Multi-Factorial Approach Associated with a New 'On/Off' Orlistat® Use in a Weight Loss Maintenance Programme: 4 Years Follow-Up

Vincent Makoundou^a Zoltan Pataky^a Elisabetha Bobbioni-Harsch^a Jean Pierre Gachoud^b
Franck Habicht^a Alain Golay^a

^a Service of Therapeutic Education for Chronic Diseases, Department of Community Medicine and Primary Care, Geneva University Hospital,

^b Roche Pharma (Schweiz) AG, Basel, Switzerland

Keywords

Weight loss maintenance · Multi-factorial approach · Orlistat®

Summary

Aim: To assess the efficacy of a specific long-term programme for weight loss maintenance using a new 'on/off' Orlistat approach in obese subjects who previously lost more than 10% of their body weight. **Methods:** 50 patients were followed up during 4 years; 34 completed the study. Subjects were followed up by physicians trained in obesity management. Anthropometrical, biological and psychological parameters were measured. Insulin sensitivity was evaluated by euglycaemic insulin clamp. Orlistat was given in case of weight relapse more than 2.5%. Subjects could take Orlistat on a voluntary basis for special occasions. **Results:** The BMI of completers remained stable (29.5 ± 0.9 vs. 30.6 ± 1.0 kg/m²). 73% of completers maintained 10% or more of their weight loss. Subjects from the no-regain group improved most of their parameters while the regain group did not. Insulin sensitivity was negatively linked to body weight during the follow up ($p < 0.01$, $r^2 = 0.20$). A negative relationship has been found between extent of the previous weight loss and the evolution of body weight during the 4 years follow-up ($p < 0.01$, $r^2 = 0.26$). Orlistat intake showed a body fat lowering effect ($p < 0.05$). **Conclusion:** 73% of subjects maintained more than 10% of their weight loss. Subject with a large weight loss amount are at high risk for weight regain. The Orlistat 'on/off' intake regarding his lowering body fat mass effect seems to be efficient.

Introduction

Excess body weight is the sixth most important risk factor contributing to the health burden in the world. Obesity amplifies the risks of type 2 diabetes mellitus, hypertension, dyslipidaemia, and cardiovascular disease and is estimated to reduce average life expectancy [1].

Weight loss has a beneficial effect on several cardiovascular risk factors for obese subjects and is therefore advised to them. Several studies have reported that weight loss, induced either by increasing energy expenditure (physical activity) or by limiting energy intake (dietary restraint) is accompanied by improvement of well-known cardiometabolic risk factors such as lipid profile, hypertension, insulin resistance and type 2 diabetes [2]. Weight loss has also a positive impact on cardiac autonomic function [3]. Unfortunately, the weight loss obtained after a diet is disappointing at medium and long term, and a 90% relapse can be observed after 5 years [4]. The overarching problem in the treatment of obesity is the consistency with which weight is regained, despite treatment. This problem has led to the view that obesity is a chronic disorder which requires long-term treatment [5].

Several attempts have been made, in order to define a successful long-term weight loss. For instance, the Institute of Medicine of the National Academy of Sciences [6] suggests that successful long-term weight loss means losing at least 5% of body weight and keeping it for at least 1 year. Wing and Hill [7] proposed that successful weight loss maintainers should be defined as individuals who have intentionally lost at least 10% of their body weight and kept it off at least 1 year. Since then, both definitions have been adopted and used by other authors in several studies [8, 9].

In order to establish the definition of weight maintenance, 35 studies published since 1999 considering weight mainte-

nance have been analysed in a review article [10]; the authors recommended that long-term weight maintenance in adults should be defined as a weight change less than 3% of body weight.

The multi-disciplinary approaches, such as diet and psychological therapies, diet and physical activity, diet and drug treatment as well as patient education [7], seem to obtain the best results in the weight loss maintenance. For instance, several researches have shown that, compared to a purely dietetic approach, a better improvement in the eating behavioural disorders is observed when cognitive-behavioural therapies are associated with a nutritional approach [11–13]. A study from our group demonstrated that a 1-day motivational workshop significantly increased regular physical activity among obese patients, thus reducing the risk of obesity relapse [14].

The aim of this study was to assess the efficacy of a specific long-term program based on a multi-factor approach during 4 years for weight loss maintenance in obese patients who had previously reduced their body weight. In addition for the first time, a new ‘on-off’ schema of Orlistat administration was introduced.

