



PAPER

Predictors of weight loss and maintenance during 2 years of treatment by sibutramine in obesity. Results from the European multi-centre STORM trial

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BACKGROUND: In this report we assess pre-treatment determinants of weight loss and maintenance outcome in The Sibutramine Trial of Obesity Reduction and Maintenance (STORM), a 2y randomized, double-blind, placebo-controlled, European multicenter study examining the effect of sibutramine (Sib) on inducing and maintaining weight loss in obese subjects.

MATERIAL: A total of 605 obese patients (BMI: 30–45 kg/m²) of both gender were included from eight European centers and treated for 24 months. The patients were treated for the initial 6 months by Sib (10 mg/day) and a low-fat low-energy, individualized diet (600 kcal/day deficit). The 467 patients who achieved > 5% weight loss after 6 months were randomized 3:1 to Sib (10 mg/day) (Sib/Sib) and placebo (Sib/Pla) for weight maintenance over a further 18 months.

MAIN OUTCOME AND ANALYSES: Pre-treatment individual characteristics were assessed as predictors of 6 months weight loss (kg) and 24 months weight maintenance using simple and multivariate correlation and regression analyses.

RESULTS: In univariate analyses, the 6 month weight loss ($n=505$) was positively associated with pre-treatment body weight ($r=0.27$), height ($r=0.18$), fat-free mass ($r=0.21$) (all $P<0.001$), fat mass ($r=0.13$, $P<0.03$), and resting metabolic rate ($r=0.13$, $P<0.003$). However, no relation was found with age, gender, smoking status, age at onset of obesity, or number of previous slimming attempts. The same predictors were found for weight change to endpoint in the Sib/Sib group ($n=350$), while no predictors were identified in the Sib/Pla ($n=114$). In the multivariate regression analysis only pre-treatment body weight predicted weight loss at 6 months ($P<0.001$). Weight change (kg) to 24 months was predicted by: $4.34 + 0.07 \times \text{body weight (kg)} - 4 \times \text{treatment (Sib=1, Pla=0)} - 0.06 \times \text{age (y)}$, ($r^2=8\%$, $P<0.001$).

CONCLUSION: Only pre-treatment body weight seems to be an important independent predictor of 6 months weight loss and 24 month weight maintenance in this study on diet and Sib. As only 8% of the variation in 24 months weight change could be explained by the predictors, the clinical value of this information is limited.

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Introduction

The efficacy of pharmacological agents used in the treatment of obesity is usually expressed as an average treatment result compared with the average response to placebo. However, the between-subject variation in response to these pharmacological agents is great, with weight losses after 6 months ranging from 0 to 30 kg. Therefore, from a clinical point of view, identifying those patients who are specifically responsive to a certain pharmacological agent is clearly worthwhile.

Sibutramine is a novel anti-obesity agent that acts as a serotonergic and adrenergic re-uptake inhibitor.⁵ Several studies have shown that sibutramine, compared with placebo, produces clinically significant weight losses in a dose-dependent manner.^{3,6,12,18} In humans, sibutramine has been shown to exert its weight-reducing effect through a dual mechanism, reducing energy intake by increasing satiety and decreasing hunger, and by increasing energy expenditure, thereby reducing the decline in resting metabolic rate (RMR) accompanying loss in body weight.^{7,8,18}

The aim of the present study was to investigate if pre-treatment characteristics, such as baseline body weight, sex, age, RMR, smoking history, previous slimming attempts and age of onset of obesity can, alone or in combination, predict the individual weight change outcome during a 2 y multicenter trial on weight loss and weight maintenance.

