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Therapy of obese patients with cardiovascular disease

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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 antiobesity drugs are under development. Bariatric surgery has been shown to be effective in the treatment of obesity and its comorbidities. The available data suggest 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 antiobesity drugs.

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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].

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 proinflammatory and prooxidative 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$25–30 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 25–29.9 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 link 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 past four decades, but the decline is more pronounced in obese and overweight people, than in lean people [7]. This shows that at present 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 nonselective 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 probably 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].