Subjects and Methods

The study protocol was approved by the local Ethics Committee and was conducted in compliance with the revised Declaration of Helsinki and in accordance with Good Clinical Practice guidelines. Patients gave their written informed consent. Before study entry, patients had a multiple multi-disciplinary patient educational approach previously described [12, 13, 15], including diet, physical activity, cognitive behavioural treatment, and/or Orlistat prescription.

In our weight loss maintenance program, we enrolled 50 obese subjects aged between 18 and 65 years who previously lost $\geq 10\%$ of their body weight using the patient therapeutic educational approach described above. Other study inclusion criteria were: BMI ≥ 30 kg/m² for subjects without cardiovascular risk factors or BMI ≥ 28 kg/m² for those with risk factors (diabetes, hypertension, and hyperlipidaemia).

We defined as successful weight maintainers subjects who did not increase their body weight more than 2.5% during the 4-year follow-up. The patients were not asked to lose additional weight.

Patients were followed up on an out-patient basis by physicians trained in the field of therapeutic patient education of obese patients. Special attention was given during the follow-up to maintain the motivation for behavioural adaptations on long term. The physician was responsible to decide for further complementary therapy to be followed, e.g diet, psychological support, or another specific treatment.

Study Protocol

After baseline measurements, patients came for a visit every 2 months during the first year of the study and every 3 months until the end of the study.

All visits were face to face visits with the aim to re-enforce the key theoretical constructs of the follow-up (motivation, support, problem solving, and relapse prevention). Body weight and Orlistat adverse events were assessed at each visit. The patient received a diet counselling at baseline with an adjustment to diet with a dietician at every visit if necessary. Drug administration, food questionnaires, and cognitive-behaviour therapy were documented at each visit. Binge eating behaviour, accord-

ing to DSM-IV, was evaluated at baseline and every 6 months by Eating Disorder Inventory (EDI-2) self assessment questionnaire [17]. Anxiety and depression were assessed according Hospital Anxiety Depression Scale (HAD) questionnaire [18].

The body composition was measured by bioelectric impedance [19] (a foot-to-foot TANITA International Division, Yiewsley, UK). Brachial blood pressure was measured by a digital electronic tensiometer (OMRON 705 cp, Kyoto, Japan) – regular or large adult cuffs were used according to arm circumference – with the subject seated for at least 10 min. The mean value was used in statistical analysis.

At baseline, the insulin sensitivity was measured by an euglycaemic hyperinsulinaemic clamp [16]. Insulin was continuously infused at a rate of 240 pmol/min/m, whereas a glucose solution (20%) was infused at variable rates in order to maintain a constant plasma glucose concentration between 4.5 and 5.5 mmol/l. Plasma glucose was measured at 5- to 10-min intervals to ensure it remained within the target glucose concentration. The steady-state period for calculation of insulin sensitivity was between 80 and 120 min. Glucose uptake was measured and expressed in mg/kg lean body mass (LBM)/min). The clamp was repeated at 4 years.

In case of a weight regain defined as an increase of body weight of more than 2.5%, patients were invited to fill out a 4-day diet diary, followed by an adjustment to diet by a dietician. Orlistat also was prescribed daily (120 mg 3 times a day) as long as the body weight was higher than the 2.5% increase. In these conditions, Orlistat was given in order to avoid a relapse and to play an educational role aimed at making the patient aware of the elevated fat content of her/his diet. Participants could also ask, on a voluntary basis, for Orlistat in order to control special occasions (e.g. anniversary, social events) and to avoid eating too much. In this case, Orlistat intake was restricted to 3 consecutive days. The prescription of Orlistat was free of charge for patients included in the study.

Among the participants who completed the study at 4 years ($n = 34$), we identified two groups: the no-regain group ($n = 17$) composed of subjects with stable body weight or additional weight loss, and the regain group composed of subjects who regained more than 2.5% of their baseline weight.

Statistical Analyses

Statistics were done using Statview for Windows (version 5.0). Non-parametric Wilcoxon Signed Rank Test was used for comparison between baseline and 4-year values. Simple regression analysis was used to evaluate the relationships between changes in body weight and to analyse the effect of weight evolution on insulin sensitivity. Chi-squared test was used to compare percent frequencies of Orlistat treatment and motivational workshops between regain and non-regain groups. The results are expressed as mean $\pm$ standard error of the mean (SEM).

