Treatment Modalities of Obesity

What fits whom?

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The prevalence of obesity is increasing in both developed and developing countries, with rates reaching ~10–35% among adults in the Euro-American region. Obesity is associated with increased risks of cardiovascular diseases, type 2 diabetes, arthritis, and some type of cancers. Obesity significantly affects the quality of life and reduces the average life expectancy. The effective treatment of obesity should address both the medical and the social burden of this disease. Obesity needs to be treated within the health care system as any other complex disease, with empathy and without prejudice. Both health care providers and patients should know that the obesity treatment is a lifelong task. They should also set realistic goals before starting the treatment, whereas keeping in mind that even a modest weight loss of 5–15% significantly reduces obesity-related health risks. Essential treatment of obesity includes low-calorie low-fat diets, increased physical activity, and strategies contributing to the modification of lifestyle. Anti-obesity drugs facilitate weight loss and contribute to further amelioration of obesity-related health risks. A short-term weight loss, up to 6 months, is usually achieved easily. However, the long-term weight management is often associated with a lack of compliance, failures, and a high dropout rate. Regular physical activity, cognitive behavioral modification of lifestyle, and administration of anti-obesity drugs improve weight loss maintenance. Bariatric surgery is an effective strategy to treat severely obese patients. Bariatric surgery leads to a substantial improvement of comorbidities as well as to a reduction in overall mortality by 25–50% during the long-term follow-up. Obesity treatment should be individually tailored and the following factors should be taken into account: sex, the degree of obesity, individual health risks, psychobehavioral and metabolic characteristics, and the outcome of previous weight loss attempts. In the future, an evaluation of hormonal and genetic determinants of weight loss could also contribute to a better choice of individual therapy for a particular obese patient. A multilevel obesity management network of mutually collaborating facilities should be established to provide individually tailored treatment. Centers of excellence in obesity management represented by multidisciplinary teams should provide comprehensive programs for the treatment of obesity derived from evidence-based medicine.

Diabetes Care **31 (Suppl. 2):S269–S277, 2008**

The prevalence of obesity is increasing worldwide at an alarming rate in both developed and developing countries (1). European obesity prevalences range from 10 to 20% in men and 15 to 25% in women, whereas the prevalence of obesity among U.S. adults has reached 28% in men and 34% in women.

Excess body weight is the sixth most important risk factor contributing to the health burden of the world. Obesity amplifies the risks of type 2 diabetes, hypertension, cardiovascular disease, dyslipidemia, arthritis, and several cancers and is estimated to reduce average life expectancy (2).

A negative energy balance induced by the treatment of obesity should lead to a reduction of fat stores and an appropriate preservation of lean body mass. Among the most important goals of obesity treatment are a preferential reduction of abdominal fat, an amelioration of obesity-related health risks, an improvement in comorbidities and in quality of life, and a reduction in mortality rate (3,4). A successful treatment of obesity should have an important impact on medical resources utilization and health care costs. Physicians and other health care professionals face a great challenge in assisting obese patients not only to lose weight but also to achieve weight loss maintenance.

Obesity treatment should be individually tailored and the age, sex, degree of obesity, individual health risks, metabolic and psychobehavioral characteristics, and outcome of previous weight loss attempts should be taken into account. In the future, hormonal and hereditary factors affecting weight loss should also be considered.

It is necessary to set realistic goals before starting the treatment of obesity. Both physician and the patient should know that a weight loss of 5–15% reduces obesity-related health risks significantly. Unrealistic expectations concerning the weight loss frequently results in weight management failure.

WHAT KIND OF LOW-ENERGY DIET SHOULD BE RECOMMENDED?

— A low-energy diet recommended for the treatment of obesity should be low fat (<30%), high carbohydrate (~55% of daily energy intake), high protein (up to 25% of daily energy intake), and high fiber (25 g/day). A high-carbohydrate low-fat energy-deficient diet is usually recommended for weight management by medical societies and health authorities (3,4). A moderate decrease in energy intake (−2.5 MJ/day) could result in a slow (~2.5 kg/month) and sustained weight loss. Until now, most studies have revealed that the total energy intake and not the macronutrient composition determines the weight loss in response to low-energy diets over a short period of time.

In spite of the generally accepted role of altered fat consumption in influencing an energy balance, an agreement has not been achieved concerning the effects of low-fat diets per se on the weight loss. A meta-analysis of 16 dietary intervention

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The authors of this article have no relevant duality of interest to declare.

