

Major Complications and Management Options of Obesity.

Shreja Patel¹, Mir Saleem²

¹Nova Southeastern University.

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ABSTRACT

Obesity is a disorder that consists of many factors, which has become a global epidemic since it is associated with various crucial diseases, such as diabetes, cardiovascular diseases, hypertension, stroke, sleep apnea, as well as other conditions. In order to manage obesity, a variety of strategies are taken into account in order to direct attention on those with current weight problems as well as those that are at a high risk of developing obesity. Therefore, obesity prevention should be focused during the early ages as there is a high risk of developing it in the later years. This article focuses on the risk factors of obesity as well as many preventive treatment options for obesity.

Keywords: Obesity, Sleep Apnea.

INTRODUCTION

Obesity is defined as the body mass index equal to or greater than 30 and less than 40, severe obesity is when the BMI is greater than or equal to 40, and being overweight is when the BMI is equal to or greater than 25 and less than 30.^[1,2] Obesity has been declared an epidemic and is a major global problem among both men and women. In the U.S. one third of the adults are obese, which is the leading cause of preventable death.^[3-5] Worldwide prevalence of obesity and overweight increased from 29% in 1980 to 37% in 2013 among adult men and women.^[4] If the linear trend continues, then 51% of US adults will be obese by 2030 with 130% increase in severe obesity.^[1] Obesity is associated with increased risk of diabetes mellitus, cardiovascular diseases, hypertension, hyperlipidemia, stroke, arthritis, obstructive sleep apnea, and many other diseases.^[3,4] The prevalence of childhood and young adult obesity is significantly increasing due to unhealthy life style habits, and decrease in physical activity that is influenced by parental sedentary life style.^[2,5] The estimated cost of obesity in the USA is more than \$147 billion annually.^[1,3]

Complications of Obesity

Firstly, Type 2 diabetes is a severe risk for obese individuals. In a study by Daosi et al., of 3,637 patients, 86% of the obese patients had type 2 diabetes.^[6] Type 2 diabetes and obesity are directly

correlated because insulin resistance leads to raised blood glucose levels which in turn increases the adipose tissue fat.^[7] Body fat is divided into 80% subcutaneous fat and 20% visceral fat of the total.^[7] However, visceral fat is a greater contributor to obesity since visceral fat cells are correlated to the excessive production of adipocytokines which causes inflammation and insulin resistance.^[7] The adipocytes in the visceral tissue have a higher rate of lipolysis, which is the breakdown of fats into fatty acids compared to the subcutaneous fats. Obesity leads to the release of excessive fatty acids from an increase in lipolysis. The increase in fatty acid (lipotoxicity) causes insulin receptor dysfunction leading to insulin resistance.^[7] In normal individual, blood sugar levels don't rise, as insulin will turn down gluconeogenesis, while individuals with insulin resistance, the blood sugar levels continue to increase because gluconeogenesis continues.^[7] The rapid increase in the number of people with type 2 diabetes is directly correlated to weight gain and obesity.

Along with type 2 diabetes, cardiovascular disease is another risk for obese individuals. Cardiovascular disease (CVD) is a heart condition that involves diseased vessels, structural problems, and blood clots and is the leading cause of death worldwide except in Africa.^[8] According to Bacha, longitudinal studies in adults show that obesity is a risk factor for coronary heart disease and heart failure; an increment of 1 unit of body mass index increases the risk by 5% for men and 7% for women.^[9] Adipose tissue is surrounded by an extensive capillary network, and after a meal, the adipose tissue blood flow increases. Adipose tissue is what makes up a majority of the total body weight, and a big amount of fluid can be seen in the interstitial space of the

Name & Address of Corresponding Author

Dr. Mir Saleem
Nova Southeastern University.

adipose tissue. This large amount of fluid plays a vital role in obese individuals that have cardiovascular diseases if the volume is redistributed into the circulation. Blood flow in the adipose tissue is adjusted by beta-receptors that cause vasodilation,^[10] therefore, the fluid in the interstitial compartment is not attainable. Although cardiac output increases with total mass fat, the insertion in adipose tissue decreases with increasing obesity. Generally, for obese individuals, the cardiac workload is greater, which causes ventricular and atrial chamber dilation and cardiomyopathy. The most frequent death in obese individual is due to dilated cardiomyopathy that causes fatal arrhythmia, where the heart does not beat properly.^[10] As was seen with type 2 diabetes, there is a strong correlation between obese patients who suffer from cardiovascular disease.