Results

50 patients, 45 women and 5 men (age 43.3 ± 1.5 years, BMI 29.5 ± 0.9 kg/m²) participated in the study. 34 subjects completed the study. 16 drop-outs were registered: 3 patients underwent bariatric surgery, 1 patient became pregnant, and 12 did not adhere to the protocol.

Among the completers and before the weight loss phase, the mean body weight was 99.6 ± 2.6 kg and the mean BMI 35.7 ± 0.9 kg/m². At the beginning of the 4-year follow-up, the mean body weight was 82.2 ± 2.2 kg and the mean BMI 29.5 ± 0.9 kg/m². Patients lost on average 17% of their initial body weight, before the beginning of the 4-year multi-factorial weight loss maintenance programme.

Table 1. Anthropometric and psychological characteristics of no-regain group (n = 17) at baseline and at 4 years

Parameters	Baseline	4 years
Body weight, kg	80.5 ± 3.4	77.2 ± 3.4**
BMI, kg/m ²	31.1 ± 1.3	29.7 ± 1.3*
Waist, cm	94.9 ± 2.9	92.2 ± 3.5
Hip, cm	108.5 ± 2.7	104.3 ± 2.7**
Waist/hip ratio	0.9 ± 0.1	0.9 ± 0.0
Fat mass, kg	33.5 ± 2.4	30.4 ± 2.6*
% Fat mass	40.6 ± 1.5	38.7 ± 1.7*
HAD		
Anxiety subscale	9.6 ± 1.0	9.3 ± 1.2
Depression subscale	6.4 ± 1.1	5.4 ± 1.3
EDI	67.0 ± 9.1	57.3 ± 9.2**

Values are mean ± SEM.

*p < 0.05, **p < 0.01 versus baseline.

Table 2. Biological characteristics of no-regain group (n = 17) at baseline and at 4 years

Parameters	Baseline	4 years
Fasting glucose, mmol/l	5.4 ± 0.3	5.5 ± 0.2
Total cholesterol, mmol/l	5.4 ± 0.3	5.2 ± 0.3
High density lipoprotein, mmol/l	1.5 ± 0.2	1.4 ± 0.08
Low density lipoprotein, mmol/l	3.5 ± 0.3	3.0 ± 0.2
Triglyceride, mmol/l	1.5 ± 0.5	1.5 ± 0.4
Systolic blood pressure, mm Hg	121.9 ± 4.2	114.8 ± 3.8
Diastolic blood pressure, mm Hg	78.0 ± 2.0	71.9 ± 1.6*
Glucose uptake, mg/kg LBM/min	7.9 ± 0.7	9.3 ± 0.9

Values are mean ± SEM.

*p < 0.05 versus baseline.

Table 3. Anthropometric and psychological characteristics of the regain group (n = 17) at baseline and at 4 years

Parameters	Baseline	4 years
Body weight, kg	77.7 ± 3.5	87.2 ± 4.6 **
BMI, kg/m ²	28.2 ± 1.2	31.6 ± 1.6 **
Waist, cm	89.2 ± 3.4	98.9 ± 4.1 **
Hip, cm	102.5 ± 2.6	113.2 ± 5.6 **
Waist/hip ratio	0.9 ± 0.1	0.8 ± 0.0
Fat mass, kg	27.4 ± 2.5	36.7 ± 3.5 **
% Fat mass	34.9 ± 1.8	40.7 ± 2.1 **
HAD		
Anxiety subscale	7.8 ± 1.0	7.6 ± 1.2
Depression subscale	4.4 ± 1.1	4.4 ± 1.1
EDI	57.3 ± 7.4	54.8 ± 6.8

Values are mean ± SEM.

