

Results of obesity treatment

A.J. Scheen

(1) Division of Diabetes, Nutrition and Metabolic Disorders, Department of Medicine, CHU Sart Tilman (B35), B-4000, Liège, Belgium

Résultats du traitement de l'obésité

A.J. Scheen

L'obésité est une maladie chronique de telle sorte que les résultats de son traitement doivent s'évaluer à long-terme. Cet article de synthèse analyse les résultats, avec un recul d'au moins une année, de trois approches anti-obésité, à savoir les modifications du style de vie, les traitements pharmacologiques et les méthodes chirurgicales. Les interventions diététiques comprennent des régimes avec restriction calorique modérée ou sévère (diètes à très basses calories). Même si la perte de poids initiale est plus importante, il n'y a pas d'études démontrant de façon péremptoire que ces dernières sont plus efficaces à long-terme que les premières. L'exercice physique paraît peu efficace pour induire une perte de poids, mais paraît plus important pour éviter une reprise de poids après un amaigrissement. Cependant, les résultats à long-terme des modifications de style de vie sont souvent décevants en raison d'un défaut d'observance. Plusieurs études de longue durée (1- 2 ans), incluant plusieurs centaines de sujets dans des protocoles contrôlés versus placebo, ont démontré l'efficacité de deux médicaments anti-obésité, l'orlistat, un inhibiteur de la lipase intestinale, et la sibutramine, un régulateur central de l'appétit. Les deux médicaments augmentent, de façon significative mais relativement modeste en moyenne, la perte de poids, doublent environ le nombre de sujets bons répondeurs (amaigrissement ≥ 5 or 10 % du poids initial) et favorisent le maintien de la perte de poids jusqu'à deux ans de suivi. Par comparaison aux traitements médicaux, les méthodes chirurgicales entraînent une perte pondérale beaucoup plus importante chez les patients avec obésité morbide, en particulier lors d'un suivi de plusieurs années. L'amaigrissement est plus marqué avec la dérivation gastrique, qui s'accompagne d'une certaine malabsorption digestive, qu'avec la gastroplastie, une technique de restriction gastrique pure. Les facteurs de risque associés, comme les marqueurs de l'insulinorésistance et le diabète de type 2, sont remarquablement corrigés, mais on ne dispose pas encore d'études contrôlées concernant la morbidité et la mortalité. Dans tous les cas, la prise en charge de l'obésité requiert une approche multidisciplinaire pour garantir les meilleures chances de succès.

Mots-clés : Obésité, médicaments, régime alimentaire, exercice, gastroplasie, orlistat, sibutramine.

Results of obesity treatment

Obesity is a chronic disease so that results of obesity treatment should only be evaluated on a long-term basis. The present paper aims at analyzing the long-term (1 year or more) results of three anti-obesity approaches, i.e. lifestyle modifications, pharmacological treatments and surgical procedures. Dietary interventions include diets with moderate calorie restriction and very-low energy diets (VLED). Even if an initial greater weight loss is observed with VLED, no study has conclusively shown that the long-term approaches including VLED are better than non-VLED programmes. Physical activity is not the most efficient method of initial weight loss, but it appears to be more crucial for maintaining weight loss once it has occurred. In general, long-term results of lifestyle modifications are disappointing because of poor compliance. Several 1-2 year large-scale randomized placebo-controlled clinical trials with orlistat, an intestinal lipase inhibitor, and sibutramine, a central appetite regulator, have demonstrated that both drugs significantly, although modestly on average, increase weight reduction, almost double the number of responders (weight loss ≥ 5 or 10 % of initial body weight) and improve weight maintenance up to 2 years. Surgical procedures provide a much greater weight reduction than medical interventions in patients with morbid obesity, particularly after a follow-up of several years. Weight loss is greater with gastric bypass, inducing some malabsorption, than with gastroplasty, a pure gastric restriction technique. Associated risk factors such as markers of insulin resistance syndrome and type 2 diabetes are remarkably reduced, but no prospective study of morbidity or mortality is available yet. In all cases, the management of obesity requires a multidisciplinary approach to improve the success rate.