This article is based on a presentation at the 1st World Congress of Controversies in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this article were made possible by unrestricted educational grants from MSD, Roche, sanofi-aventis, Novo Nordisk, Medtronic, LifeScan, World Wide, Eli Lilly, Keryx, Abbott, Novartis, Pfizer, Generx Biotechnology, Schering, and Johnson & Johnson.

Abbreviations: PYY, peptide YY; VLCD, very-low-calorie diet.

DOI: 10.2337/dc08-s265

studies demonstrated that a reduction in dietary fat without intentional restriction of energy intake causes weight loss, which is more substantial in heavier subjects (5). A recent lifestyle intervention study of the Diabetes Prevention Program Research Group demonstrated that besides the increased physical activity, the lower percent calories from fat predicted weight loss over 3.2 years of follow-up (6). On the other hand, a meta-analysis of six randomized controlled trials specifically targeting weight loss failed to find significant differences in the effects of low-fat diets and other weight loss diets in obese and overweight subjects (7). It should be considered that the ratio between saturated, monounsaturated, and polyunsaturated fatty acids in ingested fats influences metabolic and cardiovascular risks of obesity including insulin resistance. In a recent statement, the American Diabetes Association recommends to limit an intake of saturated fats to <7% of total calories and to minimize an intake of trans fat (8). Incorporating fish meals rich in n-3 fatty acids in a weight management diet favorably affects cardiometabolic health risks including lipid profile and hypertension (9). However, a high intake of fish oil has been shown to increase moderately blood glucose level and to decrease insulin sensitivity in subjects with type 2 diabetes (10).

Recently, several studies evaluated the role of low-carbohydrate diets in weight management (11). These diets have been advocated because they induce many favorable effects such as a rapid weight loss, a decrease of serum insulin and triglyceride levels, and a reduction of blood pressure as well as a higher suppression of appetite (partly due to ketogenesis, partly due to a higher protein intake). However, several unfavorable effects of low-carbohydrate diet administration have been demonstrated, such as an increased loss of lean body mass, increased levels of LDL cholesterol and uric acid, and an increased urinary calcium excretion. An extremely low intake of carbohydrate may lead to an unwanted energetic efficiency. This energetic efficiency is due to the suppression of the sympathetic nervous activity and to the development of low T_3 syndrome. Long-term studies are needed to evaluate the overall changes in nutritional status, body composition, metabolic health risks, and adverse events in response to low-carbohydrate diets. Without that evaluation, low-carbohydrate diets cannot be recommended (12).

Increased content of protein in a diet contributes to better weight loss maintenance because proteins are more satienting and thermogenic than carbohydrates and fats. Westerterp-Plantenga et al. (13) demonstrated that high protein intake sustained weight maintenance after very-low-calorie diet (VLCD)-induced weight loss.

Studies made on the role of foods with a low glycemic index and the role of increased calcium intake in reducing fat stores in human obesity have so far brought conflicting results (14–16).

VLCDs contain ≤3.5 MJ/day and provide high-quality protein with a minor intake of fat. Vitamins, minerals, and trace elements are added to cover recommended daily allowances. VLCDs may form a part of a comprehensive program undertaken by either an obesity specialist or other physician trained in nutrition and dietetics. Although the short-term weight loss induced by VLCD is greater than that induced by standard low-calorie diets, there is no consensus whether VLCDs per se produce greater long-term weight losses than low-calorie diets (17–19). According to meta-analyses conducted by Saris (18) and Anderson et al. (19), a greater initial weight loss using VLCDs with an active follow-up weight maintenance program, including behavior therapy, nutritional education, and exercise, improves weight loss maintenance. An administration of VLCD should be limited for specific patients (i.e., those in whom rapid weight loss is indicated by a physician) and for short periods of time. Indications and contraindications for VLCD administration should be strictly followed. VLCDs should not be prescribed for patients with kidney and liver disease. On the other hand, an administration of a VLCD is a reasonable approach in obese patients with type 2 diabetes. However, in diabetic patients treated by antidiabetic agents as well as in patients with hypertension treated by antihypertensive drugs, the drug dosage should be modified during the VLCD treatment to avoid hypoglycemia or an inappropriate blood pressure decrease.