**p < 0.01 versus baseline.

During the 4-year follow-up the BMI remained stable. At the end of the 4-year follow-up period, there were no statistically significant differences between the baseline and 4-year

Table 4. Biological characteristics of regain group (n = 17) at baseline and at 4 years

Parameters	Baseline	4 years
Fasting glucose, mmol/l	4.8 ± 0.1	5.4 ± 0.4
Total cholesterol, mmol/l	4.9 ± 0.2	5.0 ± 0.3
High density lipoprotein, mmol/l	1.4 ± 0.1	1.5 ± 0.1
Low density lipoprotein, mmol/l	3.1 ± 0.2	3.1 ± 0.2
Triglyceride, mmol/l	0.8 ± 0.1	1.0 ± 0.2
Systolic blood pressure, mm Hg	120.1 ± 2.4	123.9 ± 3.1
Diastolic blood pressure, mm Hg	77.1 ± 1.5	79.6 ± 2.0
Glucose uptake, mg/kg LBM/min	7.8 ± 0.7	7.6 ± 0.8

Values are mean ± SEM.

body weight (79.1 ± 2.4 vs. 82.1 ± 3.0 kg) or BMI (29.5 ± 0.9 vs. 30.6 ± 1.0 kg/m²). At 4 years, 73% of the patients who completed the study (i.e. 27 out of 34) successfully maintained 10% or more of their weight loss when compared to their body weight before weight loss.

Anthropometric and psychological parameters of subjects within the no-regain group are presented in table 1. A significant further reduction of body weight (80.5 ± 3.4 vs. 77.2 ± 3.4 kg; p < 0.01), BMI (31.1 ± 1.3 vs. 29.7 ± 1.3 kg/m²; p < 0.05), % fat mass (40.6 ± 1.5 vs. 38.7 ± 1.7%; p < 0.05), hip circumference (108.5 ± 2.7 vs. 104.3 ± 2.7 cm; p < 0.01) was observed at the end of the 4-year follow-up. Among the psychological parameters, EDI score was significantly reduced (67.0 ± 9.1 vs. 57.3 ± 9.2; p < 0.01).

Biological and cardiovascular parameters at baseline and at 4 years in the no-regain group are presented in table 2. The no-regain group showed a reduction of diastolic blood pressure (78.0 ± 2.0 vs. 71.9 ± 1.6 mm Hg; p < 0.05). There was a tendency to glucose uptake improvement (7.9 ± 0.7 vs. 9.3 ± 0.9 mg/kg LBM/min; p = 0.06).

The regain group showed statistically significant differences at 4 years as compared to baseline in terms of body weight, BMI, fat mass as well as waist and hip circumferences (table 3).

Biological and cardiovascular parameters in the regain group (table 4) remained stable.

When evaluated in the overall group, simple regression analysis showed that the evolution of insulin sensitivity was significantly and negatively linked to body weight evolution during the follow-up period (p < 0.01, r² = 0.20) (fig. 1). A significant and negative relationship between the extent of weight lost during the weight loss period and the extent of body weight recovered during the follow-up period was also observed (p < 0.01, r² = 0.26) (fig. 2).

Percent frequencies of Orlistat intake concerning occasional and continuous intake, or occasional and no intake, were not different between the regain and no-regain groups (occasional and continuous intake 47.0% vs. 35.3%, occasional and no intake 53.0% vs. 64.7%; p = 0.76) (table 5).

Fig. 1. Relationship between Δ glucose uptake and Δ body weight during the 4-year follow-up.

Table 5. Chi-squared analysis of percent frequencies of orlistat treatment or motivational workshops in no regain and regain sub-groups

	Percent frequencies	
	regain (n = 17)	no regain (n = 17)
Orlistat intake ^a		
Occasional + continuous	47.0	35.3
Occasional	41.2	47.1
No	11.8	17.6
Motivational workshops ^b		
Diet + physical activity	11.8	23.5
Psychological	35.3	29.4
No	53.0	47.1

^aOrlistat treatment $p = 0.76$.

^bMotivational workshops $p = 0.66$.

Table 6. Factorial ANOVA of 4-years evolution Δ % fat mass in regain and no-regain sub-group as a function of the orlistat treatment^a

	Δ fat mass, %	
	regain (n = 17)	no regain (n = 17)
Orlistat intake		
Occasional + continuous	32.0 $\pm$ 4.8 (n = 8)	-13.6 $\pm$ 6.3 (n = 6)
Occasional	31.9 $\pm$ 9.3 (n = 7)	-12.7 $\pm$ 5.5 (n = 8)
No	176.7 $\pm$ 163.3 (n = 2)	9.8 $\pm$ 2.0 (n = 3)

^aValues are mean $\pm$ SEM, effect of orlistat treatment alone $p = 0.004$.

Effect of the interaction of weight evolution and orlistat treatment: $p = 0.04$.