Hypertension is the most common health problem related to obesity.^[11] It is roughly two times as prevalent among the obese population compared to the non-obese population.^[11] White coat hypertension, confirmatory ambulatory blood pressure parameters, and nondipping blood pressure was higher in overweight and obese people in comparison to normal weight individuals.^[12] Abnormal renal sodium and water reabsorption, impaired pressure natriuresis, and activation of the sympathetic nervous system which plays a major role in obesity-related hypertension. Obese individuals have higher day and nighttime heart rate variability, and impaired decrease in blood pressure at night compared to normal weight individuals.^[12] Juonala et al found that obese children were more likely to have hypertension, diabetes type 2, cardiovascular diseases, elevated low-density lipoprotein levels, and low high-density lipoprotein levels. However, obese children who developed into adult normal weight will have significant lower cardiovascular risk.^[29]

Treatment Options

Obesity is a severe, enduring medical condition, which leads to various conditions that are life threatening. In fact, it is continuing to increase rapidly worldwide which is quite debilitating. Therefore, in order to control the obesity rates, there are many rational strategies that overcome the foremost issues associated to the prevention of:

- I.) Normal weight individuals that are developing into over weight
- II.) Overweight individuals who are becoming obese
- III.) Individuals that used to be overweight or obese and are regaining weight and
- IV.) An established condition that is becoming worse.^[1]

Helpful management strategies must be integrated in order to help solve the issues. The evaluation of obesity must be completed frequently by the

measuring the BMI, measuring the waist circumference, etc. in order to gauge risk factors. Based off of the evaluation, the designated treatment will be recommended. Treatments involve lifestyle modification, such as diet modification and increased physical activity, behavioral therapy, pharmacology therapy, and bariatric surgery.

Lifestyle Modification

Diets, such as high protein and low carbohydrate diets, very low fat diets, very low calorie diets, on line weight loss diets, Mediterranean diets, balanced nutrient diets, and portion controlled diets are effective and induce weight loss.^[13]

In two major studies the DPP and Look AHEAD, body weight reduction on an average of 5-10 kg occurs mainly in first 6 months. Also significant improvement in lipid levels and blood pressure were observed.^[13]

The Framingham Nutrition study focused on diet quality, which revealed that a lower quality diet (higher nutritional risk scores) were at a greater likelihood to become overweight or obese.^[3] Decreasing the daily caloric intake by 500 kilocalories leads to a decrease in body weight between 5-10 % and a decrease in body mass index (BMI) by 2.0 and 2.9 kg/ m².^[14] All diet plans help weight loss and no one diet is superior, but the important thing is to adhere to the diet, and the negative energy balance through restriction of calories, which helps achieve weight loss.^[13,15]

One change in lifestyle is participating in physical activity to reduce sedentary behavior.^[2] Evidence shows that participating in adequate physical activity improves various factors, such as energy balance, maintains weight after weight loss, increases sensitivity to insulin, enhances beta-cell function, and regulates both blood pressure and cholesterol.^[16] Rigorous, medium to high intensity workouts have a more significant impact on weight loss compared to slow walking. In order to reduce the risk of chronic disease, exercising about thirty minutes per day is sufficient, however, to maintain healthy weight or lose weight, at least an hour per day is necessary. Due to sedentary life style, non-exercise activity thermogenesis (NEAT) is significantly declined. Modification of sedentary life style by climbing stairs instead of using elevators, walking after a meal, parking away from the work place, doing work while standing etc. will prevent overweight and obesity.^[17]