Diets with a strict limitation of energy intake leading to semistarvation should be strictly avoided because of serious health hazards that relate to deficiencies of several nutrients. Exaggerated lipid mobilization accompanied by an increased level of free fatty acids, together with a lack of essential amino acids and potassium and magnesium deficiencies might promote life-threatening cardiac arrhythmias (20). It should be taken into account that obesity is frequently associated with a prolongation of the QT interval, which per se predisposes to cardiac arrhythmias. Rapid weight loss results in an increased biliary excretion of cholesterol, which potentiates the formation of biliary stones. An increased production of ketones and ketonuria, which are the results of semistarvation, prevents urinary urate excretion and leads to excessive hyperuricemia, which could result in a gout attack.

It should be kept in mind that diets providing <5 MJ/day might yield deficiencies of several micronutrients, which could exert untoward effects not only on nutritional status but also on the weight management outcome. Meal replacement diets (substitution of one or two daily meal portions by VLCD) may be a useful strategy and have been shown to contribute to nutritionally well-balanced diet and weight loss maintenance (21).

It is recommended to divide the daily food intake into four to five daily meal portions. Nutritional tables with the traffic light system might help an obese patient to choose an appropriate low-energy meal.

PHYSICAL ACTIVITY — Physical activity should be an integral part of the comprehensive obesity management and should be individually tailored to the degree of obesity, age, and presence of comorbidities in each subject. Physical activity not only contributes to an increased energy expenditure and fat loss, but also protects against the loss of lean body mass, improves cardiorespiratory fitness, reduces obesity-related cardiometabolic health risks, and evokes sensations of well-being. Aerobic physical training leads to improvement in oxygen transfer to muscle, which promotes an increased utilization of abundant fat stores instead of the limited glycogen stores. Physical activity of a moderate intensity, 30 min in duration, performed 5 days a week is recommended. This activity conducted for a month represents an energy deficit that might contribute to 0.5 kg of weight loss. Patients should be aware of the realistic goals with regard to the expected exercise-induced weight loss as well as of the beneficial effects of exercise per se on cardiometabolic risks. To opti-

mize weight loss, exercise should be increased to 60 min for 5 days a week. Obesity is usually a result of a lack of daily habitual physical activity. Therefore, activities such as walking, cycling, and stair climbing should be encouraged (22). Engagement of physical activity in weight management is positively related to the level of education and, on the other hand, inversely associated with the occurrence of serious comorbidities, with age and with degree of overweight (22). For patients with severe arthritis and problems with mobility, exercising in heated water is recommended. Vigorous physical activity that leads to joints overloading, such as jumping, should be avoided. Strength exercise modalities do not increase lipid oxidation but should be used, especially in less mobile disabled individuals, for protection of lean body mass and amelioration of health risks. Any kind of regular physical activity represents an important factor that contributes to long-term maintenance of weight loss (23). Surprisingly, adding structured exercise to diet counseling does not alleviate metabolic syndrome in obese men better than diet only (24).

PSYCHOLOGICAL FACTORS AND BEHAVIORAL MODIFICATION OF LIFESTYLE

— Psychological factors influence both weight loss and, more importantly, long-term weight loss maintenance. Behavioral modification of lifestyle should be included in the weight management strategies. Behavioral management includes several techniques such as self-monitoring, stress management, stimulus control, reinforcement techniques, problem solving, rewarding changes in behavior, cognitive restructuring, social support, and relapse prevention training (25,26). Behavioral therapy can be provided in clinical and commercial settings or as self-help programs. Group counseling results in comparable long-term weight loss as individual counseling. However, initial individual counseling is sometimes preferred for severely obese subjects and for men. Behavioral treatment of obesity in children should address the whole family or at least the mother of an obese child. Data on the efficacy of behavioral programs carried out in controlled settings show that weight losses average nearly 9% in trials lasting ~20 weeks (25). The major limitation of these programs is the high likelihood that individuals will regain weight once the behavioral treatment is ended. Wing and Hill (27) defined successful weight loss maintainers as "individuals who have intentionally lost at least 10% of their body weight and kept it off at least 1 year." According to the U.S. National Weight Control Registry, a low level of depression and dietary disinhibition and medical triggers for weight loss are associated with successful weight loss maintenance (27). Behavioral modification of lifestyle, especially self-control over daily energy balance, plays a crucial role in long-term success of weight management. Self-monitoring weight, dietary intake, and daily physical activity on a regular basis is an important determinant of weight loss maintenance. Consistent eating patterns, including regularly eating breakfast, also influence the outcome of weight management. It is obvious that special attention should be paid to patients who are prone to failure in long-term weight management. More frequent dietary counseling as well as the use of anti-obesity drugs (see the next paragraph) contribute to a better outcome of long-term weight management. This counseling might be traditional patient visits or can be provided by phone, e-mail, or Internet chat applications (28). Psychological support is necessary for patients with depression or dietary disinhibition. Psychologist should train patients how to cope with situations triggering dietary disinhibition (e.g., stress, anxiety, and depression).

