Module 23.2

Non-surgical Interventions in Severely Obese Patients

Learning Objectives

- Definition of obesity grades;
- Epidemiology of severe obesity;
- Causes of obesity;
- Goals of therapy;
- Weight reduction interventions
  - Nutritional;
  - Other lifestyle;
- Short- and long-term outcomes of programmes of weight reduction therapy;
- Importance of weight-maintenance programmes.

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Key messages

- Overall prevalence of obesity is increasing;
- Prevalence of severe obesity is increasing at a much faster rate than the prevalence of moderate obesity;
- Severely obese patients are characterized by several alterations that persist unchanged after weight loss and that may be linked to genetic predisposition;
- Conventional (non-invasive) therapy of severe obesity is based on lifestyle modification and includes diet, exercise and behaviour therapy;
- Diets are defined by grades of caloric restriction and macronutrient composition;
- Low-energy diets contain 800-1500 kcal/d and very-low-energy diets ≤800 kcal/d. Either fat or carbohydrate restriction may be defined as well;
- No diet regimen is definitively proved to be superior to another in the long-term;
- Long-term results of the conventional treatment of severe obesity are discouraging. While patients may lose significant weight, only few maintain a satisfactory level of body weight at 5 years;
- Intense structured programmes for weight reduction combined with structured maintenance treatment by multi-disciplinary teams may achieve best results: among persons who complete such programmes, a 25% loss of their initial weight may be achieved, and they can maintain approximately 60% of this weight loss at 6 years.
1. Introduction

Obesity is a substantial public health crisis in a large part of the world. The prevalence is increasing rapidly in numerous industrialized nations worldwide. Due to its related morbidities, obesity has become a major medical and economic issue that deserves urgent attention.

1.1 Definitions

Obesity is characterized by an excess of adipose tissue. Normal, healthy men have a body fat percentage of 15-20%, while normal, healthy women have a percentage of approximately 25-30% (1). Body Mass Index (BMI), represents the ratio between the weight (kg) and the square of the height (m). Among several classifications, the most widely accepted classifications are those from the World Health Organization (WHO), based on body mass index (BMI). The WHO designations (for Caucasians) are as follows:

- Grade 1 overweight (commonly and simply called overweight) - BMI of 25-29.9 kg/m$^2$
- Grade 2 overweight (commonly called obesity) - BMI of 30-39.9 kg/m$^2$
- Grade 3 overweight (commonly called severe or morbid obesity) - BMI ≥40 kg/m$^2$
- The cut-off for each grade should be varied according to the individual’s ethnic background. Recently, the bariatric literature subdivide the Grade 3 overweight to morbid obesity - BMI of 40-50 kg/m$^2$ and super obesity - BMI greater than 50 kg/m$^2$ (2).

1.2 Comorbidities

Severe obesity causes twice the rate of morbidity and mortality as moderate obesity (3). In severely obese persons, excess mortality increases in proportion to increasing BMI: Odd’s ratios of 2.44 and 2.12 (BMI of 45-49.9 kg/m$^2$) and of 4.81 and 3.72 (BMI ≥50 kg/m$^2$) were recently reported, for men and women respectively (4). For persons with severe obesity (BMI ≥40), life expectancy is reduced by as much as 20 years in men and by about 5 years in women (5). Cardiovascular, respiratory diseases and violent deaths are the main causes of mortality in these individuals (4). In addition, relationships have been shown between the degree of obesity and a poor quality of life (6), and with increased rates of prejudice and stigmatisation (7). Apart from total body fat mass, some other aspects of obesity have been associated with comorbidity:

- Fat distribution; abdominal obesity is strongly correlated with the metabolic and clinical consequences of obesity (8).
Waist circumference; significantly increased cardiovascular risk exists in men with waist circumferences of greater than 94 cm (37 in) and in women with waist circumferences of greater than 80 cm (31.5 in), as well as waist-to-hip ratios of greater than 0.95 in men and of greater than 0.8 in women (9).

Age of obesity onset; independently of adult BMI, an elevated BMI during adolescence is strongly associated with the risk of developing obesity-related disorders later in life.

Intra-abdominal pressure by itself may contribute to the pathogenesis of comorbidities such as, reflux oesophagitis, pseudotumour cerebri and thrombophlebitis (10).

