body's use of energy[12].

PATHOLOGIES AND EFFECT ON HEALTH WITH OBESITY

Obesity is associated with a higher incidence of several pathologies.

Diabetes mellitus:

Obesity is the most common primary form of diabetes and impaired glucose tolerance. In obese patients, adipose tissue releases high amounts of non-esterified fatty acids, glycerol, pro-inflammatory cytokines, and hormones. They are linked with the development of insulin resistance, which generates hyperinsulinemia with reduction of insulin receptors and overstimulation of pancreatic cells[13]. Both Insulin resistance and hyperinsulinemia conditions are currently considered an outcome of the interaction between increased body weight and underlying genetic

factors. It has also been reported that although the degree of insulin sensitivity may be quite similar between the nondiabetic offspring of parents with type 2 diabetes and the offspring of nondiabetic parents whose body weight is close to the ideal weight, insulin sensitivity declines more rapidly with increasing body weight in those with a family history of diabetes[14].

CardioVascular Disease:

Obesity can associated with an increase risk for metabolic diseases and cardiovascular disease (CVD). These are further, increase in body fat indirectly contributes to CardioVascular disease, through thromboembolic disease and these are major cardiovascular disease risk factors, including hyperlipidemia, type 2 diabetes, high blood pressure and metabolic syndrome[15]. Metabolic syndrome is defined as a combination of the following features: central obesity, high serum triglyceride (TG) levels, low serum high-density lipoprotein (HDL), cholesterol levels, hypertension, and elevated fasting blood glucose levels[16].

Respiratory Disease:

Obesity is associated with an increased risk of chronic respiratory disorders like asthma, obstructive sleep apnea, obesity hypoventilation syndrome (OHS), and pulmonary hypertension. These condition affects in acute respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disease (COPD)[17]. Obesity leads to alterations in respiratory mechanism, airway resistance, breathing pattern, respiratory drive, and gas exchange. These changes are thought to be due to the increased elastic load posed by excess weight on the thorax and abdomen, pulmonary blood volume is increased, and ventilation–perfusion mismatch[18].

Cancer:

Overweight or obese may be develop or increase cancer risk and growth. The possible reasons that obesity is associated with cancer include:

- Increased levels of insulin and insulin growth factor-1 (IGF-1), which may help to develop some cancers. Chronic, low-level inflammation, which is more common in obese people and is linked with an increased risk for cancers. Higher amounts of estrogen produced by fat cell, which may increase the risk of cancers, such as breast cancers. Fat cells may effect processes that regulate and growth cancer cell[19].
- Hepatocellular cancer is also associated comorbidity of fatty liver in obesity, which, after progressing from steatonecrosis to cirrhosis, becomes a risk factor for hepatocellular cancer. In these obese patients, High leptin levels are found and may be a growth-promoting factor for this cancer.
- Pancreatic cancer also associated to obesity as a result of inflammatory adipokines, which not only upset glucose transport, causing insulin resistance, but combined with hyperinsulinemia, hyperglycemia, and lipotoxicity, all may lead to pancreatic β-cell inflammation and their exhaustion[20].

ANTI-OBESITY DRUGS FOR LONG TERM USE

Antiobesity drugs usually workdone by suppressing appetite, inhibiting fat absorption, or increasing energy consumption and thermogenesis. Some of the drugs have been developed specifically to body weight loss.

1. Orlistat

Orlistat is a selective inhibitor of pancreatic lipase, which thereby moderates the intestinal digestion and absorption of fat, approved for use of both the FDA and European Medicines Agency(EMA). It is available as a drug (120 mg t.i.d. before food), and at 60 mg as an over-the-counter preparation. people with obesity using orlistat lose an extra 2.9–3.4 kg weight over 12 months, gastrointestinal side effects, reduced absorption of fat-soluble vitamins and steatorrhea are occur[21]. The main mechanism of orlistat is the inhibition of gastric and pancreatic lipases, thereby blocking the hydrolysis of triglycerides and absorption of fatty acids carried out by the intestinal endothelium. This mechanism inhibits the absorption of approximately one-third of the fatty acid consumed with food. As a result, it reduces calorie absorption without affecting the appetite[22]. Additional metabolic benefits associated with orlistat use include decreased blood pressure (systolic, 1.15 mmHg; diastolic, 1.07 mmHg) and reduced circulating lipids (total cholesterol, 0.30 mmol/l; low-density lipoprotein (LDL) cholesterol, 0.27 mmol/l; triglycerides, 0.09 mmol/l). Common side effects of orlistat include fatty/oily stools, increased defecation, fecal urgency, and flatus with discharge[23]. Orlistat several causes of gastrointestinal side effects, such as diarrhea, flatulence, bloating, abdominal pain, and dyspepsia[24].

