

Review Article

Weight Loss Is Still an Essential Intervention in Obesity and its Complications: A Review

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The prevalence of obesity is more than 20% in many developed countries and it increases in developing countries. Obesity is associated with metabolic disorders, cardiovascular diseases, pulmonary diseases, digestive diseases, and cancers. Although other specific treatments for these complications exist, weight loss is still an essential intervention in obesity and its complications. Therapeutic life change, behavior modification, pharmacotherapy, and surgery are major approaches to weight loss. In addition, medicine used in diabetes such as Glucagon-like peptide-1 analogues may be a new type of medicine for obesity, at least for those obese patients with diabetes.

1. Introduction

In 2005 the International Association for the Study of Obesity reported that the prevalence of obesity, defined by $BMI \geq 30 \text{ kg/m}^2$ is more than 20% in many European countries [1]. Future obesity for adults in the United States was projected on the basis of National Health and Nutrition Examination Study. By 2030, 86.3% American adults will be overweight or obese; 51.1% of them will be obese. Total health-care costs attributable to obesity/overweight would double every decade to 2030, accounting for 16–18% of total US health-care costs [2]. In China, a fast developing country, the prevalence of overweight and obesity also increased in the last two decades. The prevalence of overweight and obesity in 2008 in Chinese population aged 20 years or older reached 24.9%, 4.9% in women and 30.8% and 6.0% in men, respectively [3]. Timely and effective development and implementation of corrective approaches are needed to avoid the catastrophic health and social consequences.

2. Obesity and Chronic Diseases

Obesity is associated with a cluster of metabolic risk factors for coronary heart disease (CHD), known as metabolic syndrome. Abdominal obesity is an essential component of

this syndrome, other components include impaired glucose regulation and type 2 diabetes mellitus; hypertriglyceridemia and/or low serum HDL-cholesterol levels; hypertension. In addition, increased serum levels of C-reactive protein; apolipoprotein B; small, dense LDL particles are also associated with abdominal obesity [4, 5]. The epidemic of obesity is accompanied by the increase of these metabolic risk factors. The drastic increase in the prevalence of obesity has played an important role in the spread of diabetes not only in the United States [6, 7], but also in China. The prevalence of diabetes increases from 12.8% in those with a BMI of 25.0 to 29.9 kg/m^2 to 18.5% in those with a BMI greater than 30 kg/m^2 . This increase even occurs in rather lean population in Chinese, that is, the prevalence of diabetes increased from 4.5% in those with a BMI < 18.5 kg/m^2 to 7.6% in those with a BMI of 18.5 to 24.9 kg/m^2 [8]. The association of hypertension and obesity has been described elsewhere [3, 9–12]. Consequently, the increase of BMI is associated with the increased cardiovascular diseases (CVD). For instance, the average BMI in patients with stroke is 25.5 kg/m^2 , compared with 23.7 kg/m^2 in those without CVD in Chinese [3]. The risk of fatal and nonfatal myocardial infarction and ischemic stroke increases consistently with increasing BMI in other population [13, 14].

Obesity is also complicated with pulmonary diseases such as obesity hypoventilation syndrome [15]. The Pickwickian syndrome is a severe form of the obesity-hypoventilation syndrome, involving extreme obesity, irregular breathing, somnolence, cyanosis, secondary polycythemia, and right ventricular dysfunction.

Moreover, obesity is associated with a few digestive diseases. The risk of symptomatic gallstones increases linearly with BMI [16, 17]. Obesity is associated with nonalcoholic fatty liver disease (NAFLD) that encompasses a spectrum ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. Most of the available data suggests that steatosis affects approximately 75%, steatohepatitis approximately 20%, and cirrhosis approximately 2% of obese patients [18–20].

Overweight and obesity also increase the risk of cancer. A prospective study in more than 900,000 US adults [21], shows overweight and obesity could account for 14% of all deaths from cancer in men and 20% of deaths in women. A meta-analysis of 282,137 incident cases [22], demonstrated that in men, a 5 kg/m² increase in BMI was strongly associated with oesophageal adenocarcinoma and with thyroid, colon, and renal cancers. In women, strong associations between a 5 kg/m² increase in BMI and endometrial, gallbladder, esophageal adenocarcinoma, and renal cancers were recorded. Associations were stronger in men than in women for colon cancer. A stronger association in Asia-Pacific populations between increased BMI and premenopausal and postmenopausal breast cancers was recorded. Moreover, the risk of osteoarthritis of weight-bearing joints is increased in overweight and obese persons and the knees were most often involved [23].

Compared with general obesity, abdominal obesity seemed to be more harmful than general obesity. The risk of diabetes increases with increases in abdominal fat mass, waist circumference, or waist-to-hip circumference ratio independent of BMI value [24, 25]. Excess body fat deposited viscerally rather than elsewhere in the body is associated with higher risk for hypertension [26]. Abdominal fat mass is a risk factor for stroke independent of BMI, but not independent of diabetes, smoking, and hypertension [27].

