Medical Therapy for Obesity: Present and Future

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Key words: obesity, co-morbidity, diabetes, cardiovascular disease, stroke, pharmacotherapy

Abstract

The prevalence of obesity worldwide has risen sharply during the last four decades. The etiology of obesity is complex and includes a host of genetic influences in addition to the overconsumption of energy coupled with a sedentary lifestyle. Obesity is known to cause or exacerbate many co-morbid conditions such as diabetes, hypertension, dyslipidemia, coronary heart disease, stroke, certain cancers, arthritis and obstructive sleep apnea. Modest weight losses of 5–10% of actual weight are related to significant improvements in co-morbid conditions, but unfortunately the rate of recidivism with short-term therapy for obesity is high. The recent recognition of obesity as a chronic disease that should be treated with long-term programs and possibly with polypharmacy, and the alarming increase in its prevalence, have prompted extensive research and the development of new pharmacotherapy.

IMAJ 2004;6:760–765

The prevalence of overweight and obesity has increased sharply during the last four decades, becoming the leading health problem in developed countries in the 21st century [1,2]. Obesity is associated with increased morbidity and mortality because it causes or exacerbates co-morbid conditions such as diabetes, hypertension, hyperlipidemia, coronary heart disease, stroke, osteoarthritis, sleep apnea and certain cancers [3]. The pattern of distribution of fat has clinical importance as well, with abdominal obesity being associated with a higher risk of cardiovascular and metabolic disease than a more peripheral fat distribution [4]. Modest weight losses of 5–10% have been shown to significantly improve co-morbid conditions [3]. Despite the expected health benefits from weight loss, long-term success with medical therapy has been disappointing, with 90–95% of persons who lose weight subsequently regaining it [2].

Although there is a strong genetic component for development of obesity, the increased prevalence of the disease is best explained by an energy imbalance due to overconsumption of palatable caloric-dense foods in conjunction with decreased physical activity in a susceptible population. Obesity is now viewed as a chronic disease, probably necessitating lifelong therapy similar to other chronic disorders. There is an urgent need to develop population strategies to prevent obesity in all ages and ethnic groups.

Etiology

Body weight is determined by the interaction among genetic, environmental and psychosocial factors. Energy imbalance, meaning the difference between food intake and energy expenditure (resting metabolism and physical activity), is thought to be the main culprit accounting for weight gain. Even small energy imbalances over time can have a great impact on weight [2]. Weight homeostasis is coordinated by a complex system with the afferent arm emanating from the adipose tissue and gastrointestinal and nervous systems. The integration of the different signals is processed in the central nervous system which, in turn, regulates energy expenditure and energy intake. It is due to the interaction and redundancy between systems that the present approaches of energy deprivation alone or single pharmacotherapies have failed in the treatment of obesity.

Hypocaloric diet and exercise are the cornerstones for weight loss

There has been a rapidly increasing expansion of knowledge regarding the origins of obesity. Leptin, discovered in 1994, is a hormone synthesized and secreted from adipose tissue and whose main function is to indicate the state of fat reserve centrally, affecting food intake and energy expenditure [5]. Leptin deficiency was found to be the cause of obesity in only a few human cases with the vast majority of obese patients demonstrating high leptin levels, in proportion to fat mass, suggesting a state of leptin resistance [6]. A decrease in fat mass due to weight loss causes a decrease in leptin levels, which – through different mechanisms – increases appetite and decreases metabolic rate, preventing further weight loss.

New gut hormones have been discovered, joining the already known gut hormones (e.g., cholecystokinin) with important roles in the regulation of hunger and satiety. Ghrelin, a gut hormone secreted from the stomach and duodenum, plays an important role in feeding initiation and cessation, with its levels rising before meals and rapidly decreasing at the end of the meal [7]. PYY is a

peptide secreted postprandially by endocrine cells lining the distal small bowel and colon. This hormone is secreted in proportion to calories ingested and promotes satiety. PYY secretion was found to be reduced in obese subjects, and its infusion reduced hunger in both obese and lean subjects [8]. Another gut-derived hormone, glucagon-like peptide 1, a product of the glucagon gene expressed in endocrine cells of the intestinal mucosa, has an insulinotropic effect and promotes satiety, therefore decreasing food intake [9].

Centrally acting neurotransmitters involved in appetite control include orexogenic (appetite-stimulating) peptides such as neuropeptide Y, endogenous opioid peptides, endocannabinoids and melanin-concentrating hormone, among others [9]. There are also anorexigenic (appetite-suppressing) hormones of which the most significant is α-MSH, a product of the *POMC* gene and the endogenous agonist of melanocortin receptor 3 and 4 (MC3-R and MC4-R). Mutations in MC4-R were found in 0.5–5.8% of cases of obesity in humans, making it the most common form of monogenic obesity. Other central anorexigenic hormones include corticotropin-releasing hormone and cocaine and amphetamine-regulated transcript.