Key words: Obesity, drug therapy, gastroplasty, diet, exercise, orlistat, sibutramine.

INTRODUCTION

The prevalence of overweight and obesity is increasing in all countries. Obesity must be considered as a major public health problem [66] since it markedly increases the risk of comorbidities and complications, reduces life expectancy and diminishes quality of life [36, 42]. Guidelines for treating obesity have been published during the last few years, especially in the United States [13, 38] and in France [5].

Obesity results from a chronic imbalance between a relatively excessive energy intake and a relatively insufficient energy expenditure. Thus, from a theoretical point of view, treating obesity should be a simple task as it only requires to reduce caloric intake and/or to increase physical activity. However, from a practical point of view, everybody involved in the treatment of obesity knows that such simple objectives are extremely difficult to reach so that obesity management remains a real medical challenge [49, 66]. In addition, even if the beneficial health effects of modest weight loss have been emphasized [16], especially in overweight diabetic patients [50], most obese patients have unrealistic weight loss expectations, regarding both the rapidity of weight reduction and the desirable final body weight. Finally, most of them are ready to make efforts during a limited period of time rather than on a long-term basis, which explains the high risk of weight regain.

Numerous clinical trials have investigated the effects of various anti-obesity approaches, but most of these studies were of limited duration, not exceeding a few months. It is recognized that obesity is a chronic disease and that only approaches able to induce long-term weight reduction should be considered as valuable strategies for treating obese subjects. That is the reason why anti-obesity drugs should first prove both efficacy and safety in 1-2 year randomized clinical trials before being accepted for treating obese patients [43]. Clinical trials investigated body weight changes as well as, in numerous cases, ancillary markers, for instance, cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidaemia, ... Even if preliminary data showed that intentional weight loss reduces mortality among overweight individuals with diabetes [64], no prospective study focusing on the impact of weight loss on morbidity and mortality of obese subjects has been published yet.

The present review aims at analyzing the long-term (after at least 1 year follow-up) results of three main anti-obesity therapeutic approaches in adults : 1) lifestyle interventions, i.e. comprehensive programmes combining dietary advices and physical exercise ; 2) pharmacological treatments, especially orlistat and sibutramine ; and 3) surgical procedures, more particularly gastroplasty and gastric bypass.

LIFESTYLE INTERVENTIONS: DIET AND EXERCISE

Diet

Various dietary interventions have been proposed for the treatment of obesity [49, 60]. They can be schematically divided into diets with moderate but prolonged caloric restriction (as example, daily energy requirement minus 500-600 kcal) and very-low calorie diets (VLCD or VLED for very-low energy diet: total energy intake not exceeding 800 kcal/day, containing 0.8-1.5 g/day high-quality protein and the recommended daily allowances of minerals, vitamins and trace elements) during a few weeks followed by a classical low-calorie mixed diet [37, 40]. VLCDs are very effective to obtain rapid weight loss and improvement of metabolic disorders, such as diabetes mellitus [48]. However, if initial weight loss is significantly greater and more rapid with VLCDs, the long-term efficacy of such diets remains questionable. Among the many reports on successful use of VLCDs, few have provided comprehensive information on weight maintenance, such as the number of subjects entering the programme, attrition rate, follow-up rate, and amount of weight loss at the end of therapy as well as 1 to 5 years later [40]. For the comparison of outcomes after weight reduction programmes with and without VLCDs, a systematic review of the randomized trials with a minimum of 30 patients and 1 year follow-up or more was performed [37]. At the end of the programmes the mean weight loss with VLCDs ranged from 9.2 to 19.3 kg and that of the non-VLCD programmes from 6.2 to 14.3 kg. The studies with 1- or 2-year follow-up have shown a mean weight loss of 7.2-12.9 kg with VLCDs and 5.7-9.5 kg without VLCDs. Thus, no study has conclusively shown that in the long-term VLCD-programmes are better (or worse) than non-VLCD programmes [37, 60].