3. Mechanism Underlying Chronic Complications and Intervention in Obesity

Although a great progress has been achieved in the study of mechanism underlying chronic complications in obesity, we are yet to clarify the specific mechanism. Insulin resistance is hypothesized to be the common underlying pathogenic mechanism of metabolic syndrome [28]. The ectopic accumulation of triglycerides in nonadipose tissue may be involved in the pathogenesis of insulin resistance [29]. However, according to data obtained from nondiabetic subjects in the Framingham Offspring Study, insulin resistance might not be the only precedent condition in metabolic syndrome, other independent physiologic process may be involved [30]. For instance, IKK β /NF- κ B in the mediobasal hypothalamus—in particular in the hypothalamic POMC

neurons may represent a primary pathogenic link between obesity and hypertension [31].

4. Weight Loss: An Essential Intervention for Obesity Complicated with Chronic Diseases

Weight loss has been proved to be an essential for the prevention, and treatment for obesity-related chronic diseases [22]. Sustained modest weight loss among obese persons would yield substantial benefit, reducing the lost number of years of life with hypertension, hypercholesterolemia, type 2 diabetes and the expected lifetime incidence of CHD and stroke [32, 33].

Modest weight loss over short-term (6 weeks) and longer-term (6–12 months) periods is associated with reduction in subsequent cardiovascular mortality for the following 4–5 years even in those with preexisting cardiovascular disease [34]. In morbidly obese subjects, bariatric surgery effectively induces weight loss and improvement in sleep-disordered breathing severity and symptoms [35]. Weight loss program also reported to have resulted in a highly significant improvement in symptoms in overweight patients with knee osteoarthritis [23]. Weight loss may not be a desirable for patients with cancer, however, it improved quality of life in breast cancer survivors [36]. Systematically review of 78 randomized trials has shown that lifestyle-induced weight loss was safe intervention for NAFLD, and that a weight loss \geq 7% improved histological disease activity, but was achieved by <50% patients [37].

Nevertheless, we should be aware of the side effect of weight loss. The risk of gallstones increases during weight loss, particularly when weight loss is rapid [38]. This increased risk is related to increased bile cholesterol supersaturation, enhanced cholesterol crystal nucleation, and decreased gallbladder contractility [39]. In a small 6-month study, asymptomatic gallstones developed in 6/11 of subjects following the lower fat diet, but in none with the higher fat regimen [40]. A daily dose of 500 mg of ursodeoxycholic acid for 6 months is effective prophylaxis for gallstone formation following gastric restrictive procedures [41].

5. Approaches to Weight Loss

Currently available weight-loss treatments include dietary intervention, increased physical activity, behavior modification, pharmacotherapy, and surgery. In China, acupuncture has been applied in the treatment of obesity, but no well-designed clinical trial has been reported.

5.1. Dietary Intervention. Negative energy balance is more readily achieved by decreasing food intake than by increasing physical activity for most obese people. Many obese persons can achieve short-term weight loss by diet alone, but successful long-term weight maintenance is much more difficult. However, dietary intervention is still considered as the cornerstone of weight-loss therapy. Weight-loss diets

can be classified according to their energy content. Low-calorie diets (LCDs) contain 800 to 1500 kcal/day and are consumed as liquid formula, nutritional bars, conventional food, or a combination of these items. Very-low-calorie diets (VLCDs) contain less than 800 kcal/day and are generally high in protein (70–100 g/day) and low in fat (<15 g/day). The NIH guidelines recommend a more aggressive energy deficit of 500 to 1000 kcal/day for persons with more severe obesity (BMI \geq 35.0 kg/m²). Individuals intended to reduce body weight should continue to be advised on regularly self-monitoring of energy intake and expenditure as well as creating a consistent daily energy deficit [42]. Low-fat diets have traditionally been prescribed for weight loss because such diets facilitate energy restriction, due to their low energy density. Low-carbohydrate diets have been evaluated as a potential therapy for obesity in RCTs. The mechanism responsible for the decrease in body weight associated with a low-carbohydrate diet can be completely explained by a decrease in total energy intake [43].

5.2. Physical Activity. There is a profound increase in energy expenditure during exercise. However, moderate endurance exercise, such as brisk walking for 45 to 60 minutes, 4 times a week, usually induces only minor weight loss in 1 year. Although exercise alone is not an effective strategy for inducing initial weight loss, increasing physical activity is an important component of successful long-term weight management. Fat-free mass (FFM) represents a key determinant of the magnitude of resting metabolic rate (RMR), which follows a decrease in lean tissue could hinder the progress of weight loss. Exercise training promotes a favorable change in body composition for weight loss [44]. Weight-loss maintenance requires expending approximately 2500 kcal/wk during exercise [45, 46]. This level of energy expenditure can be accomplished through vigorous activity (aerobics, cycling, or jogging) for approximately 30 min/day or more moderate activity for 60 to 75 min/day.