Energy expenditure is regulated by the brain through the activation of efferent pathways, primarily the sympathetic system. Activation of adrenoreceptors, especially β3-adrenoreceptors that are expressed in humans predominantly in visceral adipose tissue, regulates lipid metabolism and thermogenesis. There is also great research interest in the uncoupling proteins, which are mitochondrial proteins whose function is to uncouple substrate oxidation from the generation of ATP in adipose tissue, thereby regulating energy expenditure. Modulation of energy expenditure is crucial since changes in body weight are coupled to compensatory changes in energy expenditure opposing the change in weight [10].

Co-morbid conditions related to obesity

Obesity is related to increased morbidity and mortality because it causes or exacerbates many co-morbid conditions [Table 1].

Table 1. Obesity-associated co-morbidities

Type 2 diabetes mellitus
Hypertension
Coronary heart disease
Dyslipidemia
Stroke
Obstructive sleep apnea
Non-alcoholic steatohepatitis
Cholelithiasis
Cancer
Postmenopausal breast cancer
Endometrial carcinoma
Colon cancer
Gallbladder cancer
Prostate cancer
Osteoarthritis

Type 2 diabetes mellitus

Diabetes is strongly associated with obesity, with the increased prevalence of obesity being accompanied by a 25% increase in the prevalence of type 2 DM in the past decade [11]. In the Nurses' Health Study, increases in body mass index within the normal range were associated with a fourfold risk of developing type 2 DM (women with BMI <22 kg/m^2, as compared to women with BMI 23–25 kg/m^2). The risk of developing type 2 DM was 93 times higher in women with BMI >35 kg/m^2 compared to women with BMI <22 kg/m^2. Weight loss of 5 kg in this cohort was associated with a 50% reduced risk for developing type 2 DM [12]. Lifestyle changes (weight reduction, increase in fiber, decrease in total and saturated fat consumption, and physical activity) have been shown to prevent the progression to type 2 DM in high risk individuals [13]. Visceral adiposity confers a higher risk for insulin resistance and glucose intolerance at any given BMI [4]. Moderate weight reduction (5–10% of actual weight) has been shown to markedly improve insulin resistance and glucose control [3].

Hypertension

Hypertension is clearly correlated with BMI but the precise mechanism by which obesity causes hypertension is not yet clear. In obesity-mediated hypertension there is an increase in sympathetic activation and increased sodium resorption, possibly resulting from insulin resistance and/or hyperleptinemia [14]. Hypertension is three times more common in obese subjects than in normal weight individuals and a moderate weight loss has been shown to lower blood pressure [3].

Moderate weight loss of 5–10% of actual weight improves obesity-related co-morbidities

Cardiovascular disease

Excess weight confers a higher risk for coronary heart disease in both men and women [15]. Obesity is related to a cluster of risk factors such as hypertension, glucose intolerance and hyperlipidemia, which are known to cause and exacerbate CAD. Recently, obesity was shown to be an independent risk factor for developing congestive heart failure, with obese subjects having twice the risk of developing CHF as non-obese subjects [16]. The risk of CAD already increases in BMIs within the normal range [17], and with abdominal obesity.

Metabolic syndrome

The metabolic syndrome encompasses a cluster of risk factors conferring a high risk for the development of cardiovascular disease and type 2 DM. The hallmarks of the syndrome are abdominal

DM = diabetes mellitus
BMI = body mass index

CAD = coronary artery disease
CHF = congestive heart failure

Table 2. Diagnostic criteria for the diagnosis of the metabolic syndrome according to ATP III guidelines: Patients should fulfill at least 3 of the diagnostic criteria

	Men	Women
Waist circumference	⩾ 102 cm	⩾ 88 cm
Triglycerides	⩾ 150 mg/dl	⩾ 150 mg/dl
High density lipoprotein-cholesterol	< 40 mg/dl	< 50 mg/dl
Blood pressure	⩾ 130/⩾ 85	⩾ 130/⩾ 85
Fasting glucose level	⩾ 110 mg/dl	⩾ 110 mg/dl

obesity, glucose intolerance, hyperinsulinemia, hypertension, a characteristic dyslipidemia (elevated triglycerides and low high density lipoprotein-cholesterol) and a prothrombotic/pro-inflammatory profile [18]. The Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III) included the metabolic syndrome as a secondary target of therapy beyond elevated cholesterol in recognition of the increased risk of cardiovascular disease in these patients, at any cholesterol level. Weight reduction and regular physical activity are the first-line therapy recommended for patients with the metabolic syndrome [19]. Table 2 shows the diagnostic criteria for the metabolic syndrome according to the ATP III.

