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Therapy of obese patient with Cardiovascular Disease

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Abstract

Obesity has reached epidemic proportions and is a significant public health concern. Obesity is associated with increased diabetes, cardiovascular and kidney disease, and associated morbidity and mortality. Despite the increasing public health problem of obesity, there is a dearth of effective treatment options. Following the FDA mandated withdrawal of sibutramine, the treatment options for obesity were limited to orlistat as the only pharmacological treatment option for long term management of obesity. Recently two new medications (Belviq and Qsymia) were approved by FDA for long term management of obesity. Many other anti-obesity drugs are under development. Bariatric surgery has been shown to be effective in the treatment of obesity and its comorbidities. The available data suggests that even modest weight loss improves diabetes and cardiovascular disease (CVD) risk factors. We summarize the treatment options for obesity and the efficacy of these options in ameliorating cardiovascular risk factors. We also focus on the recently approved anti-obesity drugs.

INTRODUCTION

Malnutrition has probably affected more people than any other medical problem over the centuries. The problem of under-nutrition has lessened in most parts of the world with the economic and educational efforts over the past century. However, over time the paradigm has shifted from under-nutrition to over-nutrition, at least in the industrialized nations. Obesity has reached alarming proportions and a significant number of disease-related deaths can be attributed to obesity and its comorbidities [1-3].

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A small energy excess, if sustained over long periods of time, can lead to significant weight gain and obesity. This is illustrated, for example, if an individual consumes about 8 Kcal in excess of his daily needs every day for 30 years, he will gain about 10 kg [1]. This increased weight gain then increases risk for diabetes and CVD.

CARDIOVASCULAR RISK AND OBESITY

Obesity is a pro-inflammatory and pro-oxidative state associated with the accumulation of dysfunctional adipose tissue. The endocrine and paracrine functions of adipose tissue are altered, which in turn disrupt vascular homeostasis and endothelial function [4]. This vascular pathology and atherosclerosis clinically present as coronary heart disease and cerebrovascular disease.

There is increasing data to support the association between obesity and risk for CVD. Obesity and its comorbidities, hypertension and glucose intolerance, increase morbidity and mortality rates in adults [2]. However, the relationship between cardiovascular sequelae and increased adiposity in people with an average BMI ($\sim 25\text{-}30\text{ kg/m}^2$) is less studied [3]. A meta-analysis of prospective studies of a relatively lean Japanese population, showed that there was a linear association between BMI and ischemic and hemorrhagic stroke [5]. Interestingly, this study highlights a positive association between the progressive increase in BMI within the normal and overweight range and the risk of CVD [5]. An analysis of the Framingham study also pointed to the positive association between overweight (BMI $25\text{-}29.9\text{ kg/m}^2$) and relative risk of hypertension and CVD sequelae [3].

Investigators recently analyzed data from four prospective studies and determined that obese children were at increased risk for type 2 diabetes, hypertension, dyslipidemia, and carotid artery atherosclerosis. Further, they found that if these children lost weight and attained normal BMI by adulthood, their risk for these comorbidities matched that of people who were never obese [6]. The available data links obesity to CVD and it also suggests that the treatment of obesity can improve CVD outcomes. A review of five cross sectional surveys highlighted that CVD risk has decreased over all BMI groups in the last four decades, but the decline is more pronounced in obese and overweight people, than in lean people [7]. This shows that at current an obese person might be at a lower risk of CVD disease compared to a person with same BMI four decades ago. This change could be related to increased awareness, improved lifestyle, early detection, and aggressive treatment of other CVD risk factors such as hypercholesterolemia and hypertension [7].