Although meta-analysis of studies done in the U.S. demonstrated that success in weight loss maintenance has improved over the past decade (19), much more research is required to reveal how to sustain the changes in lifestyle behavior. No study thus far has documented long-term maintenance of weight loss with behavior therapy or a maintained positive effect on obesity-associated comorbid conditions. Strategies to achieve better long-term goals are designed to make necessary behavioral changes. Cooper and Fairburn (29) emphasize that long-term adherence to behavioral lifestyle changes should be addressed by a new cognitive behavioral approach to the treatment of obesity that is based in a cognitive conceptualization of weight control. However, it seems that the differences between standard behavior therapy and cognitive-behavioral therapy of obesity are more at the theoretical level than in their practical implementation (30). Therefore, clinicians who are engaged in the long-term treatment of obese patients should use both cognitive and behavioral strategies within the context of a standard behavioral lifestyle modification program (30).

Two studies that have focused on prevention of type 2 diabetes—the Diabetes Prevention Program (31,32) and the Finnish Diabetes Prevention Study (33,34)—are excellent examples of the implementation and efficacy of behavioral modification of lifestyle. The Diabetes Prevention Program enrolled 3,234 overweight and obese patients with elevated fasting and postload plasma glucose who were randomized to receive placebo, metformin, or intensive lifestyle modification (31). The lifestyle modification program used in the Diabetes Prevention Program (32) resulted in a weight loss of 6.7 kg at 1-year follow-up, compared with weight losses of 2.7 and 0.4 kg in the metformin and placebo groups, respectively. At the 4-year follow-up, lifestyle, metformin, and placebo groups maintained weight losses of 3.5, 1.3, and 0.2 kg, respectively. The average follow-up was 2.8 years. Behavioral modification of lifestyle reduced the incidence of type 2 diabetes by 58% and metformin by 31%, as compared with placebo. Even more interesting are the results of the extended follow-up (34) of the Finnish Diabetes Prevention Study (33). In the initial study (33), lifestyle modification resulted in weight loss of 3.5 ± 5.5 kg compared with 0.8 ± 4.4 kg in the control group and a reduction of 58% in the incidence of diabetes, which was directly related to changes in lifestyle. After a median of 4 years of active intervention period, participants without diabetes were further followed up for a median of 3 years. During the total follow-up, beneficial lifestyle changes achieved by the participants in the intervention group were maintained after discontinuation of the intervention, and the incidence of type 2 diabetes was 4.3 per 100 person-years in the intervention group compared with 7.4 per 100 person-years in the control group (34).

DRUG TREATMENT OF OBESITY

— Anti-obesity drugs have been developed to assist weight loss in combination with lifestyle management, to improve weight loss maintenance, and to reduce obesity-related health risks. Pharmacotherapy of obesity should be applied as a part of the comprehensive obesity management, which includes lifestyle modification (3,4).

Anti-obesity drugs affect different targets in the central nervous system or pe-

ripheral tissues and aim to normalize regulatory or metabolic disturbances that are involved in the pathogenesis of obesity. Currently, only three anti-obesity drugs have been successfully used in long-term weight management, conducted over period of 1–4 years (35–37). It is expected that lifelong treatment with anti-obesity drugs will be required to specifically target the particular abnormality. Pharmacotherapy of obesity has been indicated for the treatment of obese adults (≤65 years). Several studies have been recently conducted to evaluate efficacy and safety of anti-obesity drugs for children and adolescents (38,39) as well as for the elderly (40). Consequently, the U.S. Food and Drug Administration has approved the drug orlistat for use in children and adolescents.

