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The Effect of Sibutramine on Energy Expenditure and Body Composition in Obese Adolescents

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Context: Childhood obesity is now considered to be an epidemic. Drug therapy in this age group remains a topic of research.

Objective: The objective of this study was to examine the effect of treatment with sibutramine (10 mg) on body composition and energy expenditure in obese adolescents.

Design: The study was conducted as a randomized, double-blind, placebo-controlled trial.

Setting: The study was set in an obesity research center.

Patients: The patients were 24 obese adolescents (age 12–17 yr, 11 boys); four patients withdrew.

Intervention: Intervention was sibutramine (Meridia) or placebo in combination with an energy-restricted diet and exercise plan for 12 wk, followed by an identical, but medication-free, treatment period (follow-up).

Main Outcome Measure: Change in body mass index (BMI) SD score (BMI-SDS) was the principal measure of efficacy. Body composition and total energy expenditure were measured by stable isotopes and further calculated according to the four-component model, using underwater weighing and dual x-ray absorptiometry. Basal metabolic rate (BMR) was measured by ventilated hood and adjusted for sex and body composition (BMR_{adj}).

Results: After intervention, the decrease in BMI-SDS was comparable in both groups. During follow-up, BMI further decreased in the placebo group but stabilized in the sibutramine group. Changes in the percentage of fat mass were not different between both groups. BMR_{adj} decreased in the placebo group and remained constant in the sibutramine group. During follow-up, BMR_{adj} decreased in the sibutramine group and increased in the placebo group. Changes in total energy expenditure were not significantly different.

Conclusion: The effect of sibutramine on BMI-SDS was not significant. Sibutramine may diminish the decrease in BMR_{adj} associated with energy restriction in obese adolescents. **(*J Clin Endocrinol Metab* 92: 1409–1414, 2007)**

OBESITY IN CHILDHOOD and adolescence is increasing worldwide and considered to be an epidemic in many industrialized countries. Although children, and especially adolescents, suffer from its psychosocial consequences, public health professionals are concerned above all for the increase in diabetes and cardiovascular diseases in the young generation (1).

The primary goal of a treatment program should be achievement of healthy eating and increased physical activity, eventually leading to improvement in body mass index (BMI). Pharmacologic therapy of obesity is only recommended when complications require rapid weight loss, and should only be used in specialized pediatric obesity treatment centers (2). Recently, two randomized controlled trials in obese adolescents were published, demonstrating the additional effect of sibutramine in a 6-month treatment program (3, 4). Sibutramine is a tertiary amine that has been shown to induce a dose-dependent weight loss and to enhance the effects of a low-calorie diet for up to 2 yr in adults (5). The antiobesity activity of sibutramine results from its dual mode of action: it reduces energy intake by increasing satiety (6), and it increases energy expenditure by stimulating thermogenesis (7, 8). Whether sibutramine has the same effects on energy metabolism in obese adolescents has not been investigated before. The present study was designed to evaluate the effect of sibutramine, in combination with an energy-restricted diet and exercise program, on body composition and energy expenditure in obese adolescents.

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Abbreviations: BMI, Body mass index; BMI-SDS, BMI SD score; BMR, basal metabolic rate; BMR_{adj}, adjusted BMR; FFM, fat-free mass; FM, fat mass; HR, heart rate; PAL, physical activity level; SMR, sleeping metabolic rate; TBMC, total bone mineral content; TBW, total body water; TEE, total energy expenditure.

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Subjects and Methods

Subjects

Obese adolescents from the regional public health department and pediatric outpatient clinic of the University Hospital Maastricht participated in the study. Participants were between 12–18 yr of age, initially selected for BMI greater than or equal to the 97th percentile, and further selected for triceps skinfold thickness greater than or equal to the 97th percentile for age and sex (9) with persisting obesity despite previous

professionally supervised weight loss attempts (97.5th percentile is equivalent to 2 SD). Patients with endocrine causes or other secondary causes of obesity were excluded as well as patients with any significant physical or medical illness, that could influence the results of the study. Subject characteristics are shown in Table 1. Pubertal assessment was defined by Tanner stages (10, 11). Before the start of the study, the adolescents gave oral approval, confirmed by written informed consent by the caregivers. The study was approved by the Medical Ethical Committee of Maastricht University.