2. Epidemiology

The prevalence of obesity in the world has increased dramatically since 1980, except in very poor countries. Approximately 78 million adults above age 20 (37.5 million men and 40.6 million women) and 12.5 million children and adolescents (5.5 million boys and 7 million girls) in the United States are obese (11). Available data from the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project suggest that at least 15% of men and 22% of women in Europe are obese (12,13). Specific data on severe obesity are available for United States and Great Britain. In the USA, from 2000 to 2005, the prevalence of obesity (BMI ≥30 kg/m²) increased by 24%, the prevalence of severe obesity (BMI ≥40 kg/m²) increased by 50% and the prevalence of the super obese with BMI ≥50 kg/m² by 75%; the overall prevalence of subjects with BMI ≥40 kg/m² was 2.2% in 2001 and 3.07% in 2005 (14). In Great Britain severe obesity has tripled in men (from 0.2% to 0.8%) and doubled in women (from 1.4% to 2.6%) in the period 1993-2002 (15).

3. Causes of Obesity Including Genetics

Obesity is a disease caused by the interaction of genetic factors with the environment and with psychological, sociological and social factors. It is likely that the genetic determinants are multiple, with each single variant producing a moderate effect.

3.1 Homeostatic Regulations

Several alterations in the homeostatic regulation of energy balance that may be dependent upon genetic factors are found in obese persons. Two of the more prominent are: homeostasis of food intake when the individual is provided with excess food, and defence against shortage of food. The genetic trait or ‘thrifty gene’ that encourages fat storage in times of prosperity - when highly palatable, calorifically dense foods are readily available at low cost - probably represents an important survival mechanism that served to protect our ancestors in times of famine.

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Energy balance is tightly regulated in humans by a homeostatic mechanism based on a complex system of signalling to metabolic sensing neurons. This signalling system is organized in localized, interconnected sites in the brain. The most important neuro-transmitters are neuro-peptide Y (NPY), Agouti-related peptide (AgRP) and proopiomelanocortin (POMC) which releases $\alpha$-melanocyte stimulating hormone ($\alpha$-MSH). They are located in the arcuate hypothalamic nucleus (ARC). The sensing neurons have synaptic interconnections with each other and projections to neuroendocrine as well as autonomic efferent areas. Examples of such autonomic efferent areas are the paraventricular nucleus and lateral hypothalamic area. Release of $\alpha$-MSH induces a potent catabolic drive: food intake is inhibited, energy expenditure is stimulated and adipose stores are depleted. On the contrary release of NPY provides a potent anabolic effect, stimulating food intake and reducing energy expenditure. ARC NPY neurons release AgRP, which is a functional antagonist at melanocortin receptors. Leptin is produced by adipose tissue in direct proportion to its amount. Glucose and insulin inhibit NPY and AgRP and stimulate POMC's neuronal activity. It is hypothesized that obesity-prone humans have a raised threshold for sensing and responding to peripheral inhibitory signals, thus allowing them to eat beyond their metabolic needs. This phenomenon has been demonstrated in rodents: obesity-prone rats have reduced leptin and insulin signalling in the ARC and consequent reduced anorectic responses (16). While obesity-resistant rats provided with high fat, high calorie diets readily down-regulate their caloric intake, obesity-prone rats take almost 4 weeks to do so (17). By then, their body weight and adipose set-points are irreversibly elevated (18). A similar phenomenon was shown in post-obese humans who exhibit a persistent reduction in resting energy expenditure (19). This is a contributing factor to why maintaining weight loss after successful dieting is difficult.

A second homeostatic regulation comes to the body’s defence when energy intake is restricted below metabolic needs. This mechanism is no different between lean and obese individuals (20). It may represent the most important factor determining the inability of post-obese individuals to sustain weight loss over long periods of time. When dietary intake is reduced, sympathetic activity is increased, inducing both glucose and fatty acid release from their stores, and is associated with a marked drop in leptin production. Reduced leptin levels in turn induce reduction of muscle and other thermogenic organ sympathetic activity, causing a decrease in resting energy expenditure. Leptin reduction also dysinhibits NPY/AgRP and inhibits POMC neurons, causing a strong rise in desire for food ingestion.

The region of human chromosome 2 containing the POMC gene is considered as a susceptibility locus for human obesity (21), and mutation in the melanocortin 4-receptor gene has been observed to be associated with a remarkable 100% occurrence of binge eating (22).
3.2 Environmental and Psychosocial Factors Combine with Genetic Predisposition

When ready access to highly palatable, calorifically dense foods, provided in supersized portions, is combined with positive psychosocial factors associated with meal taking, this encourages eating far beyond the limits set by the homeostatic systems. Studies in rats have demonstrated that even relatively obesity-resistant animals may become obese if exposed to highly palatable diets (23), although these animals don’t maintain obesity when the palatability of the diet is reduced. External environmental factors, therefore, act synergistically with genetic factors in the development of obesity.