Behavioral Therapy

Lifestyle changes by reducing calorie intake and increasing physical activity can result in about 10% loss of initial body weight. To fortify behavioral therapy for management of obesity is to assist a shift from maladaptive eating and exercise patterns to healthy eating and regular exercise. The behavioral therapy factors are self-monitoring, stimulus control,

goal setting, social support, slower eating, behavioral contracting, increase physical activity and education. Self-monitoring includes keeping daily records of food intake and exercise that helps recognize the personal behavior. Stimulus control modifies the physical environment by purchasing high fiber diet, avoiding fast foods, not keeping unhealthy and high calorie foods in the house, and avoiding sweetened drinks.^[18-21]

A weight loss study includes an initial phase (3-6 months) group meeting, which is followed by a maintenance phase (6-12 months) where participants who received behavioral intervention revealed a weight loss of 10.6% in the initial phase and 8.6% in the follow up phase.^[18]

Perri and colleagues concluded that individuals who attended every other week group maintenance sessions for the year after the weight reduction, maintained 13.0 kg of their 13.2 kg end of treatment, but those who did not receive therapy maintained only 5.7 kg of 10.8 kg loss.^[19]

Pharmacology Therapy

National Institutes of Health suggested that every individual begins treatment with diet modification, exercise, and behavioral therapy. Pharmacotherapy is the next step if these lifestyle changes do not foster a weight loss equivalent to 10 % of initial weight or at least 0.5 kg/week over 6 months. Pharmacotherapy is recommended for individuals with a body mass index (BMI) greater than 30 kg/m² or a BMI higher than 27 kg/m² plus one or more associated comorbidities like hypertension, dyslipidemia, coronary artery disease, type 2 diabetes mellitus, or sleep apnea. After initiating therapy within the first 4 weeks if the patient does not lose at least 2 kg, then the response to that medication is low, and the patient should increase the dosage, stop the previous drug, or substitute it with another type of medication. The medication may be continued if significant weight loss occurs on a medication or the initial weight loss is maintained since it is effective and the side effects are endurable.^[22]

Currently the available medications are Orlistat, Liraglutide, Naltrexone/Bupropion, Phentermine/Topiramate ER, and Lorcaserin—the Food and Drug Administration approve the later 4 in last 4 years for chronic weight management. The guidelines setup by FDA for approval of weight loss medications is at least a 5% mean weight loss after 1 year of treatment, in the study at least 35% of the patients treated achieved this weight loss goal.^[23]

Orlistat is an inhibitor of gastric and pancreatic lipases that result in malabsorption of approximately 30% of ingested fat. It has no side effects but since there is no absorption, it needs derivative fat-soluble vitamins to avoid vitamin deficiency. In a randomized study, 892 subjects received placebo 3 times a day or orlistat, 120 mg 3 times a day for 52

wk. In the first year, subjects that were treated with orlistat lost more weight - 8.76kg than placebo treated subjects- 5.81 kg. Orlistat leads to important reductions in total and low-density lipoprotein cholesterol and in systolic and diastolic blood pressure.^[22]

Combination of Phentermine a sympathomimetic drug and Topiramate an antiepileptic drug has demonstrated efficacy in reducing weight by appetite suppression, decreased food consumption, increase satiety, increase metabolism and altering taste. The EQUIP trial evaluated 2 doses of phentermine/topiramate ER in patients with obesity. The average body mass reduction ranged from 5.1% to 10.9% and the responses were dose related. For patients taking the maximum dose of 15/92 mg, 66.7% to 70.0% of patients attained $\geq 5\%$ weight loss and 47.2% to 48.0% of patients attained $\geq 10\%$ weight loss from baseline. Phentermine/topiramate ER was also associated with dose-dependent progress in systolic and diastolic blood pressure, LDL-C cholesterol, HDL-C cholesterol, and triglycerides compared with the placebo. Contraindications to phentermine-topiramate include pregnancy, glaucoma, and hyperthyroidism. Phentermine/topiramate ER is an FDA schedule IV controlled substance.^[23]