5.3. Behavior Modification. Behavior modification for the treatment of obesity is perhaps the most important but difficult approach. It usually involves multiple strategies to modify eating and activity habits [47]. These strategies include: eating stimulus control, self-monitoring, problem-solving skills, cognitive restructuring, social support, and relapse prevention. Treatment by an enhanced brief lifestyle counseling (including medications) in primary care results in about a 4.6 kg in 2-year trials [47].

5.4. Pharmacotherapy. Conventional obesity therapy is associated with a high rate of relapse. Pharmacotherapy becomes a key method for the treatment of obesity. Unfortunately, Orlistat is only available medicine for long-term therapy, but the efficacy is limited [48, 49]. Pharmacotherapy alone is less successful than being part of a comprehensive weight-loss program that includes diet, exercise, and behavior modification [50]. Benzphetamine HCl, phendimetrazine tartrate, phentermine, diethylpropion hydrochloride, mazindol, and orlistat are the drugs currently approved by the US Food

and Drug Administration for the treatment of obesity. All currently approved weight-loss drugs act as anorexiant, with the exception of orlistat. Anorexiant affect the monoamine system in the hypothalamus and thereby enhance satiety. In the last several years, fenfluramine, phenylpropranolamine, sibutramine, and dexfenfluramine were withdrawn from the market because of the increased incidence of either valvular heart disease or cardiovascular diseases/stroke associated with their use [51, 52]. All anorexiant drugs, except mazindol, are derived from β -phenylethylamine, the amphetamine precursor. The structures of these drugs have been chemically altered to reduce the potential for abuse. Even though, these anorexiant medications are strictly regulated for short-term therapy. A low-dose anorexiant has been tested for long-term therapy. In a phase 3 extension study, a controlled release of phentermine/topiramate (an anticonvulsant) in conjunction with lifestyle modification resulted in up to 10.5% weight-loss for 108 weeks and is well-tolerated. It may provide an effective option for the sustained treatment of obesity [53].

Orlistat works by binding to lipases in the gastrointestinal tract and blocks the digestion of dietary triglycerides. This inhibition of fat digestion reduces micelle formation and, subsequently, reduces the absorption of long-chain fatty acids, cholesterol, and certain fat-soluble vitamins. Excretion of about 30% of ingested triglycerides, which is near the maximum value, occurs at a dose of 360 mg/day (120 mg t.i.d with meals). Orlistat has no effect on systemic lipases because less than 1% of the administered dose is absorbed [54]. Orlistat is notorious for its gastrointestinal side effects, steatorrhea. Serious liver injury events including liver failure in patients using orlistat were collected by FDA's Adverse Event Reporting System. The most commonly reported adverse events of serious liver injury were jaundice, weakness, and abdominal pain. Even though no definite association between liver injury and orlistat has been established, FDA urges both healthcare professionals and consumers to report side effects from the use of orlistat [55].

Metformin has shown its efficacy for weight loss in obese patients with type 2 diabetes [48]. GLP-1 analogs or GLP-1 receptor agonists used in type 2 diabetic patients also demonstrated a weight loss effect [56]. Therefore, they could be potential medications to treat obesity or an approach for weight loss. Theoretically, fat loss could also be achieved through a decrease in the size and number of adipocytes through apoptosis, so that targeting adipocyte apoptosis could be a novel strategy for obesity therapy [57].

5.5. Surgical Therapy. Bariatric surgery is a safe and effective treatment for morbid obesity and related metabolic diseases [58]. It can be categorized as those that primarily cause gastric restriction and those that primarily cause biliopancreatic bypass, subsequently, nutrient maldigestion and malabsorption [50–60]. Perioperative mortality rate after bariatric surgery is less than 0.5% when the procedure is performed by experienced surgeons in experienced centers [61–63]. Among them, three-fourths of the deaths are due to anastomotic leaks and peritonitis and one-fourth are due to pulmonary embolism. Laparoscopic surgery may be a safer treatment than open surgery. Compared with open

surgery, laparoscopic surgery is associated with lower risk of wound infection and incisional hernia. As an elective procedure, bariatric surgery should be carefully selected, extensively evaluated, and optimized in order to achieve optimal outcomes. In 1991, guidelines for the surgical treatment of obesity were established by an NIH Consensus Conference, since then these guidelines had hardly been changed [64, 65]. According to these guidelines, eligible candidates for surgery include patients with a BMI 40 kg/m² or more or those with a BMI of 35.0 to 39.9 kg/m² and one or more severe medical complications of obesity.

In summary, obesity becomes a world-wide epidemic, the chronic complications result in huge burdens for the patients, family, and society. Although progresses have been made in the management of obesity, an effective safe intervention remains to be developed.

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