2. Liraglutide

Liraglutide (Saxenda) is an injectable glucagon-like peptide 1 (GLP-1) derivative that was approved by the FDA in 2014 for weight management (dose, 3.0 mg subcutaneous [SC] daily)[25]. The lower dose of liraglutide (Victoza) was approved in 2010 for the treatment of T2DM; the recommended dose is subcutaneous (SC) administration of 1.8 mg daily[26]. Liraglutide improves weight loss by enhancing satiety via hypothalamic stimulation and delaying gastric emptying, thereby reducing food intake[27]. The Mechanism of Liraglutide are GLP-1 is secreted from after meals the distal ileum, proximal colon, and the vagal nucleus of the solitary tract and exhibits multiple effects as an incretin hormone. Its mainly regulate blood glucose by inhibiting glucagon secretion and enhancing insulin secretion from the pancreatic βeta-cells in a glucose-dependent manner . In addition, GLP-1 slows gastric emptying, induces postprandial satiety and fullness, and reduces appetite and food consumption by working on the hypothalamus, limbic/reward system, and cortex[28].

Treatment with Liraglutide lowers waist circumference, lipids, HbA1c, BP, blood sugar, and insulin to an extent proportional to the achieved weight loss. More common side effects include nausea/vomiting and pancreatitis[29].

3. Lorcaserin

Lorcaserin (1*R*-8-chloro-1-methyl-2,3,4,5-tetrahydro- 1H-2-benzazepine; Belviq) is a specific 5-hydroxytriptophan (5-HT) 2C agonist and was approved for use by the FDA in 2012[30]. The Mechanism involves Lorcaserin reduce food intake by increasing satiety through its serotonin anorectic effect by stimulating the proopiomelanocortin (POMC) receptors in the arcuate nucleus of the hypothalamus[31]. lorcaserin can suppress appetite and hunger without triggering pulmonary hypertension or valvular heart defects[32]. The use of lorcaserin is associated with an additional annual weight loss of about 3.2–3.6 kg as well as improvements in metabolic parameters including blood pressure (systolic, 0.61 mmHg; diastolic, 0.49 mmHg) and lipids (total cholesterol, 0.35 mmol/l; LDL cholesterol, 0.35 mmol/l) and triglycerides. The common side effects of lorcaserin are nausea,vomiting, headache, dizziness, fatigue, dry mouth, cough, constipation, hypoglycemia, and back pain[33].

Clinical Efficacy:

Three clinical studies provided evidence for the approval of lorcaserin, They are **BLOOM** (Behavioral Modification and Lorcaserin for Overweight andObesityManagement) and **BLOSSOM** (Behavioral Modification and Lorcaserin Second Study for Obesity) and **BLOOM-DM** (Behavioral Modification and Lorcaserin for Overweight and Obesity Management in Diabetes Mellitus)[34].

4. Phentermine/topiramate

Phentermine/topiramate (Qysmia®) as the first combination agent for the long-term management of obesity was approved by the FDA in 2012[35]. Phentermine is a sympathomimetic that stimulates noradrenaline is to enhance the release of norepinephrine, dopamine, and serotonin through mechanism suppressing appetite, and Topiramate which acts as a glutamate antagonist, carbonic anhydrase inhibitor, and a gamma-aminobutyric acid agonistis is an anticonvulsant that augments the weight loss associated with phentermine use though the mechanism of appetite suppression[36]. It is an effective weight loss agent with studies observing 6.6–8.6 kg weight loss over 12 months. Two available approved doses are (phentermine 7.5 mg/ topiramate 46 mg and phentermine 15 mg/topiramate 92 mg). Some side effects of phentermine/topiramate ER include insomnia, paresthesia, dizziness, dry mouth, dysgeusia, and constipation[37].