Lorcaserin is a serotonin 2C receptor agonist, which has an effect on anorexigenic neurons in the hypothalamus, inhibiting appetite stimulation and promoting satiety. Two trials (BLOOM, BLOSSOM) included obese or overweight individuals without diabetes. The average body mass reduction from baseline was 5.8% with the approved 10-mg, twice- daily dose of lorcaserin, compared with a 2.2% average weight reduction in the placebo groups. On average, 44.1% of patients attained 5% weight loss, and 20.5% of patients attained $\geq 10\%$ weight loss from baseline in the twice-daily lorcaserin group, compared with 20.5% and 7.3% of placebo patients achieving $\geq 5\%$ and $\geq 10\%$ weight loss, respectively. Lorcaserin is a serotonergic drug and so will cause serotonin syndrome when combined with medications that act on neurotransmitter, such as selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors, or drugs that may affect the clearance of serotonin, such as lithium, tramadol, or dopamine antagonists. Lorcaserin also led to significant reductions in BMI, waist circumference and blood pressure.^[23]

The combination of Naltrexone with Bupropion was approved in 2014. Bupropion is a dopamine and norepinephrine reuptake inhibitor, which is commonly used as an antidepressant and for cessation of smoking. Naltrexone is an opioid receptor antagonist permitted to treat alcohol and opioid dependence. Naltrexone and Bupropion produce a synergistic effect and act in the hypothalamic melanocortin system and the

mesolimbic reward system, both regulates food intake and body weight. On average, based on ITT-LOCF data, 52.4% of patients attained $\geq 5\%$ weight loss and 28.3% of patients attained $\geq 10\%$ weight loss from baseline in the high-dose Naltrexone-Bupropion group, compared with 23.6% and 9.7% of patients in the placebo group, respectively. Combination naltrexone-bupropion is contraindicated in patients who have epilepsy, uncontrolled hypertension, and opioid taking medications.^[23]

Liraglutide is an injectable long acting glucagon-like peptide-1 receptor agonist used to treat type 2 diabetes. It was found that Liraglutide causes weight loss that prompted the drug company to evaluate the drug for the treatment of obesity. Liraglutide act in the hypothalamus and other brain regions that regulate appetite as well as direct effects on the gut to reduce food intake via vagal signaling and delayed gastric emptying, causing early satiety. The SCALE clinical trials were used to document liraglutide's safety and efficiency in the treatment of obesity and help the drug gain FDA approval for this indication in 2014 at a 3-mg dose, compared to the 1.8- mg dose used in the treatment of diabetes. In these trials, treated patients lost an average of 6.5% of their base line body mass after 1 year of treatment, compared with a 1.6% reduction in the placebo group. Approximately 56% of the active treatment patients were able to achieve $\geq 5\%$ weight reduction, with 28% achieving $\geq 10\%$ weight reduction from baseline at 56 weeks, compared with 23.4% and 7.9%, respectively, in the placebo groups. Liraglutide is available only by subcutaneous injection, requiring patients to learn and implement injection technique.^[23]

Since there is no for sure first-line agent, the decision for treatment should be based on individual factors.

Bariatric Surgery

Bariatric surgery should be factored in for all patients with a BMI of 40 or higher and in patients with a BMI of 35 or higher with obesity-related comorbid conditions. Since the bariatric surgery requirement of a BMI of 35 or higher was established, emerging evidence has supported the clinical and cost effectiveness of surgical intervention in patients with a BMI of 30 to 35 who do not achieve substantial weight and comorbidity improvement with nonsurgical methods. However, most guidelines (and third-party payers) still support withholding surgical intervention until the BMI is 35 or higher. A multifaceted team with medical, surgical, nutritional, and psychiatric ability should evaluate candidates.^[24,25]

Bariatric surgical procedures result in reduced stomach capacity (restriction), malabsorption of ingested nutrients, hormone changes that suppress appetite, or a combination of these mechanisms.