3.3 Fat Oxidation

Some individuals have genetically determined low fat oxidation, which may facilitate the onset of obesity. When these individuals are exposed to high-fat diets and limited physical activity, obesity develops. Fat oxidation is not as tightly regulated as carbohydrate and protein oxidation. Stubbs et al. monitored energy intake and expenditure in normal individuals fed for 7 days with ad libitum intake of diets of constant composition (24). They demonstrated a positive carbohydrate and protein balance on one day followed by negative balance of the same macronutrients on the subsequent day. No similar feedback was observed for fat balance.

Familial deviations in respiratory Quotient (RQ), the ratio between CO₂ produced and O₂ utilized during oxidation processes, are recognized, both in Pima Indians (25) – a population predisposed to obesity – and in some Caucasians (26). A high 24-h RQ, indicating relatively low fat oxidation, is a recognized risk factor for weight gain. The Baltimore Longitudinal Study showed that the adjusted relative risk of gaining >5 kg in initially non-obese men with an RQ >0.85 was 2.42 compared to those with an RQ <0.76 (27). The defect in fat oxidation persists after weight loss, in the resting, post-absorptive and in the postprandial states (28). In post-obese women exposed to a high-fat diet, postprandial fat oxidation was 2.5 times lower than that observed in the control group. Low fat oxidation led to positive balance and storage of fat (29).

Obese subjects also have reduced lipid oxidation in skeletal muscle, which plays an important role in whole body lipid oxidation (30). This phenomenon persists during both rest and exercise, and remains unchanged after weight loss. The percentage of plasma Free Fatty Acid (FFA) uptake oxidized correlates inversely with BMI (r=-0.455 at rest and r=-0.459 during exercise) (31). One possible explanation for reduced FFA oxidation might be the composition of skeletal muscle fibres, which is primarily under genetic control. Obese individuals have more type II non-oxidative muscle fibres and fewer type I oxidative muscle fibres than lean controls (32). The defect in FFA oxidation is located in both the mitochondrial β-oxidation (PPARα peroxisome...
proliferator-activated receptor-α, and CPT1B carnitine palmitoyl-transferase 1) and the peroxisomal oxidative (ACOX1 acyl-coenzyme A oxidase 1) pathways (33). Perilipins are lipid droplet-associated proteins. Perilipins are critical regulators of basal (non-stimulated) adipocyte lipolysis, a process central to maintaining normal energy balance and utilization (34). Perilipins, which are elevated in obese subjects, increase cellular triglyceride storage by decreasing the rate of triglyceride hydrolysis, and regulate the release of triglycerides at times of need. A significant positive relationship \((r=0.55; \ p <0.01)\) exists between perilipin expression and the percentage of body fat (35). Genetic studies have demonstrated that variations at the Perilipin's (PLIN) locus are related to obesity risk (36). Severely obese subjects carrying one of four polymorphisms genotyped at the PLIN locus (PLIN 14995A>T) are resistant to a 1-year dietary weight reduction intervention (37).

4. Goals of Therapy

The aim of treating obesity is to reduce both morbidity and mortality. In people with class I and class II obesity, weight loss of 5%-10% is associated with a significant improvement in health, even though normalization of body weight is not achieved. Weight reduction of 5-10% is associated with decrease in severity and occurrence of diabetes type II (38), metabolic syndrome (39), psychosocial difficulties (40), and cardiovascular risks (41). The guidelines released by the American College of Cardiology (ACC), the American Heart Association (AHA), and The Obesity Society (TOS) in 2013, state that clinically meaningful health improvements can even be seen with weight loss in the range of 2%-5% (42,43). Severely obese patients require a larger weight loss to achieve the same objectives, although a precise definition of the desirable weight loss is currently unknown. In a recent study on severely obese patients (initial BMI 52.7 kg/m²), a significant improvement in most metabolic blood markers and blood pressure was reported in patients who attained an average weight loss of 38.2% (percentage of their initial weight) (44). Patients subsequently maintained, up to 2-5 yrs, an average weight loss of 18-19% but unfortunately the evaluation of their risk factors at that time was not reported. Data from patients who underwent bariatric surgery, with an average weight loss of ≥ 20% showed substantial improvement of most comorbid conditions (45). On the available evidence, sustained weight reduction of 20% should be the goal of therapy in severely obese persons. Obesity is a chronic disease, therefore the main aim of the therapy is life-long maintenance of a more “healthy” body weight, even though this may remain above the normal range.
5. Therapy