Methods

Patients

The Sibutramine Trial of Obesity Reduction and Maintenance (STORM) is a randomized, double-blind, placebo-controlled, European multicenter study examining the effect of sibutramine on achieving and maintaining weight loss in obese subjects. The main results of the study have previously been reported by James *et al*.⁹

A total of 605 obese patients from eight European centers were included in the study. Patients were recruited from waiting lists and by local advertising. Informed consent was obtained according to the Declaration of Helsinki II, and the study was approved by the local institutional ethical committees. Obese outpatients (body mass index 30–45 kg/m²) of either sex, aged between 18 y and 65 y were eligible for inclusion. Women of childbearing potential were included if they were using adequate contraception. Patients were excluded if their obesity was of endocrine origin; if they had a pulse rate of greater than 100 beats/min or a diastolic blood pressure greater than 95 mmHg; if they had a history of severe somatic or psychiatric disease (defined in the study protocol); if they had lost or gained more than 4 kg in the past 3 months; or if they were receiving any drugs known to affect appetite.

Design

The study was designed as a 2 y, randomized, placebo-controlled, double-blind, multicenter trial.⁹ Initial weight

loss was achieved by sibutramine 10 mg once daily in combination with a low-energy diet during a 6 month open-label, active run-in period. Patients who had lost a minimum of 5% of their baseline body weight in the run-in period, and who had not gained weight (limit set at +2 kg) between months 4 and 5, or between months 5 and 6, were eligible to continue into the 18-month, randomized, double-blind, placebo-controlled weight maintenance phase. The dose of sibutramine or placebo was increased by 5 mg each time to a maximum of 20 mg once daily if the patient had gained more than 1 kg since month 6 or since the last dose increase, providing that the dose of medication had been stable for a minimum of 2 months. Likewise the dose of trial medication was reduced by 5 mg each time if the patient could not tolerate the higher dose.

All patients underwent a full medical history and physical examination at baseline (month 0), and were in good health apart from their obesity. History of obesity was recorded, including family history, onset of obesity, minimum and maximum known weight since age 18 y, weight changes in the past 3 months and previous attempts at losing weight.

Throughout the study patients were prescribed, advised and supported in following a low-energy diet. The energy content of the diet was calculated from the patient's estimated daily energy expenditure minus 600 kcal/day. Energy expenditure was estimated by multiplying RMR measured by ventilated hood technique, by a physical activity level factor (PAL), taking into account the patients occupational and leisure time activity level. The energy content of the diet was recalculated at months 3 and 6 by re-measuring RMR and PAL. The macronutrient composition of the diet recommended aimed to supply 45–50% of the energy from carbohydrates, 30% from fat and 15–20% from proteins. The patients were seen by a dietitian for either individual or group sessions at 2 week intervals during the 6 month run-in period and at monthly intervals during the 18 month weight maintenance phase. Patient adherence to the diet was evaluated from repeated 4-day food diaries completed by the patients at months 1, 3, 6, 12, 18 and 24.

Body weight was measured (on calibrated scales) every 2 weeks for the first 6 months before randomization, and monthly thereafter until the end of the study.

Statistics

Results are presented as means \pm s.d. The correlation between pre-treatment characteristics and body weight changes were examined using Pearson's correlation for continuous data and Spearman's correlation for discrete data. Subsequently, multiple stepwise regression analyses were performed to obtain the combined, independent predictors of weight loss, only variables significant at the 15% level were included in the model. All the predictors were included, irrespective of whether they were significant factors at the 5% level. Three different endpoints are used in the regression analyses. Firstly, results from the first 6 months of the study, including

all the patients who completed the run-in period were analyzed. Secondly, the body weight change from baseline to 24 months was used as endpoint, using the intention to treat principle, with the last observation carried forward, including those patients who had at least one dose of trial medication after the run-in period and at least one follow-up body weight measurement. Finally, results for the group of patients who completed the 2y study are presented (completer analysis).

Results

A total of 505 (83%), of the 605 obese patients who entered the study completed the run-in period and 467 (92%) of these patients were included in the randomized, double-blinded period, of which 352 patients were allocated to the sibutramine group and 115 patients to the placebo group

(Table 1). Data on body composition were available from five of the eight centers, and so the role of fat-free mass and fat mass could be analyzed in 292 patients completing the run-in period. Three patients withdrew early from the double-blind phase, reducing the intention to treat population to 464 patients, 350 in the sibutramine group and 114 in the placebo group (Table 2). For the completer analysis, 206 in the sibutramine group and 57 in the placebo group could be included. Mean weight loss during the run-in period was 11.3 kg (Table 1), and the mean weight loss from baseline for the completers was 10.4 ± 9.3 kg in the sibutramine group and 5.2 ± 7.2 kg in the placebo group ($P < 0.001$; Table 3).