Methodology and treatment

The trial was a randomized, double-blind, placebo-controlled, parallel-group trial of two treatment regimens. The study was divided into two phases. The first phase included a randomized treatment period of 12 wk, which included an energy-restricted diet, an exercise plan, and either 5 mg placebo or sibutramine, taken once daily in the morning. After 2 wk, the dose was increased to 10 mg daily. Knoll Pharmaceuticals BV [currently Abbott Laboratories (Hoofddorp, The Netherlands)], manufactured and provided code-numbered placebo and sibutramine capsules. Subjects received their trial and medication code according to order of entrance into the study, without stratification. The second phase consisted of a follow-up period of 12 wk with continuation of the diet and exercise plan, however, without the study medication. Throughout the study, the emphasis was put on lifestyle modification. The study complied with Good Clinical Practice guidelines (12).

Study schedule

At screening, a complete medical history and physical examination were performed.

During the intervention period, subjects visited the center at: 0 (baseline), 1, 2, 3, 4, 6, 8, 10, and 12 wk. At baseline, blood pressure, heart rate (HR), laboratory assessment, electrocardiogram, bone-age, dietary assessment, body composition, and total energy expenditure (TEE) were measured. Tanner stage was determined according to genital (boys) or breast development (girls). Blood pressure and HR, compliance with the treatment and exercise plan, as well as recording of adverse events were determined at each subsequent visit. The subject was asked to keep a daily record of the use of the trial medication and time spent on physical activity. The compliance was assessed by counting returned capsules and checking the medication and activity record. In addition, the subjects with parent(s) were seen by the study dietician for dietary evaluation. At the end of the intervention period, body composition and energy expenditure measurements were repeated. During the second (follow-up) period, the subjects visited the center at wk 13, 14, 16, 18, 20, 22, and 24, undergoing the same treatment and measurements as during the intervention period, however, without sibutramine or placebo. The follow-up period also ended with body composition and energy expenditure measurements.

Dietary and exercise advice

Dietary advice was based on energy requirements. The energy prescription was calculated from measured basal metabolic rate (BMR) multiplied by an estimated physical activity level (PAL) minus 500 kcal. The dietary intake could not be lower than 18–20 kcal per kilogram of ideal body weight with a minimum of 25% of calories provided by fat. The estimated PAL was determined using an activity questionnaire (13).

Physical activity was prescribed, based on individual preferences as well as information obtained by the activity questionnaire. The prescription contained a daily bout of exercise of at least 30 min of moderate to vigorous levels of exertions; however, the participants were encouraged to do more. Furthermore, emphasis was put on the implementation of additional physical activities, regardless of intensity, in the daily routine (14).

Measurements

Blood pressure (mm Hg) and HR (beats per minute) were measured after sitting for 5 min, using a regular adult cuff for an arm circumference of 23–33 cm or a large adult cuff for an arm circumference of 34–41 cm. Systolic blood pressure was determined by the first Korotkoff sound, and diastolic blood pressure was determined by the fifth Korotkoff sound.

Bone age assessment

Bone age was determined by assessing epiphysial maturation by the same pediatric endocrinologist using an x-ray of the left hand and standard growth data (15).

Dietary assessment

A 7-d dietary record form was handed to the parent(s) and subject after the dietician gave instructions on how to measure portion size. They were asked to record brand names, methods of preparation, and ingredients of mixed dishes. The dietician reviewed the record with the parent(s) and subject and calculated the energy intake and macronutrients. For the present analysis, only the food quotient was needed for assessment of respiratory exchange ratio to calculate TEE (16).

Body composition

In the morning, before the subjects consumed any food or drink, after voiding and while wearing underclothing, total body weight was measured on an electronic scale (E1200; Mettler Instrumente AG, Greifensee, Switzerland). The height of subjects without shoes was measured using a stadiometer. BMI was calculated by dividing total body weight in kilograms by squared height in meters. BMI SD score (BMI-SDS) was determined using the Dutch age- and sex-adjusted BMI curves (17). Body composition was assessed using a four-component reference model: total body weight = fat mass (FM) + total body water (TBW) + total

TABLE 1. Subject characteristics

	Sibutramine (6 males, 6 females)			Placebo (5 males, 7 females)		
	Mean	SD	Range	Mean	SD	Range
Age (yr)	14.1	1.0	12.3–15.3	13.8	1.5	12.0–17.4
Bone age (yr)	15.5	0.9	13.4–16.7	15.1	1.3	13.0–16.4
Tanner (1–5)	3.7	1.2	2.0–5.0	3.6	1.8	1.0–5.0
Height (m)	1.63	0.05	1.56–1.73	1.63	0.08	1.52–1.78
Weight (kg)	80.8	15.6	65.9–112.9	89.2	16.4	69.7–118.0
BMI (kg/m^2)	30.1	4.5	25.0–40.4	33.3	5.0	27.9–43.9
BMI-SDS	2.60	0.55	1.90–3.70	2.97	0.47	2.30–3.70
FFM (kg)	46.6	8.2	37.5–59.3	48.6	9.0	36.7–60.6
% FM (%)	42.1	5.2	33.3–47.9	45.5	3.9	39.7–52.2
BMR (MJ/d)	7.74	1.23	6.55–10.81	7.89	1.45	5.61–10.70
TEE (MJ/d)	12.12	1.93	9.67–15.98	12.55	2.10	8.85–16.10