5.1 Lifestyle Modifications

Life-long modification in lifestyle is required for success, including eating behaviour and enhancement of physical activity. Effective management of obesity must be based on a partnership between a highly motivated patient and a committed team of health professionals. Multidisciplinary programmes have been shown to produce and sustain modest weight loss of between 5% and 10% for the long-term (42,43). Weight-loss programmes should include 3 crucial phases: screening and assessment, the weight loss phase and the maintenance phase. In the screening phase, the clinician must have a clear idea of that individual’s expectations and motivation. Then the clinician should guide the patient to set the treatment goals. The goals should be specific, measurable, attainable, realistic and within a clear time frame.

5.2 Diets

The cornerstone of dietary prescription is a long-term reduction in total energy intake. Achieving a caloric deficit is still the most important component in achieving sustained weight loss. However, the considerable variance in individual energy expenditures and compliance with calorie-deficient plans make it difficult to predict reliably how much weight an individual will lose.

Energy expenditure is related to body weight. Therefore, weight loss tends to reduce energy expenditure, dampening the effect of caloric deficits (46). Diets are defined as: low-calorie diets LCDs (1000-1500 kcal/d), very-low-calorie diets VLCDs (≤800 kcal/d) and diets with different macronutrient compositions, such as low fat, low carbohydrate or low glycaemic index diets. Factors influencing the individual prescription of dietary recommendation include:

1. Severity of obesity;
2. Clinical indication for rapid weight loss (eg respiratory insufficiency, heart disease);
3. Number of previous weight loss attempts;
4. Current level of dietary intake;
5. Psychological profile.

The more severe the degree of obesity - especially if it is accompanied by the comorbidities mentioned above - the greater needs to be the degree of energy restriction; on the other hand the greater the number of previous attempts and the higher the current dietary intake, the more moderate the change needs to be, if compliance is to be achieved. The possibility of an underlying eating disorder should be actively investigated, and patients with psychiatric disorders should be treated accordingly. Patients should be medically supervised throughout weight reduction therapy.
5.2.1 Low-calorie Diets (LCDs)

Low-calorie diets involve reducing daily energy intake by 500-1000 kcal/day, to a level of 800-1800 kcal/day, and are composed of conventional foods. Vegetables, grains, fish and poultry should be provided, while fat-rich foods like oil, butter, cheese, high fat meat, eggs, and simple carbohydrates should be restricted. These diets are associated with a mean initial weight loss of 0.4-0.5 kg per week. The optimal macronutrient composition for low-calorie diets is subject to debate. Standard recommendations indicate provision of ≥55% of kilocalories from carbohydrates, ≤30% from fats (8% to 10% from saturated fatty acids) and approximately 15% from proteins, although the optimal division of calories between the macronutrients is uncertain.

5.2.2 Very-low-calorie Diets (VLCDs)

VLCDs have been defined by the SCOOP-VLCD Working Group as diets providing less than 800kcal/d (47). SCOOP (Scientific Co-operation on Questions Relating to Food) refers to an expert panel established at the Directorate-General Health and Consumer Protection of the European Union. VLCD are designed to produce rapid weight loss while preserving lean body mass. Typically they contain high amounts of protein (70 to 100 g/d), up to 80 g carbohydrate/d and 15 g fat/d; the formula includes 100% of the recommended daily allowance of essential vitamins and minerals. Protein is obtained from milk, soy or eggs. At least 2 L/d of non-caloric fluids are prescribed. VLCDs are prescribed for limited periods (12-16 weeks), as part of a comprehensive intervention that includes an additional period (12-14 weeks) of gradual increase in calories and reintroduction of conventional foods. Best results are achieved if the diet is associated with a structured behavioural programme. Intervention lasts at least 12-18 months, and is followed by a structured maintenance program. The SCOOP-VLCD report states that obese patients should consult their physician before starting VLCD, and it is better that such an intensive intervention should be carried out under medical supervision, even if some experts do not regard this as mandatory. The SCOOP-VLCD report (47) states that consumers may use a VLCD as a sole source of nutrition for 3 weeks before seeking medical supervision; moreover Rossner and Torgerson, reviewing the Swedish experience with VLCDs, concluded that such programmes may be provided by dieticians and nurses (48). Diet products can be purchased in Europe without a prescription, except in France. During the period of rapid weight loss, patients may experience side-effects such as dizziness (35%), constipation (33%), fatigue/weakness (20%), nausea (13%), abdominal discomfort (10%), diarrhoea (9%), headaches (6%), transient increment of serum uric acid (10%) and a rise in hepatocellular enzymes (39%) (49); these side-effects are usually mild and easily managed. A high risk of gallstone formation (12-25% of patients), requiring cholecystectomy in 25%-50%, has been reported in early studies; ursodeoxycholic
acid administration and the inclusion of additional fat may decrease this occurrence (50). Serious adverse effects including death occurred in the 1970s when products were based on low-quality proteins (hydrolyzed collagen) and did not contain vitamins and minerals. No deaths have been reported with the current formulae.