Perioperative mortality risk associated with bariatric surgery is low ($<0.3\%$). Weight loss equal to or greater than 50% of excess body weight (current weight minus ideal body weight) is considered a success. Commonly performed bariatric procedures include laparoscopic adjustable gastric banding, Roux-en-Y gastric bypass, biliopancreatic diversion duodenal switch, and sleeve gastrectomy.^[24,25]

Laparoscopic gastric banding, a restrictive procedure that forms a minute gastric pouch that consists of an adjustable outlet, which is a silicone belt that is lined with an inflatable balloon which is fastened into a closed ring that surrounds the upper stomach. The band is adjusted (via a port) to achieve early satiety without dysphagia. Three to 6 years after gastric banding, excess weight loss is 45% to 72%.^[24,25]

Roux-en-Y gastric bypass, a combination restrictive and malabsorptive procedure, involves creating a small (30 mL) proximal gastric pouch, which is separated from the distal side of the stomach and joined to the Roux limb of small bowel. Digestion and absorption of nutrients occur in the mid-small intestine. With Roux-en-Y gastric bypass, stomach capacity is reduced, as is absorption of calories. Additionally, delivery of nutrients to the mid-small intestine triggers hormone changes that suppress appetite. Three to 6 years after Roux-en-Y gastric bypass, excess weight loss is 62%.^[24,25]

Vertical sleeve gastrectomy is a restrictive procedure that requires incision of the greater curvature of the stomach. This procedure involves 70% vertical gastric resection, which forms an extended, narrow tubular gastric reservoir that does not have an intestinal bypass component. This procedure reduces stomach capacity and suppresses appetite by removing tissue that produces ghrelin, a hunger-stimulating hormone. Excess weight loss 3 to 6 years after sleeve gastrectomy is 53% to 77%.^[24]

One of the most inclusive systematic reviews examined 136 studies and 22,094 patients which underwent bariatric surgery. The review concluded with a high trend towards dissimilar weight loss outcomes across procedures. Weighted mean percentage of excess weight loss (%EWL) was 50% (32% to 70%) for adjustable gastric banding, 68% (33% to 77%) for Roux-en-Y gastric bypass, 69% (48% to 93%) for vertical banded gastroplasty, and 72% (62% to 75%) for biliopancreatic diversion duodenal switch. Type 2 diabetes rate remission was different across procedures. The rate was 48% (29% to 67%) for adjustable gastric banding, 84% (77% to 90%) for Roux-en-Y gastric bypass, 72% (55% to 88%) for vertical banded gastroplasty, and 99% (97% to 100%) for biliopancreatic diversion with duodenal switch. An identical pattern of disease remission was noticed for hypertension, dyslipidemia, and obstructive sleep apnea, with the greatest rates of remission seen in patients who had went through the biliopancreatic diversion with duodenal switch, followed by Roux-en-Y gastric

bypass, vertical banded gastroplasty, and lastly adjustable gastric banding.^[24]

High quality data from Randomized Controlled Trials have fixed that bariatric procedures are more successful compared to the medical or lifestyle interventions for inducing weight loss (26kg) and remission of type 2 diabetes, advancement in long term survival and quality of life, a decreased risk of incident cardiovascular disease and diabetes, betterment in sleep apnea and osteoarthritis, and long lasting improvements in obesity related comorbidities between patients who have went through bariatric surgery compared to non-surgical controls.^[24,26-28]

In the future, bariatric procedures will base on key physiological variables that include changes in ghrelin, leptin, glucagon like peptide-1, cholecystokinin, peptide YY, gut microbiota, and bile acids.^[24]

Patients who undergo bariatric surgery should continue dietary, physical activity, and behavioral measures and should receive nutrient replacement therapy.^[25]

CONCLUSION

Obesity is a widespread disease associated with multiple comorbid conditions, and so the WHO (World Health Organization) has declared obesity a global epidemic and NIH (National Institute of Health) has clinical guidelines and recommendations for management of obesity and overweight. A reduction of 10% body weight will have a significant beneficial impact on one's health care cost. It should be treated forcefully in the same way that it applied to other diseases. The advances in treatment, such as life style modification, pharmacology therapy, and bariatric surgery will prevent the global problem of overweight and obesity. The increase in awareness and research will bring about better treatment for the obese in the next few years.

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