Our current potential to treat obesity by drugs is limited in comparison to the drug treatment of other complex diseases such as hypertension, diabetes, and dyslipidemia. Sibutramine, as a serotonin and norepinephrine reuptake inhibitor, induces satiety and prevents diet-induced decline in metabolic rate (41). The STORM (Sibutramine Trial on Obesity Reduction and Maintenance) trial data showed that weight loss was achieved with 6 months of treatment with sibutramine and a comprehensive lifestyle management program (35). At 6 months, patients were randomized either to continue with the lifestyle program and sibutramine or to switch to a lifestyle program with placebo in a double-blind design. For those patients switched to placebo, despite the presence of the lifestyle program, weight regain was rapid over the next 18 months. Continued use of sibutramine maintained weight loss almost completely for this period of time (35). In another study, administration of sibutramine facilitated better weight loss maintenance in patients who were treated initially with a VLCD (42). Randomized 1-year trial of lifestyle modification and pharmacotherapy for obesity clearly demonstrated that the combination of sibutramine and lifestyle modification resulted in more weight loss than either medication or lifestyle modification alone (43).

Orlistat, as an inhibitor of lipase, reduces fat absorption in the intestine. The XENDOS (Xenical in the Prevention of Diabetes in Obese Subjects) study compared the weight loss and incidence of diabetes over 4 years in obese subjects who were randomized to lifestyle changes plus either orlistat or placebo (36). Patients treated with orlistat and lifestyle modification exhibited a greater weight loss and a significant reduction in diabetes incidence compared with those who underwent lifestyle modification and received placebo (36). Toplak et al. (44) recently published the results from the X-PERT study, in which a lifestyle intervention was combined with different dietary interventions and orlistat. Patients showed very good weight loss and exhibited beneficial effects on components of the metabolic syndrome.

Rimonabant, as a selective cannabinoid receptor-1 blocker, reduces food intake and tobacco dependence by blocking cannabinoid receptors in the central nervous system and affects the metabolic profile by targeting the cannabinoid system in adipocytes and hepatocytes (45). Rimonabant administration leads to significant weight reduction and improvement in cardiometabolic risk profile in four randomized double-blind clinical trials conducted in overweight or obese adults (37,45).

Recently, the anti-epileptic drug topiramate was discovered to have beneficial effects on weight control and was investigated as a weight loss drug. It even proved to have a beneficial effect on diabetes control, but because of drug safety issues, a registration for obesity and diabetes seems unlikely (46).

Weight loss induced by currently available anti-obesity drugs is only modest, reaching usually 5–8% of initial body weight. The average weight loss in the drug-treated group is 3–5% higher than in the placebo group. Drug-induced weight loss is associated with improvement in lipid profile and glycemic control. It has been shown that the lipid profile improvement after sibutramine, orlistat, and rimonabant is partly independent of weight loss. Changes in insulin sensitivity observed in patients treated with rimonabant were only attributable to weight loss alone by 49%. Identical effectiveness of both continuous and intermittent drug administration was demonstrated for several anti-obesity drugs (47). Combination treatment with sibutramine and orlistat does not influence weight loss (48). However, in the future, combination therapy with anti-obesity drugs should be expected. Special attention should be paid not only to the efficacy, but also to the potential drug interaction and safety.

Assignment of patients to a particular anti-obesity drug should respect their licensed indications and contraindications; i.e., sibutramine should not be administered to patients with uncontrolled hypertension, orlistat should not be administered to patients with cholestasis, and centrally acting drugs should be indicated with caution in patients with depression. Drugs should be administered to patients who adequately responded to the initial phase of treatment over a 1.5- to 3-month period. Nonresponders are characterized by a weight loss <1–2 kg after 6 weeks of treatment. However, modest weight loss should be expected in patients with type 2 diabetes and in those who have already lost weight with lifestyle modification. Recently, a weight loss in response to 3 months of treatment by either sibutramine (49) or orlistat (44) in conjunction with diet and exercise has been shown to predict weight loss at 1 year.

Psychological and behavioral predictors of weight loss have also been evaluated in the context of pharmacological treatments of obesity, including fenfluramine, phentermine, mazindol, and caffeine plus ephedrine (50), usually administered as combined therapy (fenfluramine + phentermine, fenfluramine + mazindol). Patients who scored higher on dietary restraint and hunger at baseline were less likely to lose weight over the 6-month period, whereas only high hunger scoring at baseline predicted lower weight loss at 12 months. However, many of the drugs used in the study by Womble et al. (50) have now been withdrawn from the pharmaceutical market.