A major problem of all low-calorie diets is long-term weight regain as soon as less strict dietary supervision is allowed. However, the published studies on long-term outcomes of such programmes have given variable results [37]. In a landmark study on comprehensive programmes combining dietary and lifestyle interventions, one-third to two-thirds of lost weight was regained within 1 year and virtually all lost weight was regained within 5 years [63]. In a prospective 2-year study, 35 % of obese subjects maintained their weight loss of 10 % or more and 42 % lost 0-10 % of their initial weight after 2 years [1]. In another long-term evaluation, a quarter of the patients

had maintained a weight loss of 10 % 7 years after therapy using VLCD [44]. In a descriptive Finnish study of weight loss maintenance, 6 and 15 year follow-up of initially overweight adults demonstrated that long-term maintenance is very rare (only 6 %) [46]. A recent study suggests that the 1-5 year prognosis for weight maintenance among individuals who reach goal weight in at least one commercial weight loss programme (i.e. Weight Watchers) may be better than that suggested by existing research essentially conducted in university or hospital settings [28]. However, a systematic review concluded that, because of many methodological limitations, the current published data are inadequate to conclude that the rate of "self-cured" obesity is higher than the rate from clinical trials [4].

Even if the results may be often disappointing in the long-term, lifestyle modifications should not be neglected, whatever the other procedures for losing weight used. A recent one-year randomized study demonstrated that the addition of group lifestyle modification to the pharmacologic management of obesity significantly improved weight loss and patients' satisfaction with treatment outcome [61], an observation which underlines the importance of a global approach for the treatment of obese subjects. Finally, life-style modifications could be very effective on other outcomes than body weight per se, at least when they are correctly followed within an intervention programme. The "Finnish Diabetes Prevention Study" demonstrated that the risk of type 2 diabetes could be reduced by 58 % after a mean follow-up of 3.2 years by changes in diet and exercise inducing a 3 kg weight reduction among high-risk overweight subjects with impaired glucose tolerance [59]. In the weight loss arm of Trials of Hypertension Prevention (TOHP) II, clinically significant long-term reductions in blood pressure and reduced risk for hypertension was achieved with even modest weight loss (only 2 kg) after a 3-year intervention programme focusing on dietary change, physical activity, and social support [58].

Exercise

Even if the favourable role of physical exercise is classically recognized, such a positive effect has been insufficiently demonstrated in long-term prospective studies [7, 24]. The effects of exercise, alone or in combination with low-energy diet, in obese adult subjects have been recently reviewed extensively [3, 65]. Ten randomized controlled trials have addressed whether exercise interventions alone will produce weight loss [review in 7, 65]. The majority of these studies showed that aerobic exercise produces some weight loss, although the effect appears to be modest, generally 1-2 kg over the duration of the study. Another 13 clinical trials examined whether the combination of reduced-energy diets and increased physical activity produces a greater weight loss than does a low-energy diet alone. Most studies favoured diet + exercise regimens over diet alone, but the difference was statistically significant in only a minority of studies. The overall lack of statistical significance was probably due to the short-time frame of the exercise programmes, small sample sizes and difficulty with adherence to exercise. Finally, a few of the prior clinical trials were extended to examine whether a regimen of diet + exercise produces better maintenance of weight loss than does diet alone. Of six studies that bear that question, two showed significant long-term effects favouring diet + exercise over diet alone ; the others were inconclusive. Interestingly enough, studies of successful weight losers consistently showed that physical activity is strongly associated with better long-term maintenance of weight loss [review in 7, 65]. Thus, even though physical activity is not the most efficient method of initial weight loss, it appears to be more crucial for maintaining weight loss once it has occurred, although additional long-term research is needed.