Tanner, Sexual development stage according to Tanner (10, 11); % FM, percentage FM. There were no significant differences between the sibutramine group and placebo group (two-sample *t* test).

bone mineral content (TBMC) and remaining fat-free mass (FFM) (18, 19).

This multicompartment model is based on the classical two-compartment model, determined by densitometry, measured by underwater weighing with simultaneous lung volume measurement. Furthermore, the FFM compartment is divided into three subcomparments, two of which are separately measured, namely TBW and TBMC (test-retest reliability 1% body fat units).

TBW was measured with deuterium dilution according to the Maastricht protocol for the measurement of body composition and energy expenditure with labeled water (test-retest reliability 0.71%) (16). TBMC was assessed by dual x-ray absorptiometry (DPX-L; Lunar Corp., Madison, WI) (calculated between measurement technical error, 1%).

Energy expenditure

TEE can be divided into BMR, diet-induced energy expenditure, and activity-induced energy expenditure. TEE was measured according to the Maastricht protocol for the measurement of body composition and energy expenditure with labeled water (16). BMR was measured by ventilated hood, as described before (20), and was adjusted for sex, FFM, and FM (BMR_{adj}) as was demonstrated in a previous study (21). BMR consists of sleeping metabolic rate (SMR) and arousal. SMR was measured during a 12-h overnight stay in the respiration chamber, an open-circuit indirect calorimeter (14 m^3), which was described in detail previously (22). The PAL was calculated as TEE/BMR. A preferable approach to adjust data with nonzero intercepts is analysis of covariance by multiple regression. In this technique, the residuals from the regression of TEE on BMR are itself a measure of activity-related energy expenditure (TEE_{res}) (23).

Statistical analysis

Differences in continuous variables between the sibutramine group and the placebo group at baseline were analyzed by the two-sample *t* test. The principal measure of efficacy was the change in BMI between the two periods. The number of patients required per treatment group to detect a difference between treatment groups in mean change in BMI at endpoint intervention of 1.0 kg/m^2, based on an estimate of variance (SD) of 0.65, an overall significance level of 5%, and a power of 90%, was nine. Allowing a drop-out rate of 25%, the number of patients needed in each group was 12. To adjust for baseline weight as a potential predictor for weight loss, the difference between both groups, in change in BMI, was evaluated by multiple regression using baseline BMI as an covariate or explanatory variable. For each body composition or energy expenditure variable, the change from baseline to endpoint was used as the dependent variable in the analysis with group and the baseline value as explanatory variables. The same analyses were performed for the change from endpoint intervention to endpoint follow-up, using endpoint intervention as a covariate. Continuous data are reported as mean ± SD. The differences in blood pressure and HR were analyzed by repeated measures ANOVA. Differences in adverse events between both groups were measured with the Mann-Whitney *U* test. The significance level was chosen at 5%. SPSS release 6.1 for Macintosh (SPSS Inc., Chicago, IL) was used as the statistical package.

After the study analysis, it was decided to use BMI-SDS as an alternative measure of efficacy, because absolute BMI usually increases in the current age range, which makes clinical interpretation difficult. BMI-SDS was calculated using the Dutch age- and sex-adjusted BMI curves (17).

Results

Subject characteristics at baseline are shown in Table 1. There were no statistical differences in age, bone age, Tanner stages, energy expenditure, or body composition between the groups.

Effects on body composition and energy expenditure—intervention period

None of the changes in body composition were significantly different between the placebo and the sibutramine group (Table 2). BMR_{adj} decreased in the placebo group compared with the sibutramine group, whereas PAL and TEE_{res} increased. The overall change in TEE was not different between the groups.

Effects on body composition and energy expenditure—follow-up period

BMI-SDS decreased in the placebo group and increased insignificantly in the sibutramine group, leading to a significant difference in change in BMI-SDS between both groups. Change in the percentage of FM was not different between the groups.

BMR_{adj} decreased in the sibutramine group and increased in the controls. Unfortunately, due to a temporary worldwide scarcity of doubly labeled water (24), TEE could not be measured in this period. As a result of this, PAL and TEE_{res} could not be determined.