Clinical Efficacy:

There are three phases, they are EQUIP, CONQUER, and SEQUEL. EQUIP and CONQUER were 1-year randomized trial, double-blind, and placebo-controlled studies. In the EQUIP study, the mean weight reduction in patients after treatment with phentermine/topiramate ER (15/ 92 mg) for 1 year was 10.9%, while that after treatment with placebo was 1.6%. Similarly, in the CONQUER trial, patients administered with 7.5/46 mg and 15/92 mg of phentermine/ topiramate ER for 1 year had a total body weight loss of 7.8% and 9.8%, respectively, as compared to the weight reduce of 1.2% in patients administeredwith placebo. Aftermore, the SEQUEL study, a 2-year extension trial, aimed at assessing the sustenance of weight loss in participants after completion of the CONQUER trial[38].

5. Naltrexone/bupropion

Bupropion (±1-(3-chlorophenyl)-2-[(1,1-dimethylethyl] amino)-1-propanone) decrease food intake by acting on adrenergic and dopaminergic receptors in the hypothalamus. Naltrexone [17-(cyclopropylmethyl)- 4,5-alpha-epoxy-3,14-dihydroxy-morphinan- 6-1] is an opioid receptor antagonist with minimal effect on weight loss on its own[39]. It acts as an appetite-suppressant by disrupting β-endorphin-mediated proopiomelanocortin (POMC) auto-inhibition. The combining bupropion with naltrexone is that naltrexone might block inhibitory influences of μ-opioid receptors activated by the β-endorphin that is released in the hypothalamus and stimulates feeding, while allowing α -melanocyte-stimulating hormone which decrease food intake to inhibit food intake. Several side effects include headache, dizziness, dry mouth, and gastrointestinal discomfort, nausea, vomiting, constipation, or diarrhea[40].

Clinical Efficacy:

Four large clinical trials (Contrave Obesity Research) COR-I, COR-II, the COR intensive Behaviour modification study (COR-BMOD), and COR-Diabetes were conducted to assess the efficacy and safety of naltrexone/bupropion[41]. The percent weight loss observed in COR-I, COR-II, and COR-BMOD in patients administered naltrexone/ bupropion 32/360 mg for 56 weeks compared to placebo was 6.1% *vs.* 1.3%, 6.4% *vs.* 1.2%, and 9.3% *vs*. 5.1%, respectively. The final study, the COR-DM trial, evaluated weight loss in patients with T2DM who were either overweight or obese[42].

SUGGESTIONS AND RECOMMENDATIONS

- Be active and walk for 30 min a day especially before breakfast to burn off fat. Exercise is the good way to get rid of excess body fat and to maintain good muscle tone.
- Make sure bowels are regular. Use extra fibers in the diet every day.
- Never eat animal fats; butter, cream, ice cream, whole milk, rich dressing, mayonnaise, and fried foods
- Eat fresh fruits and vegetables (good fiber sources). At least one meal a day should be fruits and vegetables.

- Check the doctor, underactive thyroid can cause obesity to be a problem.

CONCLUSION

Obesity is a complex, chronic disorder caused by some of factors, including dietary, lifestyle, genetic, and environmental factors. The lifestyle and behavior interventions are the fundamentals of weight reduction success, but maintaining such a healthy lifestyle is challenging. The use of some anti-obesity drug products could be considered as a supportive tool to keep obese people holding on their weight-loss goals. Many drugs treat only one part of this complex interaction and produce some side effects. It is also possible that the combination of drugs like phentermine plus topiramate and naltrexone plus bupropion could increase their anti-obesity action, but their long-term safety and tolerability should be carefully evaluated in the future. The key to successful weight loss remains good adherence to a low-calorie diet and adequate regular physical activity.

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