PHARMACOLOGICAL TREATMENTS

As obesity is a chronic disease, pharmacological treatment should be considered on a long-term basis such as for diabetes mellitus, hypertension or dyslipidaemias [41, 43]. First anorectic agents, like amphetamine derivatives, showed a greater 0.25 kg/week weight loss as compared to placebo in short-term studies (< 6 months), but were not carefully evaluated in well-controlled long-term (*i.e.* minimum 1 year) trials [review in 8, 9, 51]. In fact, the first large multicentre placebo-controlled one-year trial concerned dexfenfluramine [17], a serotonin release enhancer which was withdrawn from the market a few years later because of cardiac side-effects.

Two medications for the induction and maintenance of weight loss have been approved and launched recently, orlistat [33] and sibutramine [34]. In contrast with previous anorectic drugs, these two anti-obesity agents have been carefully evaluated in several large placebo-controlled long-term trials in which patients were generally prescribed a modest energy deficit (around 600 kcal/day) and encouraged to increase physical activity [8, 9, 33, 34, 51].

Orlistat

Orlistat is a gastric and pancreatic lipase inhibitor that blocks the absorption of about one third of the fat contained in a meal and thus promotes faecal excretion of undigested fat [33]. More than 4 800 patients received orlistat in clinical trials, including 2 153 patients who received it for at least 1 year and 884 who received it for up to 2 years. In 1-year studies, patients who received orlistat (usually at a dose of 3×120 mg/day) lost significantly more weight than patients who received placebo, although the average difference was rather modest (table I, upper part [11, 14, 18, 19, 21, 26, 45, 56]. Even more impressive, twice as many patients in the orlistat group as in the placebo group lost more than 5 or 10 % of their initial body weight. The 2-year studies which were designed to evaluate the effect of orlistat in maintaining the weight loss in the first year of treatment demonstrated significantly less weight regain with orlistat than with placebo [11, 45, 56]. Similar results in the long-term treatment of obesity with orlistat were also reported in primary care settings [18]. Finally, a study that focused specifically on prevention of weight regain after a successful period of dieting alone showed that the use of orlistat minimizes weight readjustment and facilitates long-term improvement in obesity-related disease risk factors [20].

Table I: Effects of orlistat or sibutramine in one-year placebo-controlled large studies in obese subjects (intent-to-treat analysis). All the differences between placebo and active drug are statistically significant ($p < 0.05$).

Tableau I : Effets de l'orlistat ou de la sibutramine lors des études contre placebo chez les sujets obèses (analyse en intention de traiter, les différences placebo-substance active sont significatives à $p < 0,05$).

Références	Drug	n	Weight loss kg	Responders : weight loss	
				≥ 5% initial BW	≥ 10% initial BW
Orlistat					
Sjöström <i>et al.</i> 1998	Placebo	340	-6.1	49	18
	Orlistat 360 mg	343	-10.3	68	39
Davidson <i>et al.</i> 1999	Placebo	224	-5.8	44	25
	Orlistat 360 mg	668	-8.8	66	39
Finer <i>et al.</i> 2000	Placebo	108	-1.3	21	17
	Orlistat 360 mg	110	-3.3	35	28
Hauptman <i>et al.</i> 2000	Placebo	212	-4.1	31	11
	Orlistat 180 mg	213	-7.1	49	24
	Orlistat 360 mg	210	-7.9	51	29
Rössner <i>et al.</i> 2000	Placebo	237	-6.4	-	19
	Orlistat 180 mg	239	-8.5	-	31
	Orlistat 360 mg	242	-9.4	-	38
Hollander <i>et al.</i> 1998(1)	Placebo	159	-4.3	23	9
	Orlistat 360 mg	162	-6.2	49	18
Sibutramine					
McMahon <i>et al.</i> 2000	Placebo	74	-0.5	9	4
	Sibu 20 mg	150	-4.4	40	13
Smith <i>et al.</i> 2001	Placebo	163	-1.6	20	7
	Sibu 10 mg	161	-4.4	39	19
	Sibu 15 mg	161	-6.4	57	34
Apfelbaum <i>et al.</i> 1999(2)	Placebo	78	+ 0.5	55	23
	Sibu 10 mg	82	-5.2	86	54
James <i>et al.</i> 2000(3)	Placebo	115	-7.9	57	25
	Sibu 10-15 mg	352	-10.9	80	52