Weight loss during the run-in period was positively correlated with both baseline body weight ($r = 0.27$, $P < 0.001$), height ($r = 0.18$, $P < 0.001$) and resting metabolic rate (RMR) ($r = 0.13$, $P = 0.003$; Table 4), while no significant correlation for either age, sex, smoking history, numbers of previous

Table 1 Pre-treatment characteristics and weight loss in patients completing the 6 month treatment with low-energy diet and sibutramine

	n	Mean	s.d.	Median	Range
Changes from baseline to month 6 in body weight (kg)	505	- 11.3	5.5	- 10.6	- 32.1 - (- 4.5)
Age (y)	505	40.4	10.4	41	17-65
Baseline body weight (kg)	505	102.5	15.3	101.3	67.1-160.4
Height (cm)	505	167.0	8.7	166.0	139-194
Baseline fat-free mass ^a (kg)	292	52.3	9.5	49.9	33.3-89.5
Baseline fat mass ^a (kg)	292	46.8	9.3	46.0	27.6-76.0
RMR (kcal/day)	505	1718.9	304.5	1681	1107-3213
BMI (kg/m ²)	505	36.7	4.1	36.2	29.6-45.4

^aResults on body composition measured by impedance were available from five of eight centers.

Table 2 Pre-treatment (baseline) characteristics and weight changes until endpoint based on 'Last observation carried forward'

	n	Mean	s.d.	Median	Range
<i>Sibutramine</i>					
Changes from baseline to endpoint in body weight (kg)	350	- 9.3	5.5	- 7.9	- 46.0-10.6
Changes from month 6 to endpoint in body weight (kg)	350	2.8	6.0	3.0	- 26.4-24.6
Age (y)	350	40.8	10.2	41.5	17-65
Baseline body weight (kg)	350	102.2	14.9	101.7	69.8-160.4
Height (cm)	350	167.1	8.5	166.0	150-194
Baseline fat free mass ^a (kg)	195	52.3	9.6	49.9	37.8-89.5
Baseline fat mass ^a (kg)	195	46.3	8.6	45.3	29.4-76.0
RMR (kcal/day)	350	1711.9	300.6	1677.0	1128-2780
BMI (kg/m ²)	350	36.5	4.1	36.2	29.7-45.1
<i>Placebo</i>					
Changes from baseline to endpoint in body weight (kg)	114	- 5.3	5.9	- 4.6	- 26.5-12.0
Changes from month 6 to endpoint in body weight (kg)	114	6.2	4.6	6.2	- 7.6-19.2
Age (y)	114	40.5	9.9	40.0	18-64
Baseline body weight (kg)	114	102.2	16.1	99.9	69.3-147.2
Height (cm)	114	166.4	9.2	166.0	147-189
Baseline fat free mass ^a (kg)	66	52.6	9.8	49.8	39.0-86.0
Baseline fat mass ^a (kg)	66	46.5	9.5	46.5	27.6-65.8
RMR (kcal/day)	114	1722.5	303.3	1706.0	1107-3213
BMI (kg/m ²)	114	36.8	4.1	36.5	29.6-45.4

^aResults on body composition measured by impedance were available from five of eight centers.