In our study, obese patients were treated by lifestyle intervention and sibutramine (51). Weight loss at month 12 was predicted by baseline BMI, depression score, restraint score, and total energy intake. These predictive variables accounted for 43.8% of the variance in BMI loss at 12 months. When relationships between the BMI loss and changes in studied psychobehavioral and nutritional parameters were considered after 12 months of treatment, a drop in the disinhibition score of the Eating Inventory appeared the only significant factor that correlated with the BMI decrease.

New anti-obesity drugs possessing novel mechanisms of action are likely to be available in the future. Several potential new agents targeting weight loss in obesity through the central nervous system pathways or peripheral adiposity signals are investigated in clinical trials. Gut hormones and/or their derivatives might

contribute to the treatment of obesity and provide the advantage of targeting specific appetite pathways within the brain without producing unacceptable side effects. Future goals for the drug treatment of obesity include evaluation of *1*) predictors of drug-induced weight loss and its maintenance (as for example initial weight loss and genetic, metabolic, nutritional, and psychobehavioral factors), *2*) primary drug effects on health risks, *3*) efficacy and safety of combined drug treatment, and *4*) anti-obesity drugs in children, adolescents, and the elderly patients.

BARIATRIC SURGERY — Bariatric surgery is the most effective treatment for morbid obesity in terms of weight loss, health risks, and improvement in quality of life (52,53). It should be considered for patients with BMI ≥40.0 kg/m^2 or with BMI between 35.0 and 39.9 kg/m^2 with comorbidities (3,4,52,53). Obesity surgery should be conducted in centers that are able to assess patients before surgery and to offer a comprehensive approach to diagnosis, assessment, treatment, and long-term follow-up (53). Bariatric surgery could be carefully considered in severely obese adolescents who have failed to lose weight in a comprehensive weight management program carried out in a specialized center for at least 6–12 months and who have achieved skeletal and developmental maturity. Centers performing bariatric surgery in adolescents should have extensive experience with such treatment in adults and should be able to provide a multidisciplinary team that possesses pediatric skills related to surgery, dietetics, and psychological management (52,53). In elderly patients (>60 years), the risk-to-benefit ratio should be considered on an individual basis. It is necessary to emphasize that the primary objective of surgery in elderly patients is to improve quality of life, as surgery per se is unlikely to increase lifespan (53).

In bariatric surgery, restrictive procedures as well as procedures limiting absorption of nutrients are currently available. The magnitude of both weight loss and weight loss maintenance is increasing with the following procedures: gastric banding, vertical banded gastroplasty, proximal gastric bypass, biliopancreatic diversion with duodenal switch, and biliopancreatic diversion (53). There are no sufficient evidence-based data to suggest how to assign a particular patient to a particular bariatric procedure. However, for patients with BMI >50 kg/m^2, gastric bypass or biliopancreatic diversion brings more benefits. Pure restrictive procedures are not recommended for patients with a significant hiatal hernia or severe gastroesophageal reflux disease. Gastric banding cannot contribute to further substantial weight loss in patients in whom a significantly diminished food intake has been verified before the surgery. On the other hand, it should be considered that a laparoscopic adjustable gastric banding is the safest bariatric procedure associated with only minor perioperative surgical risks.

Bariatric surgery has been proved as the most effective way of treating type 2 diabetes in severely obese patients. More than 10 years ago, Pories et al. (54) demonstrated that 83% of patients with diagnosed type 2 diabetes exhibited normal blood glucose and normal glycosylated hemoglobin levels 7.6 years after bariatric surgery. Further, 99% patients with impaired glucose tolerance normalized a glucose tolerance after bariatric surgery (54). The 10-year follow-up in the Swedish Obese Subjects (SOS) study demonstrated that a bariatric surgery is a viable option for the treatment of severe obesity, resulting in long-term weight loss, improvement in lifestyle, and, except for hypercholesterolemia, amelioration of cardiometabolic risk factors (55). After 10 years, the average weight loss from baseline was 25% after gastric bypass, 16% after vertical banded gastroplasty, and 14% after gastric banding. The group that had undergone surgical intervention had lower incidence rates of diabetes, hypertriglyceridemia, and hyperuricemia in comparison to the control group (55). The most important recent finding of the Swedish Obese Subjects study is a reduction of overall mortality by 24.6% in the surgery group versus control subjects (56). However, Adams et al. (57) reported reduction of overall mortality by 50% in comparison with control subjects 8.4 years after gastric bypass surgery. Cause-specific mortality was reduced by 94% for diabetes, 71% for coronary artery disease, 62% for other circulatory diseases, and 55% for cancer (57).