Gastrointestinal disease

The risk of developing gallstones increases with rising BMI. The risk for gallstone formation is increased during weight loss, particularly rapid weight loss, but also during weight cycling [20]. Non-alcoholic fatty liver disease is a common disorder that may progress to end-stage liver disease. Its prevalence in obese individuals has been reported to be as high as 74%; in these patients liver function tests improve with weight loss [21].

Cancer

There is epidemiologic evidence linking obesity with increased risk for certain cancers, including colon, endometrial, gallbladder and postmenopausal breast cancer [22]. In the Nurses' Health Study, women gaining more than 9 kg during adult life doubled the risk for postmenopausal breast cancer when compared to women who maintained a stable weight [23].

Calle et al. [24] recently showed that cancer mortality was increased by 52% in men and 62% in women with BMI >40 kg. In this study BMI was associated with increased mortality due to cancer of the esophagus, colon, rectum, liver, gallbladder, pancreas and kidney, and non-Hodgkin's lymphoma and multiple myeloma [24].

Clinical assessment and treatment of the obese patient

The degree of obesity is estimated by calculating the body mass index (BMI = weight/height, where weight is measured in kilograms and height in meters). The BMI is a useful measure of fatness independent of height and weight/height^2, and together with the measurement of waist circumference, can be used to determine health risk [Table 3].

The treatment of overweight and obese subjects includes diet modification, physical activity and behavioral therapy. Pharmacotherapy may be indicated in patients with a BMI ⩾ 30 kg/m^2 or with a BMI ⩾ 27 kg/m^2 with at least one co-morbidity related to obesity. Surgery for obesity may be indicated in patients with a BMI ⩾ 40 kg/m^2 or a BMI ⩾ 35 kg/m^2 with the presence of obesity-related co-morbidities.

Table 3. Classification of obesity

Underweight	<18.5 kg/m^2
Normal weight	18.5–24.9 kg/m^2
Overweight	25–29.9 kg/m^2
Obese	
Class I	30–34.9 kg/m^2
Class II	35–39.9 kg/m^2
Class III	40 kg/m^2

Adapted from the National Heart, Lung, and Blood Institute: The practical guide to identification, evaluation and treatment of overweight and obesity in adults. NIH publication # 00-4084, 2000.

An initial weight loss of 10% of initial body weight over a period of 6 months is a realistic goal for most patients. A plan including strategies and goals should be discussed between the healthcare provider and the patient.

Dietary modification

Weight loss is promoted through a negative caloric balance. The low calorie diet, providing 800–1,500 kcal/day is the cornerstone of dietary management [25]. Very low calorie diets, providing 250–800 kcal/day, are generally not indicated because they require intensive medical monitoring and the outcome at the end of 1 year of treatment with a very low calorie diet is not significantly different from that of low calorie diets [26]. A caloric deficit of 500–1,000 kcal/day will result in a desirable 0.5–1 kg weight loss per week.

Pharmacotherapy should be reserved for those with BMI ⩾ 30 or ⩾ 27 with a co-morbidity and can enhance weight loss if prescribed with diet and exercise

Caloric balance (calories ingested vs. calories burned) is the major determinant of weight loss. Macronutrient composition is a new field that has gained wide public interest. Recently several randomized trials were published comparing low carbohydrate diets to low fat diets, reinforcing its short-term safety with appropriate medical supervision and supplementation. Since the low carbohydrate diet and other popular diets do not provide the recommended dietary allowances, and there are no long-term trials on effectiveness and safety, they cannot be recommended. A low fat diet may be particularly important in weight maintenance following weight loss [27]. A diet providing 30% of calories from fat, 10–20% from protein and 40–55% as carbohydrates, as recommended by the National Cholesterol Education Program III, is also appropriate for weight loss.

Exercise therapy

Physical activity should be implemented in every weight loss program. Exercise increases energy deficit, improves co-morbid conditions, alleviates depressive symptoms and helps to maintain weight loss. Patients should be encouraged to accumulate at least 150 minutes of moderate intensity exercise per week [13,28].

Behavioral therapy

Behavior modification techniques are used in the treatment of obesity to generate a new set of eating and physical activity patterns that will induce weight loss and permit weight loss maintenance. Behavioral therapy is generally provided by weekly sessions in which the patients learn about nutrition, problem solving, stimulus-control techniques and self-reinforcement. The food diary is a simple tool that was shown to be effective in weight loss programs, especially since many obese subjects tend to underestimate their caloric intake [29].