VLCDs induce a large and rapid weight loss, but the long-term results are currently contested. A meta-analysis of the 1970-1999 US studies (51) and two reviews (52,53) concluded that VLCDs are associated with significantly greater maintenance of weight loss over a period of one to five years than conventional low-calorie diets. By contrast, a more recent meta-analysis (50), in which only trials (randomized, controlled, and lasting at least one year) directly comparing VLCDs and conventional LCDs were included, showed no differences between the two treatments one year after their completion.

5.2.3 Partial Meal Replacement

This mixed method uses a prescription of conventional foods, liquid diets and meal bars, used as partial replacement of meals (1-2/d) and as snacks (2/d). Results of the randomized trials comparing partial meal replacement with isocaloric conventional diets show a significantly greater weight loss, at one year, in those receiving the meal replacement programmes (54, 55). This method seems to simplify adherence, and allows patients to follow the dietary advice more precisely. No specific study on severely obese patients has been conducted with this method, even though it is considered and employed in the maintenance programmes.

5.2.4 Diets with Different Macronutrient Compositions

5.2.4.1 Low Carbohydrate Diets

Low carbohydrate diets have become more frequent following confirmation of the short-term success of the popular Atkins diet. The Atkins diet is a high-protein and/or high-fat, very-low-carbohydrate diet that induces ketosis. Ketone bodies tend to be generated when an individual’s daily dietary carbohydrate intake is under 50 g, and sodium diuresis is forced, which causes most of the short-term weight loss. Good data regarding the safety or long-term effectiveness of this diet are lacking. Because of the high fat content of such diets, low-density lipoprotein cholesterol (LDL-C) levels are found to be increased by at least 10% in 25% of compliant patients.

A randomized controlled trial comparing low-carbohydrate with conventional low-fat diet in severely obese patients found that, although the former produced greater initial weight reduction (56), results at 1 year were not significantly different (57). Another recent randomized trial in severely obese patients showed that dietary adherence is the single major factor accounting for the variance in weight loss, while the macronutrient composition is not an independent predictor of weight change.
In 2 recent randomized trials, not specifically in severely obese patients, weight loss with Atkins-type diets was compared with that from conventional low-fat or balanced calorie-deficit diets (59,60). Although the Atkins-type diet led to the greatest initial weight loss, weight became similar within 1 year. Long-term adherence to this diet is poor; in those studies noted, the non-compliance rate in the Atkins-type group was close to 50%. The South Beach diet, another low-carbohydrate diet, is more liberal in its carbohydrate allowance than the Atkins diet and distinguishes between what are considered to be good and bad carbohydrates on the basis of their glycemic index. It has not been confirmed that this resolves the problem in the longer term.

5.2.4.2 Low Glycaemic Index Diet

Low glycaemic index diets encourage increased fibre intake, which is associated with lowered weight even when total caloric intake is relatively unchanged. Low glycaemic index diets are better at helping to maintain weight loss than diets with a higher glycaemic index (61).

These findings suggest tailoring the diet for individual needs and preferences, taking the patient’s personality into account. Some patients appreciate a certain level of variability and are able to manage a flexible plan; in others adherence may be enhanced by a more rigid structure (62), reducing food choices and providing meal plans, with menus and recipes. This reduces temptation and the need to calculate energy intake. On the whole, defining the calories per day and keeping intake to this, is the essential route to success.

5.2.4.3 Low Fat Diet

A low fat diet is a restricted-energy diet with less than 30% of energy from fat. There is comparable weight loss at 6 to 12 months with instruction to consume a calorie-restricted (500 to 750 kcal deficit/day) lower fat diet (<30% of total calories from fat) than if advised a higher fat (>40% of total calories from fat) diet (42).