(1) Obese patients with type 2 diabetes

(2) Maintenance study after a initial period of low-calorie diet

(3) Maintenance study after a initial 6-month treatment with sibutramine

In addition, weight loss produced by orlistat therapy was consistently associated with improvements in risk factors for cardiovascular disease, including serum lipid profiles, blood pressure and blood glucose levels [26, 45, 67]. Interestingly, the sustained cholesterol-lowering effect of orlistat is beyond what would be expected from weight loss alone [35]. Impaired glucose tolerance and increased plasma insulin levels improved in orlistat-treated obese patients, decreasing the percentage of patients of this group who developed type 2 diabetes mellitus during a 2-year study period [19]. Favourable results were also reported in obese patients with type 2 diabetes. In a 1-year study, diabetic patients treated with orlistat showed greater weight loss, reduction of fasting plasma glucose and glycated haemoglobin levels and decrease in dosage requirements for oral sulphonylureas as compared to those receiving placebo [21].

Because orlistat prevents the absorption of dietary fat, the possibility of its affecting the absorption of fat-soluble vitamins was considered in 1-2 year studies. Only minimal changes in plasma levels were observed and there was no evidence of long-term clinical consequences due to these changes [11, 14, 18-21, 26, 33, 45, 56].

Sibutramine

Sibutramine is a combined norepinephrine-serotonin reuptake inhibitor that is associated with increased satiation and a resulting reduction in food intake [34]. Side-effects reported with (dex)fenfluramine (a serotonin release enhancer), such as cardiac valvulopathies and primary pulmonary hypertension, have not been associated with sibutramine. Sibutramine has been evaluated in clinical trials in about 8 200 obese patients, 1 344 of whom were exposed to the drug for > 12 months (595 on sibutramine 10mg and 749 on sibutramine 15 mg). Sibutramine, at daily doses of 10-20 mg, was associated with a 7 % to 10 % reduction in initial body weight during the first 6 months and such weight loss was maintained until 1-2 years, with only a slight tendency to weight regain which was less marked than that observed with placebo (*table 1*, lower part) [22, 32, 57]. Following a VLCD, sibutramine was effective in maintaining and improving weight loss for up to 1 year [2]. When a weight loss of at least 10 % initial body weight was considered as a criterion of success, the percentage of weight responders was multiplied by 2 to 3 with sibutramine as compared with placebo in one-year clinical trials. Such a 10 % weight reduction associated with sibutramine treatment was accompanied by significant improvement in the metabolic profile of obese subjects, with lower plasma glucose and insulin levels, and better lipid profile (reduction of triglycerides and rise of HDL cholesterol) [2, 22, 32, 34, 57]. Sibutramine treatment was associated with small increases in arterial blood pressure (2-3 mm Hg) and heart rate (2-3 bpm) that were compensated by the reduction in blood pressure determined by the weight loss, mainly in the 5 % and 10 % responders. Because of these unwanted effects, a long-term large-scale prospective trial should evaluate the impact of sibutramine in the cardiovascular risk of obese subjects.

Thus, despite obvious efficacy, neither orlistat, nor sibutramine is able to induce large weight reduction in a majority of obese patients. In a pilot study designed to assess whether adding orlistat to sibutramine would induce further weight loss in patients who previously had lost weight while taking sibutramine alone (- 11.6 % of initial body weight after 1 year), no additive effects was observed after 16 weeks of combined therapy [62]. Consequently, research to find new pharmacological alternatives, leading to a greater efficacy in the promotion of weight reduction without affecting safety, remains a main objective for the treatment of obesity [10].