HORMONAL AND HEREDITARY FACTORS AFFECTING WEIGHT LOSS

— Whereas substantial attention has been paid to the role of nutritional and psychobehavioral factors in weight management, the role played by hormonal and hereditary determinants of weight loss and weight loss maintenance has been underestimated.

HORMONAL DETERMINANTS OF WEIGHT LOSS

— Several hormones of the central nervous system, adipose tissue, and the gastrointestinal tract involved in the regulation energy balance have been described. The role of baseline hormonal levels and their response to weight management have been studied with regard to both weight loss and weight loss maintenance.

Naslund et al. (58) evaluated the role of leptin, insulin resistance, and thyroid function on weight loss maintenance in obese men who had been followed for a 2-year period of behavioral modification of lifestyle. A high baseline leptin/BMI ratio as a marker of leptin resistance was associated with failure in maintaining achieved weight loss. Multiple regression analysis revealed that 22% of variability in weight loss after the 2-year follow-up was explained by baseline leptin and insulin level together with age. The role of leptin sensitivity in determination of weight loss was confirmed in a subsequent study by Verdich et al. (59). They demonstrated a higher weight loss in response to 24-week weight management in subjects who exhibited lower baseline leptin levels after adjustment for fat mass. On the other hand, inadequately high decreases in serum leptin levels in response to weight management might negatively influence the outcome of weight reduction and predispose to weight regain (60–62) and weight cycling (63).

A recent study by Garcia et al. (64) described association between lower ghrelin levels at baseline and resistance to weight loss. Magnitude of weight loss had also been shown to be influenced by peptide YY (PYY), a hormone secreted in the distal intestine that reduces energy intake and induces weight loss. Low baseline PYY levels and the highest increases in PYY concentrations were associated with the highest weight reduction in children who underwent a 1-year weight management regimen (65). In our study of 67 women (BMI 32.4 ± 4.4 kg/m^2; age 48.7 ± 12.2 years) who had exhibited stable weight on a 7 MJ/day diet during the first week of weight management, the subjects obtained a hypocaloric diet providing 4.5 MJ/day (protein 25.3%, fat 28.7%, carbohydrate 46%) during the

subsequent 3-week period (66). The following hormonal parameters were examined both before and after the weight loss, which was on average 3.8 ± 1.6 kg: thyroid-stimulating hormone, fT3, fT4, insulin, C-peptide, prolactin, growth hormone, IGF-I, cortisol, sex hormone–binding globulin, parathormone, ghrelin, leptin, PYY, neuropeptide Y, pancreatic polypeptide, adiponectin, and resistin together with a C-reactive protein as an inflammatory marker. Baseline levels of GH, PYY, neuropeptide Y, and C-reactive protein predicted 49.8% of variability in weight loss. Higher baseline growth hormone levels and lower baseline PYY and neuropeptide Y levels predicted higher weight loss.

HEREDITARY DETERMINANTS OF WEIGHT LOSS

— It is obvious that some obese people can achieve a higher weight loss in response to the same negative energy balance than the others. The role of genetic factors in different capabilities to lose weight was identified in studies conducted in monozygotic twins, i.e., individuals who possess identical genes. The study by Bouchard and Tremblay (67) was focused on responsiveness of slightly overweight identical twins to a negative energy balance as a result of enhanced physical activity. Weight loss was similar in pairs of identical twins but differed significantly between pairs. A subsequent study by Hainer at al. (68) revealed significant similarity in weight loss in response to a 1-month weight management program with a VLCD within the pairs of obese monozygotic twins. Although body weight reduction showed wide interindividual variation, ranging between 5.9 and 12.4 kg, it was similar in pairs of monozygotic twins. Intrapair resemblance in fat loss was 17 times as high as resemblance between pairs.