However, there are differences of percent frequencies in term of psychological and motivational workshops between the regain and no-regain groups. The percent frequencies of motivational diet and physical activity workshops were twice higher

Fig. 2. Relationship between Δ body weight during the 4-year follow-up and Δ body weight during the weight loss period.

in the no-regain group than in the regain group (23.5% vs. 11.8%; $p = 0.66$). (table 5). Moreover, the use of Orlistat was statistically significantly linked to reduced body fat mass either in the regain or in the no-regain group ($p < 0.01$) (table 6). Orlistat treatment and body weight evolution showed a significant interaction ($p < 0.05$).

Discussion

When globally evaluated, both body weight and BMI of completers remained stable at the end of the 4-year follow-up as compared to baseline. However, 73% of the completers successfully maintained 10% or more of their body weight loss when compared to their body weight before weight loss.

The weight maintenance programme adopted in this study appears to be efficient if we consider that the currently used definition of successful long-term weight loss maintenance is an intentional weight loss of 10% or more of the body weight kept at least 1 year [7]. It should be noted that according to Wing and Phelan [20] only 20% of overweight individuals can achieve such a successful weight loss in the long term. Of course, these results should not be overestimated, because the patients were followed up by physicians trained in the field of therapeutic patient education and special attention was given during the follow-up to maintain the motivation for behavioural adaptations on long term. This is not always the case since not all centres dealing with obesity are able to offer a similar in-depth approach.

Subjects from the no regain group significantly improved some biological parameters like diastolic blood pressure as example for cardiovascular parameters and EDI as example for psychological parameters. It has already been demon-

strated that during weight loss, both systolic and diastolic blood pressure decreased proportionally to weight reduction [21–23].

Our results obtained for the regain group showed that biological, cardiovascular and psychosocial parameters were unchanged. In the overall group and during the follow-up period, the insulin sensitivity was significantly associated to body weight evolution. This is in accordance with previous results from our group [3] and with several studies summarized by Klein and al. [24]. For example, improvement of insulin sensitivity as a consequence of weight loss has been demonstrated several years ago by Kelley and al. [25]. Orlistat was taken in both groups in the same manner, and the percent frequency that determines the proportion of occasional, continuous or no intake was similar. Orlistat is known to facilitate both weight loss and weight maintenance, as described by Rössner and al. [26]. In our study, Orlistat treatment was linked with lowering body fat mass effect and significantly interacted with the evolution of body weight. These results confirm the role of Orlistat in management of obesity.

Finally, we found that the proportion of subjects to whom the participation to motivational diet and physical activity workshops was proposed by healthcare providers were twice higher in the no-regain than in the regain group. This difference, however, did not reach statistical significance, probably due to the small number of observations.

Our study is one among the small number of studies published concerning long-term weight loss maintenance. This study confirms the positive effect of a successful weight loss maintenance programme on biological parameters and how it is associated with improvement of binge eating disorders. In the regain sub-group, despite the increase of body weight

accompanied by worsened anthropometric parameters, others, like biological, cardiovascular and psychosocial parameters, remained stable. Data regarding weight loss before baseline showed that a larger amount of weight loss was significantly associated to a larger weight re-gain during the follow-up period. This indicates that a strong reduction of body weight could enhance a high risk of relapse.

In conclusion, this multi-factorial approach was evaluated regarding the efficacy of the 4-year weight loss maintenance programme. 73% of the completers maintained more than 10% of their body weight loss at 4 years. The evolution of anthropometric, biological and psychosocial parameters is linked to the weight evolution. The Orlistat ‘on/off approach’ regarding his lowering fat mass effect seems to be efficient for the long-term weight loss maintenance.

Acknowledgments

Acquisition of data, analysis, and statistical expertise were provided by Renate Scheiner-Sparna-Project statistician and Dr. M. Köhler GmbH, Freiburg i.Br., Germany.

Roche Pharma (Schweiz) AG supported the study by a research grant. Study fees for the hospital were received by Professor Alain Golay in order to cover the patient visits and follow up cost (the study was free of charge for the patient). The fees for the basic statistical analysis were done as described per protocol (this analysis was out-sourced and not done by Roche). All the other statistical analysis described in the manuscript were performed by the site and not by Roche.

Disclosure Statement

The other authors declare no conflict of interest.

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