SURGICAL PROCEDURES

Surgery is now considered as a classical treatment for refractory morbid obesity or severe obesity with comorbidities in well-selected patients [39, 52]. Two types of surgical procedures are regularly used [review in 23] : pure gastric restriction procedures [12], i.e., vertical gastroplasty [31] or adjustable gastric banding [6], or procedures leading to partial intestinal malabsorption, i.e., gastric bypass [15] or, in some countries, biliopancreatic diversion [53]. It has been demonstrated that bypass surgical methods result in more marked and more prolonged weight loss as compared to pure gastric reduction approaches, but at the cost of a more aggressive surgical procedure and of a greater risk of complications [23]. Whatever the selected surgical technique, it leads to much greater and sustained weight reduction as compared to medical dietary and/or pharmacological interventions [52]. In most published studies, mean weight loss averaged 30-40 kg one year after surgery [12, 23]. Afterwards, a plateau or a slight weight regain was observed in most cases. In the interim report of the « Swedish Obese Subjects » study [55], gastric surgery resulted in a maximum weight loss of 31 kg after 1 year and the maintained weight loss was still 20 kg after 8 years, as compared to no significant weight changes in the obese control group. On an average, gastric bypass resulted in a 10-15 kg greater weight reduction than gastroplasty (either vertical gastroplasty or adjustable banding) [55]. In a personal series of 505 obese patients, 91 % had body mass index (BMI) above 35 kg/m² before gastroplasty while 77 % reached a BMI < 35 kg/m² and 14% recovered a BMI < 25 kg/m², 26 months after surgery [29]. The marked and sustained weight loss observed after surgery was associated with a remarkable improvement of all biological markers of insulin resistance classically considered as cardiovascular risk factors, i.e. hyperinsulinaemia, hypertriglyceridaemia, low HDL cholesterol level, elevated fibrinogen concentration, hyperuricaemia, ... [29]. Such an improvement in the metabolic syndrome may result from the marked reduction and, in case of recovery of ideal body weight, complete reversal of insulin resistance [25]. Therefore, it is not astonishing that major and sustained weight loss associated with surgery is able to markedly and significantly reduce the progression to type 2 diabetes [27, 55]. Furthermore, in obese patients with type 2 diabetes, post-gastroplasty weight loss resulted in almost a complete reversal of diabetes with normalization of fasting blood glucose concentrations and HbA_{1c} levels allowing the interruption (or at least drastic reduction) of antidiabetic drugs in most subjects [47, 50]. In a pilot study comparing the outcome of 154 obese diabetic subjects submitted to gastric bypass with that of 78 obese diabetic

control subjects, the mortality rate in the control group was 28 %, compared to 9 % in the surgical group (including perioperative deaths) ($p < 0.0003$), after a mean follow-up of 6.2 years and 9 years respectively [30]. Such favourable results on mortality (essentially reduction of cardiovascular deaths) are in agreement with the remarkable reduction of risk factors reported in other studies [29, 54, 55].

However, long-term results of bariatric surgery are not always easy to interpret as most studies included a lot of obese patients which were lost during follow-up, which may introduce major bias in the overall analysis. Furthermore, it is noteworthy that lifestyle modifications, including diet and exercise, remain essential even after surgery in order to improve long-term efficacy and limit gastrointestinal side-effects. The ultimate value of the surgical approach for treating severely obese patients will be provided by the ongoing first large prospective study (SOS for « Swedish Obese Subjects » study) which compares outcomes following surgery with those obtained with classical medical approaches. Preliminary results after a few years of follow-up are in favour of surgery as far as weight reduction, various surrogate endpoints (diabetes mellitus, for instance) and quality of life are concerned [54, 55]. Long-term (follow-up of ten years) results regarding major complications, especially cardiovascular events, and life expectancy are awaited with great interest.

CONCLUSION

The management of obesity requires a multidisciplinary approach including dietary and lifestyle interventions, pharmacological agents if necessary, and surgical procedures in well-selected patients with refractory morbid obesity. As obesity is a chronic disease, the results of its treatment should be best appreciated on a long-term basis. Realistic goals should be proposed to the obese patients. To this respect, a 10 % body weight reduction, which is associated with a significant improvement of the metabolic profile, may already be considered as a success of the medical intervention provided that weight regain is avoided.

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