WEIGHT LOSS IN MONOGENIC FORMS OF OBESITY

— Because the monogenic forms of obesity are rather scarce, only few reports on efficacy of therapy are available. It can be expected that if the therapy of obesity would target the correction of the disorder linked to gene mutation, it should be successful. Until now, there exists only one example of a successful therapy of obesity based on gene mutation. Obesity due to leptin gene mutation was successfully controlled by administration of recombinant leptin both in adults (69) and children (70). In view of the known role of genes in the pathogenesis of obesity, some physicians may adopt a nihilist attitude to the treatment of this disorder. Nevertheless, such an approach is unjustified as shown by the last report on body weight, body fat mass, and insulin susceptibility normalization after a 11-month comprehensive weight loss intervention in three children with R236G mutation in the proopiomelanocortin gene (71). The most common monogenic form of human obesity is that caused by mutations in the gene that encodes the melanocortin 4 receptor (MC4R) and is associated with intensive feelings of hunger and hyperphagia in childhood that decreases with aging. No comprehensive clinical studies on weight loss in patients with the MC4R mutation have been published. A pilot study of Hainerova et al. (72) reported a comparable low-energy diet–induced weight loss in carriers of MC4R mutations and in their counterparts with common forms of obesity. This observation is supported by an experimental study of Butler and Cone (73), who described hyperphagia in MC4R-deficient mice fed a high-fat diet. No hyperphagia was observed when low-fat diet was introduced to these mice, thus indicating gene-environment interaction and supporting the role of low-fat diet in weight management, even in strongly genetically determined obesities.

GENETIC COMPONENT OF WEIGHT LOSS IN COMMON FORMS OF OBESITY

— Involvement of genetic factors in the development of obesity is estimated to be 40–70% (74). Almost 600 obesity candidate genes have been described (75). Some of these obesogenic or leptogenic genes might affect weight loss and weight loss maintenance (76). Polymorphisms of several obesity candidate genes have been shown to influence the outcome of weight management (76). Among the genes involved in the outcome of weight management, the ones studied include the genes affecting regulation of energy expenditure (β_3-adrenergic receptor, uncoupling proteins), appetite control (leptin, leptin receptor, serotonin receptor), eating behavior (neuromedin β), adipogenesis (peroxisome proliferator–activated receptor γ2), and development of metabolic syndrome (adiponectin). The ambiguous results observed in several of the studies could be explained by gene-gene interaction that have not been taken into account as well as by the different role of investigated genes in different ethnic, age, and sex cohorts. Moreover, weight loss in response to obesity treatment might also be influenced by changes in obesogenic and/or leptogenic gene expression induced by environmental factors such as the type of ingested nutrients and level of physical activity.

Genotyping could be of relevance in predicting the efficacy of drugs in weight management. Obese individuals with the CC genotype of the G-protein β3 subunit polymorphism (C825T) achieved higher weight loss in response to sibutramine administration compared with individuals with the TT/TC genotypes (77). Polymorphism of phenylethanolamine N-methyltransferase, an enzyme that catalyzes the conversion of norepinephrine to epinephrine, has also been shown to affect sibutramine-induced weight loss. The G-148A polymorphism homozygotes exhibited higher weight loss in response to a 3-month therapy with sibutramine (78).

More comprehensive studies on the interaction between candidate obesity genes, psychobehavioral factors, and environmental factors are needed for a better understanding of the outcome of weight management in our increasingly obesogenic environment.

COMPREHENSIVE MULTILEVEL OBESITY MANAGEMENT NETWORK

— Obesity should be tackled by health care providers as well as by health policy authorities because it is a disease with serious health consequences. The quality of obesity management depends on educating current as well as future health care providers. Effective obesity management requires a comprehensive multilevel obesity management network and the direct involvement of the health and general insurance industries as well as governments. A multilevel obesity management network of mutually collaborating facilities should be established to provide individually tailored treatment (79). A comprehensive obesity management program as a multilevel network includes obesity management centers, obesity specialists and other specialists, primary care physicians, weight loss clubs led by educated counselors and self-assessment, and media. Centers of excellence in obesity management represented by multidisciplinary teams

(obesity specialists, dietitians or nutritionists, exercise physiologists or physiatrists, psychologists and/or psychiatrists, bariatric surgeons, specialized trained nurses) should provide comprehensive programs for the treatment of obesity derived from evidence-based medicine. These centers should focus on the care of severely obese patients and those with serious health risks or who failed in their weight control. The centers should also be responsible for eliminating unproven treatment approaches that have been frequently associated with health hazards.

Acknowledgments— This study was partly supported by a grant from the Czech Ministry of Health (IGA NR/7800-4).

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