PHARMACOLOGIC TREATMENT OF OBESITY

In the past two decades there has been an active interest in the development of pharmacologic strategies that address weight loss. Several pharmacologic agents have recently been approved for management of obesity. These include the following agents:

LORCASERIN- (Belviq)

Lorcaserin a selective serotonin 2C (5-HT_{2C}) receptor agonist was recently approved by the FDA for chronic weight management in obese people. The role of serotonin receptors in weight management had been established with non-selective serotonergic agonists, which can cause serotonin-associated valvulopathy via activation of 5-HT_{2B} receptor in cardiac valvular interstitial cells [8]. Lorcaserin has been found to induce significantly more weight loss (average weight loss approximately 5.8 kg), in a significantly higher percentage of people than placebo. The weight loss with lorcaserin was found to be dose dependent except in the patients with diabetes [9]. There was a significant and meaningful improvement in the predictors of CVD risk and in the quality of life when weight loss was achieved with

lorcaserin therapy [10]. Treatment with lorcaserin 10 mg twice daily for one year led to at least 5% of weight loss in about 37% of the people with diabetes and about 48% of the people without diabetes. People who continued to take lorcaserin after one year of successful therapy were more likely to maintain the weight loss [8]. Though improvement in lipid profile was noted with lorcaserin therapy, it was not reported to be statistically significant [10]. The studies did not show significantly increased risk of serotonin-associated valvulopathy in people treated with lorcaserin, but the studies were unable to reliably exclude this risk [8,10]. However it should be noted that data from studies on a rodent model suggests that 1400 fold greater blood concentration of lorcaserin is required to activate peripheral 5-HT_{2B} receptors, than to activate CNS 5-HT_{2C} receptors [11].

The most commonly reported adverse events included headaches, dizziness, and nausea but these seldom lead to discontinuation of therapy [8]. Increased occurrence of mild symptomatic hypoglycemia was reported in diabetic patients with use of lorcaserin. The incidence was particularly high in patients taking sulfonylureas and lorcaserin concomitantly. Surprisingly, the incidence was 10.5% in patients on lorcaserin QD, compared to 7.4% and 6.3% in patients on lorcaserin BID and placebo respectively [9]. Lorcaserin also has the potential to cause serotonin syndrome especially when used with other serotonergic agents like serotonergic antidepressants [10]. The studies had other significant limitations including high discontinuation rate, lack of racial diversity, a very high percentage of female participants, exclusion of people with BMI > 45, and people with certain comorbidities of obesity.

PHENTERMINE and TOPIRAMATE Extended Release (Qsymia)

This new combination of an old weight loss drug and a drug that was known to cause weight loss when used for other indications was recently approved for chronic management of obesity. Phentermine is a sympathetic amine and the topiramate component promotes weight loss by decreased calorie intake and possibly by increased energy expenditure and decreased energy efficiency as well [12]. It will be available in 7.5/46 and 15/92 dose drug combinations.

Therapy with high dose combination 15/92 for 56 weeks was associated with at least 5% weight loss in about 70% of subjects and at least 10% weight loss in 48% of subjects, with an absolute weight loss of about 10 kg [13]. Patients successfully treated with this combination had improvements in their blood pressure, fasting glucose LDL cholesterol, HDL cholesterol, and total cholesterol [12,13]. Long term use beyond 56 weeks might be associated with sustained benefits and possibly improved tolerability [14]. The most common reported adverse events included dry mouth, paresthesia, constipation, insomnia, dizziness, and dysgeusia [13].

These studies also had certain limitations, including the absence of a comparator arm, lack of ethnic diversity, and a disproportionately high number of female participants [13]. This drug combination was studied in a population with multiple comorbidities of obesity and in patients with mild depressive symptoms. Still the results were encouraging. This drug combination was tolerated well, though it might need to be discontinued in patients who develop nephrolithiasis, metabolic acidosis, cognitive, or psychiatric adverse events [13]. The use of Qsymia in patients with clinically significant depression has not been evaluated and its use in patients with glaucoma, hyperthyroidism, unstable heart disease, or recent stroke is not recommended.

ORLISTAT

Orlistat is a pancreatic lipase inhibitor which induces weight loss by causing dose dependent fat malabsorption. Multiple studies have shown excess weight loss with a combination of life style modification and orlistat, than with life style modification alone. [15]. Data from XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study showed that the use of orlistat in addition to life style modification in obese people with impaired glucose tolerance can decrease the incidence of diabetes over four years. Risk reduction of 37.3% was conferred by the combination over life style modification alone [16].