Pharmacotherapy

Pharmacotherapy may be indicated in patients with a BMI $\geqslant$ 30 kg/m^2 or $\geqslant$27 kg/m^2 and at least one co-morbidity related to obesity, after diet and lifestyle changes alone have failed. Obesity is a chronic disease for which the traditional medical therapy consisting of diet, exercise and short-term drug therapy has proven unsuccessful in the long term. On the other hand, pharmacologic therapy for obesity has gone through waves of optimism, particularly after Weintraub et al. [30] were able to demonstrate that weight loss could be maintained for prolonged periods (3 years), with behavioral therapy and treatment with a combination of phentermine and fenfluramine only to be dealt a swift blow when fenfluramine was withdrawn from the market in 1997, along with dexfenfluramine due to a high incidence of cardiac valvulopathies associated with its use.

Weight loss medications that are currently available fall into two categories: drugs that decrease food intake (decreasing appetite or increasing satiety) and drugs that decrease fat absorption. Drugs that decrease food intake work centrally by increasing levels of norepinephrine, serotonin, or both.

- *Phentermine* is a noradrenergic centrally active drug approved by the U.S. Food and Drug Administration for short-term use, generally up to 12 weeks. Phentermine was shown to be safe and effective in the treatment of obesity [31], although most of its recent long-term use was in conjunction with fenfluramine. The prescribed dose of phentermine ranges between 15 and 37.5 mg/day, given as a single dose in the morning. Side effects include insomnia, dry mouth, palpitations, hypertension and constipation.
- *Sibutramine* (Reductil®) is a serotonin and norepinephrine reuptake inhibitor, introduced to the market in 1997 for the treatment of obesity. In Israel sibutramine is approved for long-term use up to 1 year, while in the U.S. it is FDA approved for long-term use up to 2 years. Sibutramine has been evaluated in several multicenter trials lasting up to 24 months [32]. The weight loss promoted by sibutramine is related to a dose-dependent decrease in food intake due to decreased appetite and early satiety and a questionable effect on thermogenesis [33]. In a dose-ranging (10,15 and 20 mg), placebo-controlled, double-blind study of 1,047 patients, at 6 months, 67% of subjects achieved a 5% weight loss, 35% lost 10% or more of initial weight, while 20% of placebo-treated patients lost >5% of their original body weight [34]. The same rate of weight loss was observed in multiple trials. Overall, patients treated with sibutramine lose 5–8% of their body weight and 3–4 kg more than placebo-treated patients. It is important to emphasize that once therapy is stopped patients regain weight [35]. Weight reduction achieved at 4 weeks predicts the weight loss achieved at 6 months. Sibutramine was also shown to be effective in maintaining weight loss after a very low calorie diet. Patients treated with sibutramine for 1 year maintained a 15% weight loss, with the placebo group regaining part of the weight lost through the very low calorie diet [36].

  Sibutramine is given once daily in the morning, with a usual starting dose of 10 mg/day. The dose can be increased to 15 mg or decreased to 5 mg. The drug is well tolerated, with the most common side effects being constipation, insomnia and dry mouth. Nevertheless, increases in blood pressure and pulse may occur, requiring monitoring and deferring therapy in patients with uncontrolled hypertension. There is no need to taper the dose before discontinuing the medication and side effects are reversible once the drug is discontinued.

- *Orlistat* (Xenical®) is an inhibitor of pancreatic lipase, preventing hydrolysis of dietary fat and impairing digestion of approximately 30% of dietary fat. It is the only nutrient absorption inhibitor presently approved for use for weight loss. Orlistat is presently FDA approved for long-term use up to 2 years with the same length of continuous use approved in Israel. Orlistat has recently been FDA approved for use in obese adolescents. The weight loss effect is promoted by a decrease in caloric absorption due to partial malabsortion of fat intake. Orlistat is significantly more effective than placebo in promoting weight loss. In a multicenter randomized, double-blind, placebo-controlled study with different doses of orlistat for 1 year, patients treated with orlistat lost significantly more weight than those treated with placebo (7.0 kg, 7.9 kg in the 60 mg or 120 mg group, compared to 4.1 kg in the placebo group). A higher proportion of patients treated with orlistat maintained a weight loss of $\geqslant$ 5% after 2 years [37]. Prospective randomized placebo-controlled trials showed that orlistat-treated patients had an average weight loss of 9% of their original weight during the first 6 months of therapy, resulting in an excess weight loss of 3–4 kg compared to placebo-treated patients [35]. Orlistat therapy, along with lifestyle changes, promoted a 37% risk reduction in developing type 2 DM in obese patients treated with the drug for 4 years [38].