TABLE 2. Changes in body composition and energy expenditure from baseline to endpoint intervention and from endpoint intervention to endpoint follow-up for completers

	From baseline to intervention				From intervention to follow-up			
	Sibutramine (6 M/5 F)		Placebo (5 M/7 F)		Sibutramine (6 M/5 F)		Placebo (3 M/6 F)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Height (m)	1.21	0.82	0.77	1.02	0.84	1.11	0.92	1.26
Weight (kg)	−2.81	3.37	−2.05	3.54	2.63	2.85	0.13	4.22
BMI (kg/m^2)	−1.5	1.1	−1.1	1.6	0.7	1.1	−0.3	1.2
BMI-SDS	−0.22	0.20	−0.09	0.13	0.08	0.11	−0.04[a]	0.12
FFM (kg)	−0.60	2.69	0.10	2.01	2.50	2.07	1.73	2.88
% FM (%)	−1.62	2.39	−1.31	1.74	−1.30	3.32	−2.10	2.98
SMR (MJ/d)	−0.36	0.45	−0.28	0.40	0.34	0.67	0.28	0.50
BMR (MJ/d)	−0.10	0.52	−0.52	0.85	−0.19	0.78	0.50	0.72
TEE (MJ/d)	−0.20	1.30	0.75	1.46				
PAL	−0.02	0.22	0.25[a]	0.25				
BMR_{adj} (MJ/d)	0.20	1.01	−0.67[a]	1.52	−0.56	1.44	0.87[a]	1.47
TEE_{res} (MJ/d)	−1.10	1.67	0.52[a]	1.50				

Sibutramine, Subjects treated with sibutramine; Placebo, subjects treated with placebo; TEE_{res}, residuals from the regression of TEE on BMR; M, males; F, females.

[a] Changes are significantly different between groups (analysis of covariance); $P < 0.05$.

TABLE 3. HR and diastolic and systolic blood pressure results from baseline to endpoint intervention and endpoint follow-up for completers

	Baseline				Intervention				Follow-up			
	Sibutramine (6 M/6 F)		Placebo (5 M/7 F)		Sibutramine (6 M/5 F)		Placebo (5 M/7 F)		Sibutramine (6 M/5 F)		Placebo (3 M/6 F)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
HR	74.4	11.3	68.3	7.4	86.2	18.8	74.0	8.2	75.3	6.8	77.3	10.1
DBP (mm Hg)	69.3	6.9	74.6	8.1	68.2	7.3	65.0	8.2	68.2	8.6	67.8	8.4
SBP (mm Hg)	112.3	6.8	115.7	8.6	118.7	9.0	119.8	10.6	116.5	9.5	115.1	13.0

The changes in HR, DBP, and SBP between the sibutramine and the placebo group were not statistically significant (analysis of covariance). DBP, Diastolic blood pressure; SBP, systolic blood pressure; M, males; F, females.

Dropouts

One subject of the sibutramine group discontinued the intervention period prematurely. Inclusion of this subject at intervention endpoint did not alter the results (last observation carried forward method; data not shown).

At the beginning of the follow-up period, three subjects, all from the placebo group, dropped out of the study because of lack of efficacy during the intervention period (average weight gain, 2.1 kg, compared with 0.2 kg in the whole group). When these subjects were included at endpoint of follow-up, the changes in BMI-SDS were no longer significant between the groups (last observation carried forward; data not shown). Unfortunately the subjects declined to participate in further measurement of energy expenditure and body composition and, therefore, these measurements could not be used in the intention to treat analysis.

Safety

Within the placebo group, the diastolic blood pressure dropped significantly during intervention ($P < 0.001$). Within the sibutramine group, the changes in HR and blood pressure from baseline to intervention endpoint were not significant (Table 3). Between both groups, however, none of the changes in HR or blood pressure were significantly different. There were no statistically or clinically significant electrocardiographical changes between both groups. During the follow-up period, no significant changes in HR or blood pressure were recorded. Four subjects treated with sibutramine had a HR of more than 100 beats per minute on two occasions, whereas in two of these subjects, one of the visits was during the follow-up period. Furthermore, two subjects, one receiving sibutramine, the other placebo, had a diastolic blood pressure higher than 85 mm Hg on two occasions. The highest measured systolic blood pressure was 155, observed in the heaviest subject of the placebo group. During the whole study period, 41 adverse events were reported in the sibutramine group, compared with 22 in the placebo group; however, the difference was not significant. Abdominal complaints were scored significantly higher in the sibutramine group ($P < 0.01$). In the sibutramine group, one subject dropped out because of symptoms of clinical depression (Table 4).