NALTREXONE SR/BUPROPION SR

This combination has been shown to induce significant weight loss in initial studies and is under review for FDA approval [15].

PHARMACOLOGIC WEIGHT LOSS WITH TREATMENT FOR DIABETES

Type 2 diabetes is commonly associated with obesity, CVD, and hyperlipidemia. Some medications used for the treatment of diabetes can cause weight gain, but a few are being studied for their potential to cause weight loss.

LIRAGLUTIDE

Liraglutide is a GLP-1 analogue used for treatment of type 2 diabetes at doses up to 1.8 mg. It has been shown to be an effective and safe treatment for weight loss in patients without diabetes. In a recently completed study, subjects taking liraglutide in doses of 2.4 to 3 mg, had weight loss of 7.8 kg over two years [17]. Usually the weight stabilized after about 36 weeks of therapy and was maintained thereafter if treatment was continued [17]. Another observation was that people with higher baseline BMI lost more weight with liraglutide therapy [18]. The weight loss was associated with improvements in blood pressure, prevalence of pre-diabetes, and in levels of HDL, triglycerides, plasminogen activator inhibitor-1, and highly sensitive C reactive protein [17]. The most common reported adverse events were nausea and vomiting.

EXENATIDE

Exenatide is another GLP-1 receptor agonist which is thought to induce weight loss by increased satiety and decreased food intake [19]. In a relatively small RCT it was demonstrated that 48% of the people lost at least 5% of their baseline body weight and about 24% lost at least 10% of their baseline body weight when they were treated for 24 weeks with exenatide in addition to life style modification [19]. The treatment was associated with decreased waist circumference and improved blood pressure (9.2 mmHg average drop in SBP) and glycemic control [19]. Results from another study with 12 participants suggest possible efficacy of exenatide in reducing BMI and body weight gain in children and adolescents with extreme obesity [20]. Common dose limiting adverse effects are nausea and vomiting, but these can be reduced with gradual escalation of the dose [21].

METFORMIN

Metformin, an insulin sensitizer, is considered a first line pharmacological treatment for obese people with diabetes. It is known to cause weight loss or prevent weight gain in diabetic patients. Some of the effects of metformin on energy metabolism are considered to be similar to physical exercise [22]. Contrary to what is seen with calorie restriction, metformin decreases the adipose mass without significantly reducing lean body mass [22]. The results of the Diabetes Prevention program showed an average weight loss of 3.5 kg at two years and 3.1 kg (3.5%) at about nine years in subjects highly adherent to metformin

therapy. Nearly 50% of the people who were highly adherent to metformin treatment during the duration of the study lost at least 5% of their baseline body weight (Table-1) [22]. Treatment with metformin results in improvement in lipid parameters, endothelial function, and other CVD risk factors [23].

BARIATRIC SURGERY

The most commonly performed bariatric surgical procedures are gastric bypass and laparoscopic adjustable gastric banding [15]. Many studies have shown effectiveness of bariatric surgery in weight loss and in improvement or resolution of comorbidities including diabetes, hypertension, dyslipidemia, and obstructive sleep apnea [24]. Many studies have reported excess weight loss of approximately 60% with gastric bypass and 45% with gastric banding [25,26]. Even though the popularity of bariatric surgery has increased and the rate of complications has decreased over time, some of the complications can cause significant morbidity. These complications include enteric leak, hemorrhage, obstruction, perforation, marginal ulcer, dumping syndromes, short bowel syndrome, and nutritional deficiencies to name a few [27,28].

DIET/EXERCISE AND BEHAVIOR THERAPY

Low calorie diets with a calorie content of 800-1200 Kcal/day has been shown to promote modest weight loss [15]. Calorie deficits of about 600 Kcal/day are effective for weight loss and risk factor modifications [29]. The addition of exercise to dietary manipulation has additional benefits including increased weight loss and improved cardiopulmonary fitness [15]. The NIH guidelines for weight loss stress pharmacological and surgical modalities for weight loss should not be used independent of life style modifications [15].