5.2.4.4 Comparison of Diet Programs

Comparing the Zone (a low carbohydrate), Ornish (a very low-fat diet), and Atkins (a very low carbohydrate) diets to each other and to a typical balanced, calorie-restricted (Weight Watchers) diet Dansinger et al. found them all to have a similar impact on weight (63). The Ornish diet and the Atkins diet had the poorest compliance rates. At 1 year, the researchers observed no significant differences in weight loss among the 4 diets. Compliance and caloric deficits were more important predictors of weight loss and improvement in cardiovascular risk surrogates than specific dietary composition.
A 2-year study found low-carbohydrate and low-fat diets to be similar in inducing weight loss. However, the study also found that the low-carbohydrate diet was associated with more favourable changes in cardiovascular disease risk factors while better achievement of sustained weight loss was seen with the low-fat diet (59).

5.3 Exercise

The recommendations on physical activity for weight loss are usually 30-60 minutes moderate activity per day for 5-7 days a week (51). Increased physical activity and exercise for at least 300 minutes a week is associated with significant weight reduction and longer maintenance of the weight loss (65). Walking, that is considered moderate activity, may be the simplest and most feasible activity to suggest. The recommended level corresponds respectively to ≈ 1000-2100 kcal activity/week. Since approximately 27% of the diet-induced weight loss can be from loss of muscle, the addition of exercise to caloric restriction is important. Studies have shown that muscle mass loss is reduced to approximately 13% of the total weight loss when diet and exercise are combined (66). At the beginning of the weight-loss treatment, severely obese subjects need a personalized plan of physical activity based on their particular clinical conditions. The coexistence of cardiac or respiratory dysfunction, or the presence of hypertension or osteo-articular problems necessitates medical supervision and/or the involvement of exercise physiologists. Structured weight-losing programmes now usually include an exercise physiologist to tailor and manage the initial physical activity.

5.4 Behaviour modification

The behavioural approach provides a structure that facilitates the meeting of goals for energy intake and expenditure. The key components are: self-monitoring, goal setting, stimulus control, cognitive strategies, social support, and reinforcement.

1. **Self-monitoring** of: food intake, drink, physical activity and changes in body weight is taught to make patients aware of their eating and activity patterns, and of the influence of environmental settings, times and social and psychological factors on their behaviour;

2. **Goal setting** is directed to set changes in the patient’s behaviour; goals are directed in order to create an environment conducive to weight loss. The technique involves creating small, specific goals that allow a complex task like losing weight to be broken down into simple steps;

3. **Stimulus control** is directed in order to change the antecedents of overeating and under-exercising, decreasing the cues that promote overeating (buffets, high-risk occasions, etc …) and inactivity (eg watching television,…), and increasing those cues associated with healthy eating and physical activity. Patients are also encouraged to keep a graph of their progress and to use a grocery list;
4. **Cognitive strategies** help patients identify and change negative thoughts that may precede or follow overeating or inactivity. Patients are invited to monitor and record thoughts and feelings linked to eating; thinking patterns are then reframed in a way encouraging the behavioural change;

5. **Social support** by spouses or significant others may increase the patient’s success both in helping the reorganization of eating and exercise and in supporting new behaviours;

6. **Reinforcement** can arise from tangible rewards for weight loss like improved mobility and breathing, decreased joint pain, compliments from others; weight maintenance may require additional positive reinforcement.

Behavioural weight-loss programmes include weekly treatment sessions of 60 to 90 minutes each, for approximately 6 months, and subsequent “maintenance” sessions for an additional 6-12 months. Sessions are usually delivered in small groups (~ 10 participants), or individually.

### 5.5 Anti-obesity Medication

Currently, the only FDA-approved drugs for the long-term treatment of obesity are orlistat (Xenical), lorcaserin (Belviq), and the combination of phentermine and extended-release topiramate (Qsymia). No good data are available concerning the effect of these drugs in severe obesity.

#### 5.5.1 Orlistat

Orlistat inhibits the action of pancreatic lipase, reducing triglyceride digestion and absorption. Sustained weight loss of 9-10% over 2 years was shown by two major clinical trials showed (67). Some of its effect is undoubtedly from reduction in fat intake as the patient discovers that this limits the unpleasant drug-induced steatorrhoea that otherwise ensues.

#### 5.5.2 Lorcaserin

Lorcaserin decreases food consumption and promote satiety by activating 5-HT2C receptors on anorexigenic neurons in the hypothalamus. Lorcaserin approval was based on 3 double-blind, randomized, placebo-controlled trials that found lorcaserin (along with diet and exercise) to be more effective than diet and exercise alone at helping patients lose 5% or more of their body weight at 1 year, and managing the weight loss for up to 2 years (68, 69, 70).