slimming attempts or age of onset of obesity was found. The correlation between weight change during the run-in period and baseline body weight is shown in Figure 1. Analyzing the weight change during the run-in period by stepwise analyses of regression, only baseline body weight ($P < 0.001$) and RMR ($P = 0.08$) were predictors of weight loss during this period. Three variables were selected as predictors of weight loss from baseline to 24 months, using the ‘last observation carried forward’ principle: baseline body weight, treatment group and age. The regression equation was: weight loss (kg) = $4.24 + 0.08 \times \text{baseline body weight} - 4.52 \times \text{treatment group} - 0.06 \times \text{age}$ (where 0 = sibutramine and 1 = placebo for treatment group). The ensuing squared partial regression coefficients and P -values were $r^2 = 0.026$, $P < 0.001$; $r^2 = 0.057$, $P < 0.001$; $r^2 = 0.006$, $P = 0.10$. Together these three determinants explained 9% ($r^2 = 0.09$) of the total variation. If BMI was also included for the month 6 to endpoint analyses, two predictors were selected, treatment group and BMI, resulting in the equation: weight loss (kg) = $3.01 - 3.53 \times \text{treatment group} - 0.16 \times \text{BMI}$, explaining 7% of the total variation. The squared partial regression coefficients and P -values were $r^2 = 0.063$, $P < 0.001$; $r^2 = 0.011$, $P = 0.03$. The same predictors were apparent for the completer analysis, except that age was not a predictor for change from baseline analysis.

The two treatment groups were also analyzed separately. In the placebo group no variable predicted significantly change from baseline to end-point, while change from month 6 depended on only baseline weight: weight loss = $2.16 - 0.13 \times \text{baseline weight}$ (partial regression $r^2 = 0.11$ ($P < 0.001$)). In the sibutramine group the corresponding analyses produced the following: weight loss from

baseline = $2.03 - 0.08 \times \text{age} + 0.10 \times \text{baseline weight}$ (partial regressions $r^2 = 0.009$ ($P = 0.10$) and $r^2 = 0.041$ ($P < 0.001$)); change from month 6, weight loss = $2.16 - 0.13 \times \text{BMI}$ (partial regression $r^2 = 0.008$ ($P = 0.13$)).

Discussion

The present analysis of predictors of weight loss is by far the most comprehensive according to a literature search. Previous studies have typically been conducted in only 50–100 patients followed for 3–12 months.^{1,10,13,14,16,19} Our study showed that only body weight, treatment group and, to a lesser extent, age predicted weight loss and weight maintenance outcome and that the power of the prediction was quite low as only 7–8% of the variation in weight change could be accounted for by these predictors. Using BMI did essentially not increase the predictive power, probably due to the high correlation between body weight and BMI in this population of subjects. The present finding that heavier patients typically lose more weight than lighter patients, due to their higher energy expenditure, is in agreement with previous studies.^{2,10,14–17} Thus Wadden *et al*, in a study examining the effect of 4 months of treatment with VLCD alone or in combination with behavioral therapy in 76 obese women, found that initial bodyweight, weight loss during the first month of treatment and attendance were the most clinically useful correlates of weight loss both at the end of treatment as well as at 1 y follow-up.¹⁶ Furthermore Bild *et al*, in a 2 y longitudinal observation study (CARDIA), found that weight loss in young adults was most consistently associated with greater baseline fatness together with low initial physical fitness level and self perception of being

Table 3 Pre-treatment (baseline) characteristics and weight changes until endpoint based on analysis of patients completing the double-blind until month 24

	n	Mean	s.d.	Median	Range
<i>Sibutramine</i>					
Changes from baseline to month 24 in body weight (kg)	206	− 10.4	9.3	− 8.8	− 46.0–10.6
Changes from month 6 to month 24 in body weight (kg)	206	2.6	7.1	2.9	− 26.4–24.6
Age (y)	206	41.4	9.7	42.0	19–62
Baseline body weight (kg)	206	102.8	14.8	101.5	74.1–160.4
Height (cm)	206	167.4	8.4	166.0	150–194
Baseline fat free mass ^a (kg)	117	52.6	9.4	49.9	40.6–82.0
Baseline fat mass ^a (kg)	117	46.4	8.7	45.2	29.4–76.0
RMR (kcal/day)	206	1724.4	302.2	1666.5	1223–2780
BMI (kg/m ²)	206	36.7	4.2	36.4	29.7–45.0
<i>Placebo</i>					
Changes from baseline to month 24 in body weight (kg)	57	− 5.2	7.2	− 4.3	− 26.5–12.0
Changes from month 6 to month 24 in body weight (kg)	57	7.2	5.6	7.3	− 7.6–19.2
Age (y)	57	41.3	10.0	42.0	18–60
Baseline body weight (kg)	57	104.8	17.0	102.3	80.7–147.2
Height (cm)	57	167.7	10.0	167.0	147–189
Baseline fat free mass ^a (kg)	33	53.1	9.2	50.9	29.1–63.2
Baseline fat mass ^a (kg)	33	47.0	9.6	45.4	29.1–63.2
RMR (kcal/day)	57	1778.9	324.4	1760.0	1321–3213
BMI (kg/m ²)	57	37.1	3.8	37.2	30.7–45.2

^aResults on body composition measured by impedance were available from five of eight centers.