Discussion

The current study was designed to investigate the effect of sibutramine compared with placebo on energy metabolism and body composition in obese adolescents in combination with lifestyle intervention. After the study, the results were reanalyzed with the change in BMI-SDS according to current clinical practice. The two treatment groups significantly decreased their BMI-SDS during the 3-month intervention, but there was no additional effect of sibutramine. Possibly, the strict lifestyle management, which is the first-line therapy for pediatric overweight, may have masked any potential effect of the study drug. When comparing this study with the two previous studies in obese adolescents (3, 4), the relatively small sample size with high range in SD could be an explanation for this negative finding, as well as the lower mean baseline weight of the sibutramine group (on average 8.4 kg lower) compared with the placebo group. However, statistical correction for this effect did not alter the results. During follow-up, the placebo group further decreased in BMI-SDS compared with the sibutramine group, which could be interpreted as a rebound and adverse effect of sibutramine. However, the increase in BMI was mainly caused by an increase in FFM, even leading to a further negative trend in the percentage of fat mass in the sibutramine group. Furthermore, in the intention to treat analysis, including the dropouts in the placebo group, the difference in change in BMI-SDS was no longer significant.

The main new finding in this study is a possible effect of sibutramine on resting energy expenditure, illustrated by a stable BMR_{adj} during energy intake restriction. Although energy intake restriction cannot be objectively demonstrated in this study design, one could speculate that energy restriction in adolescents primarily will lead to a decrease in energy expenditure rather than weight loss, as a mechanism to protect body growth. Indeed, despite the energy restriction, the average height increased in the study group (Table 2). To detect these changes in BMR, adjustment for body composition and gender is needed, as was demonstrated in one of our previous studies on energy expenditure in a large international cohort of adolescents (21). Furthermore, the current finding is consistent with a study in obese adolescent girls (25), in which BMR, also adjusted for FM and FFM, remained decreased as long as the energy restriction was continued. After discontinuation of sibutramine, BMR_{adj} decreases, which may be a rebound effect, but more likely reveals the energy restriction-related decrease in resting energy expenditure that previously was masked by the active drug. In the control group, the resting energy expenditure seemed to normalize, which suggests loss of compliance to the energy-restricted diet.

TABLE 4. Adverse events by treatment group for intervention and follow-up period

	Sibutramine (n = 12)	Placebo (n = 12)
Total no. of adverse events reported	41	22
Total no. of subjects reporting adverse events	12	9
Total no. of withdrawals due to adverse events	1	0
Most common reported events (no. of patients reporting)		
Flu syndrome	6	6
Headache	2	3
Abdominal complaints	7[a]	0
Agitation	3	1
Increased appetite	4[b]	2
Rash	2	0
Dizziness	3	1
Dysmenorrhea	3	0
Joint problem	2	2

The average number of adverse events reported per subject was not significantly different between the sibutramine and the placebo group (Mann-Whitney U test, $P = 0.16$).

[a] $P < 0.01$.

[b] During the follow-up period.

A recent animal study suggested that locomotion is the major determinant for sibutramine-induced increase in energy expenditure (26). In our results, however, physical activity was not influenced by sibutramine. In contrast, both measures of physical activity-related energy expenditure, namely PAL and TEE_{res}, increased in the placebo group compared with the sibutramine users. This might suggest that weight loss caused by sibutramine is mainly an effect of energy intake restriction, whereas weight loss in the control group is an effect of increased physical activity.

In the present study, no cardiovascular changes were observed during sibutramine intervention, which confirms the findings published in this journal previously (3). A recent meta-analysis found small effect for changes in systolic and diastolic blood pressure with sibutramine in adults, whereas the effect on weight loss was larger (27).

The most frequent reported adverse event in the sibutramine group was "abdominal complaints." Six of the seven subjects mentioned these problems during the intervention period, one during follow-up. Often abdominal pain in children is a reaction to emotional stress (28). This may explain the lack of reports of nervousness, which is a known complaint in treated adults (5). The symptoms of clinical depression observed in one subject consisted of insomnia, headache, and loss of interest and loss of appetite. Surprisingly, there was a weight gain during this period. After the termination of the study, the symptoms disappeared, as was confirmed by both mother and subject.

In the present study, sibutramine, in a once daily dosing of 10 mg and in combination with an energy-restricted diet and exercise prescription, did not result in an additional decrease in BMI or in BMI-SDS. Sibutramine seems to diminish the decrease in BMR during weight loss in obese adolescents. A future longer and larger trial may elucidate the place of sibutramine in the treatment of obese adolescents.

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