  The recommended therapeutic dose of orlistat is 120 mg before or immediately after each meal (three times daily). It is also possible to omit the dose if the designated meal does

FDA = Food and Drug Administration

not contain fat. The drug is minimally absorbed with the major side effect being steatorrhea, especially if the diet consists of more than 30% of calories as fat [39]. It is recommended to take a multivitamin apart from the ingestion of the drug because of concern of impaired absorption of fat-soluble vitamins. Gastrointestinal side effects may be lessened by introducing the medication gradually and by adding fiber to the diet.

Future pharmacotherapy for the therapy of obesity

Obesity therapy poses a healthcare challenge due to its epidemic proportions and economic consequences. The tremendous scientific interest in the field, with a wide variety of drugs at different stages of clinical research, is therefore not surprising. Currently under research are drugs that decrease food intake, drugs that impair macronutrient absorption or affect fat metabolism, and drugs that increase thermogenesis.

A few drugs that are already FDA approved for other conditions are now being evaluated for their effect on weight loss. Clinical trials are evaluating the safety and efficacy of topiramate, wellbutrin and metformin as weight loss medications.

The hope that leptin would be the cure for obesity was short lived. Although leptin therapy in physiologic doses did not promote a significant weight loss, a trial of pharmacologic doses of leptin was able to show a dose-dependent weight and fat loss in obese and lean subjects. Another possible clinical use of recombinant leptin is for maintenance of weight loss through diet.

Gut hormones provide an exciting new field in obesity therapy and are being extensively researched. Glucacon-like peptide 1 has an insulinotropic effect, inhibits gastric emptying and increases satiety. Since the hormone is rapidly metabolized, resistant analogues and peptidase inhibitors are presently being evaluated in clinical trials and appear to be promising drugs for the treatment of obese patients with type 2 DM [40]. In early stages of evaluation as potential targets for obesity are cholecystokinin receptor agonists, ghrelin antagonists and PYY agonists.

Beta 3 adrenoreceptor agonists are currently being evaluated for weight loss. Non-selectivity with activation of β1 and β2 receptors and poor oral availability are the main problems encountered in clinical trials so far. There is great research interest in the area of the uncoupling proteins but their role in human physiology still needs to be elucidated.

Recombinant ciliary neurotrophic factor, a drug that was developed for treatment of amyotrophic lateral sclerosis, was shown to reduce food intake and interestingly enough there is no rebound weight gain following cessation of the drug. Currently this drug is undergoing phase III trials in obese humans. Of concern are the side effects of the drug (nausea, cough, musculoskeletal and injection site pain) and the development of antibodies that decrease drug efficacy. Another promising drug is rimonabant, an antagonist of the central cannabinoid type 1 receptor that is currently in phase III clinical trials for weight loss in obese patients [35].

Summary

Obesity is a chronic disease that has already reached epidemic proportions worldwide. The health consequences and associated economic burden on society make it imperative to develop strategies to prevent and treat obesity. The high rate of recidivism and the modest weight loss achieved by most current drugs have pushed research to seek for a multimodal approach for containment of the disease. Population-based "lifestyle change" programs, along with pharmacologic agents affecting different mechanisms involved in weight homeostasis will likely be necessary to halt this overwhelming epidemic.

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Capsule

Sexual transmission prevention of HIV

To date, no microbicide candidate has provided complete protection from vaginal acquisition of simian or human immunodeficiency virus (HIV). Lederman et al. tested a modified form of the chemokine RANTES, which is known to block HIV entry in cultured cells through the down-regulation of expressing the chemokine receptor CCR5, the dominant co-receptor used by HIV to infect cells. Topical vaginal application of a RANTES-containing formula in rhesus macaques protected against subsequent vaginal infection with a hybrid laboratory strain of the virus.

Science 2004;306:485

E. Israeli

Capsule

The molecules behind nicotine addiction

Identification of the nicotinic acetylcholine receptor (nAChR) subtypes that are critical for nicotine dependence will provide insights into addiction mechanisms and should also help to identify potential smoking-cessation targets. Tapper et al. engineered genetically modified mice in which nicotinic 4 receptors were hypersensitive to nicotine. A range of cellular assays and simple behavioral procedures showed that nicotinic activation of 4 nAChRs is sufficient to explain the development of sensitization and tolerance and also to explain the rewarding effects of nicotine.

Science 2004;306:1029

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