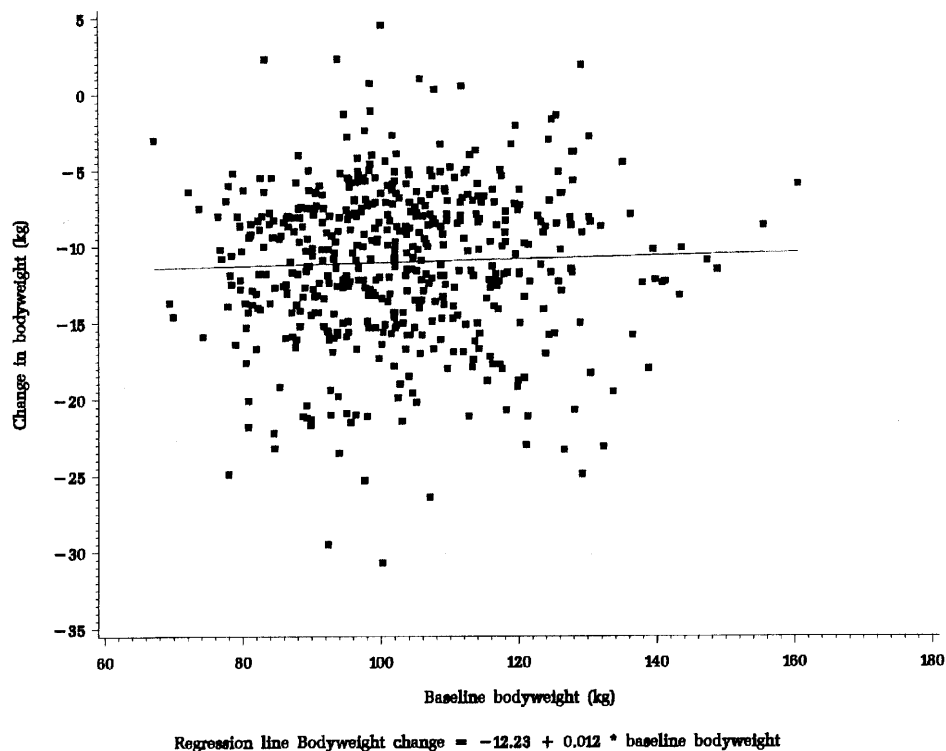


Figure 1 Scatterplot of baseline bodyweight vs month 6 weight loss.

overweight.² In other studies, no statistically significant correlation between weight loss and initial bodyweight was found.^{1,13} This could, at least partly, be explained by the relatively small number of subjects included in the studies and the duration of the trials.

In the present study weight loss during the initial 6 months of treatment was positively correlated with RMR, which is probably attributable to the high correlation between RMR and baseline body weight. This finding is in accordance with several other studies.^{1,10,15,17} However, when

Table 4 Simple correlation between weight loss and potential predictors (correlation coefficients and *P*-values)