#### 5.5.3 Phentermine and Topiramate

Topiramate, an antiepileptic agent, has been associated with an average weight loss of 5-7% of initial weight. The amount of weight loss appears to be greater with higher baseline weights. The exact mechanism of this effect is still being investigated. The adverse effects of these drugs, especially CNS effects such as
paresthaesias, drowsiness, memory loss, and confusion, is cause for concern. Qsymia contains an extended-release form of topiramate in which the dose is lower than that used for seizure management. The combination of phentermine and extended-release topiramate was approved by the FDA to be used with a reduced-calorie diet and exercise for long-term weight management in individuals with an initial BMI of 30 kg/m² or higher or 27 kg/m² or higher (overweight) with at least 1 weight-related comorbid condition (eg, hypertension, dyslipidaemia, type 2 diabetes mellitus) (71).

6. Maintenance Programmes

6.1 Importance of Maintenance Programmes

Obesity is considered a chronic disease with a strong tendency to relapse. Maintenance of weight loss and avoidance of weight regain therefore depends upon a life-long programme of behavioural change. Partial weight regain after the period of active weight loss is the rule, so the realistic aim of maintenance programmes is to limit such regain and to prevent relapse to the pre-treatment weight, stabilizing weight at a level at which significant health improvements are maintained.

6.2 Defining a Maintenance Programme

Maintenance-programmes are advisable to help patients to maintain correct behaviour. They need a multi-disciplinary approach involving physicians, dieticians, nurses, exercise physiologists, behaviour therapists and psychologists. Maintenance treatment may include: regular clinic attendance, probably with intervening phone calls, daily record keeping, prescription of physical activity, and training in relapse prevention. Maintenance programmes should last at least 6 months, but many researchers believe that longer periods might be needed. Unfortunately, patients’ compliance and motivation decrease markedly after ≥1 year, and no specific means for improving long-term compliance has yet been identified. Programmes may also offer specific schedules for weight re-gainers, aimed at intensifying efforts to lose weight or re-entering the main programme.

6.3 Factors Protecting Against Weight Regain

Maintenance of weight loss is achieved by regular physical activity, low-calorie diet (72, 73, 74), and generous consumption of vegetables and fruit (72). Behavioural and psychological factors are also of outstanding importance: it has been shown that self-monitoring and self-weighing (72, 73), as well as the level of disinhibition, hunger and depressive symptomatology are strong predictors of weight regain (75). Finally, it is important for patients to continue being involved in ongoing treatment or coaching (76, 77).
Several studies have found that high activity levels are related to better long-term weight maintenance (73, 78). In a recent study, obese patients were randomized to the standard treatment or to a high physical activity level (≥2500 kcal/d, corresponding roughly to ≥60 min/d): high exercisers not only obtained a significantly greater weight loss at the completion of the programme (18 months), but also achieved the best long-term outcomes (79). Unfortunately, this group included only 9.2% of the total participants: this, once again, emphasizes the difficulties in obtaining a stable modification of the lifestyle.

6.4 Strategies Used by Successful Weight Maintaining Individuals

The National Weight Control Registry (NWCR) is a voluntary registry established in the US of individuals ≥18 years of age who lost ≥13.6 kg, and maintained it for ≥1 year. Studies conducted on the participants to the NWCR are relevant to understanding the strategies adopted by successful weight maintainers (on average they have maintained this minimum weight loss for nearly 6 years). The most recent paper addressing this argument reports that severely obese patients who achieved an average weight loss of 54.8 ± 20 kg by non-surgical means and successfully maintained it for 5.5 years (n=210), maintained an effective level of physical activity, ranging from 800 to 1140 kcal per week, and have an average intake of 1400 ± 580 kcal/d. The proportion of fat consumed was 26.4 ± 12% (80). Currently it is not clear whether a low-fat- or a low-carbohydrate-diet affect long-term maintenance differently. Shai et al (81) showed that a low-fat, restricted calorie diet produced significantly less weight loss over 2 years compared with a low-carbohydrate, non-restricted calorie diet. However, other studies showed no significant differences in long-term weight control in participants consuming a low-fat vs. low-carbohydrate diet (82, 83). Of note, these last two studies addressed persons with class I and II obesity (82, 83), while the former considered the participants of NCWR (81). A low-carbohydrate diet seems to be linked to less dietary restraints and to a lower need for consciously controlling weight by means such as such as counting calories or holding back on meals (83).