Efficacy of Weight loss in Improving CVD

We have a clearer and better understanding of weight loss goals now than before. The recommended weight loss goal is usually quite modest compared to what is generally perceived. Over time focus has shifted to modest weight loss, as modest weight loss is achievable and it helps reduce CVD risk factors associated with obesity [15,30]. Life style interventions like calorie restriction and increased physical activity have a modest effect on weight loss [15]. Pharmacotherapy, though effective, has its pitfalls. Over time many medications have been approved for treatment of obesity and many have been withdrawn because of their adverse effects. Sibutramine's efficacy for weight loss had been established, but it was withdrawn from the market recently because of poor CVD outcomes.

An analysis of data from the PHARMO database in the Netherlands showed that people who were prescribed orlistat for weight loss, had a decreased use of prescription medications for obesity related comorbidities [31]. Various studies have shown that treatment of obesity with orlistat improves diabetes and blood pressure control and decreases the level of LDL [32]. Belviq and Qsymia were recently approved for long term weight management and initial studies have shown that these medications might be effective in improving cardiovascular risk factors associated with obesity. Treatment with Qsymia was associated with improvement in blood pressure, lipids, glycemic control, and inflammatory markers. Studies show significant weight loss with bariatric surgery and the weight loss is associated with resolution of diabetes, hypertension, and obstructive sleep apnea in about 77, 60, and 85% of the patients respectively [24]. Significant drop in total cholesterol, LDL, and triglycerides has been reported as well [24]. Recent studies have demonstrated efficacy and superiority of bariatric surgery over conventional weight loss therapy, in prevention of diabetes [33], and in the management of diabetes [34]. Findings from another study suggest the potential role for a combination of medical therapy and bariatric surgery in the treatment

of diabetes in patients with uncontrolled diabetes [35]. In fact this study suggests that this combination might be superior to intensive medical therapy for achieving euglycemia. Pontiroli et al have reported that decreased visceral adiposity is associated with decreased circulating levels of adhesion molecules (ICAM-1, Endothelin 1 and E-selectin) [36]. Others have reported that gastric bypass and gastric banding can reduce long term mortality and cardiovascular mortality [37].

CONCLUSION

Over the last few decades, the prevalence of obesity has increased and has become a significant health problem. New medications are being developed and some have shown promising results in the treatment of obesity and in improving cardiovascular risks associated with obesity. Many medications used for other indications have weight loss effects. Evaluation of these medications for weight loss seems to be a logical step especially considering the encouraging results with Qsymia and bupropion/naltrexone combination. Long term studies will be needed to evaluate and compare the efficacy and cardiovascular benefits of different weight loss interventions. The current developments paint an optimistic picture for the clinicians and the patients. Hopefully some of these new medications will provide more efficacious and better tolerated treatment options for obese patients and will decrease the need for invasive bariatric surgeries.

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Highlights

1. Belviq and Qsymia approved for long term treatment of obesity.
2. Metformin might have greater role in treatment of obesity, than is appreciated.
3. Modest weight loss has significant health benefits.

Table 1

Efficacy of weight loss medications

Medication	Percentage (approximate) of people who lose at least 5% of their body weight [*]	Adverse effects	Comments
Lorcaserin	50%	Headache, dizziness	Risk of serotonin syndrome
Qsymia	70% with high dose combination	Dry mouth, paresthesia	contraindicated in people with glaucoma, hyperthyroidism, unstable heart disease
Orlistat	50%	Flatulence, Vitamin deficiencies	Replace fat soluble vitamins
Metformin	50%	GI disturbance, diarrhea	Risk of lactic acidosis
Exenatide	50%	Nausea, vomiting	Risk of pancreatitis
Liraglutide	76% with 3 mg dose	Nausea, vomiting	Contraindicated if history or family history of Medullary thyroid carcinoma

^{*} Efficacy of some of these medications was evaluated in small studies with significant limitations (e.g. lack of gender, ethnic and racial diversity). The results might not be applicable to general population.