Correlation with weight loss	Change from baseline					Change from month 6			
	Month 6 (n = 505)	Endpoint		Month 24		Endpoint		Month 24	
		Sibutramine (n = 350)	Placebo (n = 114)	Sibutramine (n = 206)	Placebo (n = 57)	Sibutramine (n = 350)	Placebo (n = 114)	Sibutramine (n = 206)	Placebo (n = 57)
<i>Pearson</i>									
Age (y)	-0.07 (0.10)	-0.10 (0.06)	-0.09 (0.32)	-0.11 (0.13)	-0.06 (0.67)	-0.03 (0.60)	0.01 (114)	-0.05 (0.47)	0.03 (0.83)
Baseline body-weight (kg)	0.27 (<0.001)	0.19 (<0.001)	0.03 (0.77)	0.20 (0.004)	0.00 (1.00)	-0.06 (0.26)	-0.28 (0.003)	0.01 (0.90)	-0.30 (0.02)
Height (cm)	0.18 (<0.001)	0.15 (0.005)	0.03 (0.79)	0.17 (0.02)	0.02 (0.87)	0.01 (0.92)	-0.20 (0.03)	0.06 (0.43)	-0.17 (0.20)
Baseline fat free mass (kg)	0.21 (<0.001)	0.14 (0.06)	0.02 (0.85)	0.15 (0.10)	0.05 (0.79)	-0.06 (0.36)	-0.17 (0.17)	-0.09 (0.33)	-0.07 (0.68)
Baseline fat mass (kg)	0.13 (0.03)	0.14 (0.06)	0.004 (0.98)	0.15 (0.10)	-0.03 (0.85)	-0.03 (0.69)	-0.15 (0.22)	-0.03 (0.77)	-0.23 (0.19)
RMR (kcal/day)	0.13 (0.003)	0.09 (0.11)	0.004 (0.96)	0.11 (0.11)	-0.01 (0.93)	-0.05 (0.40)	-0.19 (0.04)	-0.01 (0.85)	-0.18 (0.18)
BMI (kg/m ²)	0.19 (<0.001)	0.11 (0.04)	0.01 (0.91)	0.09 (0.20)	-0.02 (0.87)	-0.08 (0.12)	-0.18 (0.051)	-0.13 (0.06)	-0.27 (0.046)
<i>Spearman</i>									
Sex	0.08 (0.06)	0.02 (0.76)	-0.04 (0.65)	0.07 (0.34)	-0.04 (0.59)	-0.08 (0.13)	-0.18 (0.06)	-0.03 (0.83)	-0.21 (0.11)
Smoking	-0.03 (0.44)	0.01 (0.86)	-0.02 (0.82)	-0.01 (0.86)	0.003 (0.96)	0.01 (0.95)	-0.01 (0.93)	0.004 (0.98)	0.06 (0.65)
Number of previous slimming attempts	-0.01 (0.86)	-0.05 (0.35)	-0.08 (0.45)	-0.04 (0.56)	-0.02 (0.82)	-0.02 (0.76)	-0.06 (0.54)	-0.16 (0.26)	-0.16 (0.25)
Age at onset of obesity	-0.05 (0.24)	-0.01 (0.87)	-0.14 (0.14)	0.004 (0.96)	0.08 (0.27)	0.02 (0.71)	0.05 (0.60)	-0.08 (0.54)	0.06 (0.66)

analyzing the data by multiple regression, no significant relation between RMR and weight loss during either the first 6 months or the entire 24 months of the study was found. This could at least partly be explained by the fact that sibutramine, as shown in previous studies, stimulates thermogenesis in humans, hereby reducing the decline in energy expenditure normally accompanying weight loss, and thus blunting the association between RMR and body weight.^{7,8}

Several other variables, biological, behavioral and psychological, have been reported as predictors of weight loss and maintenance, however none of them prove consistent. Suggested negative predictors are: an elevated postabsorptive respiratory quotient (RQ) after discontinuation of a low-energy diet showing that the endogenous lipid oxidation is low;⁴ repeated failures; and stress.¹¹ Low initial leptin levels, a large decline in serum leptin during weight loss,¹⁴ high plasma concentrations of dihydrotestosterone,¹ frequent attendance and early success¹⁶ have all been suggested as positive predictors.

Development of adequate predictors of weight loss and maintenance is important in improving the long-term results in obesity management. Only 8% of the variance in weight change was explained in this study. Thus more variables as potential predictors are needed, perhaps including initial weight loss and attendance rate. Furthermore, obesity being a heterogenous disorder with a varied and complex etiology, identification of different genotypes of obesity should improve our ability to predict weight loss and individualize treatment.

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