In conclusion, all studies agree that weight control is based on the persistence of behavioural strategies that include both restricting food intake and undertaking physical activity on a regular basis.

7. Structured Programmes Specific for Severely Obese Patients

Structured programmes, specifically designed for severely obese patients, have been proposed. All of them include the three cornerstones of treatment (diet prescription, exercise and behavioural programs) and a maintenance programme. Some aspects of the management may vary between institutions, according to local policies and funding.
A recent report of such a programme, that included 1531 severely obese patients (initial BMI 48.3 kg/m²) followed for eight years, showed encouraging results. Most of these patients (85%) were treated with LCD and only 15% with VLCD; the authors were able to calculate that participants had an average energy intake of approximately 1000 kcal/day. Overall, patients lost 28 kg (20% of their initial body weight); subjects who completed a 12-week core programme (72%) lost an average of 35 kg (25% of their initial body weight) in 38 weeks and maintained 59% of the weight lost after 6 years. Furthermore, a group of 268 (17.5%), who lost 62 kg (39.8% of their initial body weight) at the completion of the weight-losing programme, maintained 65% of the weight lost after 7.9 years (49).

Another structured programme conducted on 113 less severely obese subjects (initial BMI 40.2 kg/m²) included in the intervention arm of the Swedish Obesity Study, demonstrated that completers (49%) maintained a small but significant weight loss (3.3±10.7 kg) at 8 years, while non-completers had gained 3.2±9.7 kg after 6 years (84).

8. Conclusions on Conventional Therapy

On the whole, the results of the conventional therapy of severely obese patients are currently discouraging: not only is weight regain the rule, but the majority of patients go back to their previous weight. Therefore bariatric surgery is considered the only effective therapy in the majority of patients, even though it runs the risk of increased morbidity and mortality. Nonetheless, the increasing prevalence of class III obesity, the severity of health problems linked to this and the limited access to bariatric surgery present a challenge to improve the results of conventional therapy. Regarding this, some hopeful points reported in recent studies may be emphasized: (1) intense structured programmes allow approximately 15-18% of the participants to reach and maintain a healthy weight; (2) some interventions seem promising, even though their efficacy has not yet been clearly proven: these are (a) to induce a great weight loss in the initial part of the therapy, (b) to use diets based both on conventional food and on partial meal replacement, (c) to extend for as long as possible the follow-up time and the involvement of the patients in a well- and specifically-designed programme. Funding of specialized, intense structured programmes is needed, both to prevent borderline-severely obese patients from becoming fatter, and in order to offer persons, who are already severely obese, efficient programmes at the lowest possible cost. The cost of funding would be abundantly repaid by the reduced costs of high morbidity and of bariatric surgery.

9. Summary

Severe obesity is rapidly increasing in affluent countries and is associated with a high rate of morbidity and mortality. The excess mortality increases with increasing BMI. Obesity is considered a chronic disease caused by the interaction of genetic factors.
with the current, highly permissive, environment. The genetic determinants are multiple and interacting, and concern the complex system of peripheral signalling to central metabolic sensing neurons, which in turn regulate food intake and energy expenditure, and reduced fat oxidation. In post-obese subjects, who are hypothesized to represent the pre-obese state, most of the alterations persist unchanged. Therapy is aimed at reducing body weight and maintaining that level of weight loss which is associated with health improvement. In severely obese individuals, this level may be approximately 20% loss of the initial body weight, but the initial degree of excess weight should also to be considered. Conventional therapy is currently a very difficult task, resulting in unsatisfactory results. The goal is to induce a life-long modification in lifestyle, including eating behaviour and enhancement of physical activity. Diets are defined as low-calorie diets LCDs (1000-1500 kcal/d) and very-low-calorie diets VLCDs (≤800 kcal/d); the former are the most frequently used, while the latter, based on formulas specifically designed to replace meals completely or partially, are usually employed only in medically supervised programmes. Whether, in LCDs, a balanced distribution of macronutrients or a preferential decrease in carbohydrate or fat content is more efficient in inducing weight loss is still not known. The large and rapid weight loss induced by VLCD may be positively associated with better long-term maintenance of weight loss, but the issue is still controversial. Weight losing and weight maintaining programmes specifically designed for severely obese subjects may be at least partially successful, and they should be multidisciplinary, involving physicians, dietitians, nurses, exercise physiologists, behaviour therapists and psychologists. Maintenance of weight loss depends on the maintenance of control over the food intake and of regular physical activity; a high activity level is perhaps the most important single factor protecting against weight regain.
10. References


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