Turkish Journal of Endocrinology and Metabolism, (2005) 3 : 95-101 **ORIGINAL ARTICLE**

Early Thermogenic Response to Sibutramine in Obese Women

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Sibutramine was introduced as an energy balance regulator with the potential to modify both energy intake and heat generation in the management of obesity. Several studies have been done to investigate the effect of serotoninergic drugs on energy expenditure in humans. Most of the earlier studies found no effect of these agents on basal metabolic rate. Sibutramine has been shown to increase satiety in humans. In addition to reducing energy intake, sibutramine also increases energy expenditure in rodents by activating central efferent sympathetic nerves innervating brown fat, thus mimicking the non-shivering thermogenic response to cold. Our objective in the present study has been to asses the early (15 days) thermogenic effects of sibutramine in obese patients.

Thirty obese women (mean age 39± 11.6 yr) were enrolled in the study. Each patient received 10 mg sibutramine daily for 15 days and restricted their diets to 500 kcal/day less than the normal daily requirement. Inclusion criteria were age range 20-50 and Body Mass Index (BMI) 25-40 kg/m^2. Exclusion criteria were systolic blood pressure greater than 140 mmHg and diastolic blood pressure greater than 80 mmHg. Thermogenic response measurements were performed by direct calorimetry prior to medication and after the 15-day treatment period.

Baseline (before medication) mean thermogenic response was found to be 0.97±0.03 kcal/h/kg. It increased to 1,26±0.17 kcal/kg/h at the end of the 15-day sibutramine treatment. The difference was significant ($p<0.05$). Mean body mass index which was 33.15±3.03 kg/m^2 before treatment decreased to 32.22±3.1 kg/m^2 after treatment. Sibutramine treatment had no adverse effects during the 15 days. Mean waist circumference changed from 89.91± 11.09 to 87.76± 3.65. No changes were observed in routine blood parameters in the patients at the end of 15 days treatment.

In this study baseline mean thermogenic response was found to be 0.97±0.03 kcal/kg/h but it increased to 1.26±0.17 kcal/kg/h at the end of the 15-day sibutramine treatment ($p<0.05$) meaning that sibutramine treatment at a dose of 10 mg/day elevates body heat generation as early as 15 days after the beginning of treatment. This is in accordance with central efferent sympathetic effects that elevate heat generation.

Keywords: Thermogenic response, sibutramine, water calorimetry

Introduction

Obesity is an increasing public health issue and a major contributor to several diseases. It was introduced as an energy balance regulator with the potential to modify both energy intake and heat generation in the management of obesity. Weight loss is thought to result from its hypothalamic (Serotonin Neuronal Reuptake Inhibitor (SNRI) actions promoting satiety and elevating heat generation by way of uncoupled oxidation of nutrients (1, 2, 4, 5).

Several studies have been performed to investigate the effects of serotoninergic drugs on energy expenditure in humans. Most of the earlier studies reported that these agents had no effect on basal

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metabolic rate (5,6,7). Recently, sibutramine has come to be regarded as an agent representing centrally acting pharmaceutical compounds which effect energy expenditure (1, 3, 6). In humans, this question was taken up by Seagle et al. (8) These authors evaluated the resting metabolic rate (RMR) in 44 obese women who were instructed to live on a 1200 kcal/day diet for 8 weeks while receiving sibutramine or placebo. RMR was assessed by indirect calorimetry prior to treatment, at 3 hours after the first dose of drug (or placebo) was administred, and at the end of the 8-week weight-loss period. No statistically significant differences in RMR between sibutramine and placebo treated groups were observed, either 3-hours after treatment or 8 weeks after the weight-loss period. After 8 weeks both groups were taken off medication and they kept their weights stable for another 4 weeks. RMR was measured again and was found not to differ among groups. That there was no change in RMR after sibutramine was discontinued further suggests that the drug does not directly effect RMR. Similarly, Hansen et. al. (9) using a placebo controlled design, studied the fasting RMR and thermogenic effect of a meal in 11 nonobese men. Metabolic rate was found to be unchanged one hour after administration of 30 mg sibutramine. But, there was a significant rise in both RMR and postprandial thermogenesis compared to the placebo, particularly during the last 3.5 hours of the 5.5 hr measurement period (9).

One of our previous studies conducted on 20 obese women suggested that sibutramine effects termogenesis. Thermogenic response measurements were performed prior to medication and repeated at the end of a 12-week treatment period. Baseline mean thermogenic response was found to have increased at the end of the 12-week period (10).

The aim of the present study has been to evaluate the effect of sibutramine treatment on early thermogenic response in obese women, using a noval direct calorimetery method to be described in the following paragraphs.

Subjects and Methods

Subjects: Thirty obese women (mean age 39±11.6 yr) were enrolled in the study. Each patient received 10 mg sibutramine daily for 15 days and restricted their diets to 500 kcal/day less than the daily requirement. Inclusion criteria were age range 20-50 and Body Mass Index (BMI) 25-40 kg/m^2. Exclusion criteria were systolic blood pressure greater than 140 mmHg and diastolic blood pressure greater than 80 mmHg.

Thermogenic response measurements were performed by direct calorimetry prior to medication and after the 15-day treatment period. Patients were examined for any adverse effects of drug treatment.

Direct water immersion calorimetry: The water calorimetry system used in this study consists of 2 parts; one is a thermally insulated water tank made of double layer polyester walls with polyuretane insulation in between. The tank is equipped with a circulation pump, feed pump, heater, water level sensors and temperature sensors. Temperature is measured (to an accuracy of 0.05°C) continuously and stored in the hard disk of a PC which together with its peripherals comprise the second part of the system. When the difference between tank water temperature and ambient temperature is 15 °C or slightly more tank temperature drifts by only 0.13 C°/hour. Figure 1 shows the schematic diagram of the calorimeter and its accessories.

Before a measurement is started tank water temperature is raised to 34°C. The patient wearing only a swimming suit is then seated in the tank on a comfortable stool so that the entire body except the head is submerged in water and stays in water during the procedure which lasts a little longer than one hour. The tank holds 360 liters of water. When the patient enter into the water a volume of water equal to the patient's body volume spill out through an outlet. This volume is measured and used to calculate the volume of the remaining water in the tank. Water temperature is measured every second for 60 minutes and data are stored in the hard disk of a PC. Tank water volume, patient weight and ambient temperature are also entered into the computer. A special program using these data plots the temperature of tank water versus time (Figure 2) and from it calculates heat transferred from the patient to the tank water for the period of measurement. Heat transferred (Q in calories) from the patient to the water in the tank is calculated from the simple relation:

$Q = mc\,\Delta T$ (Eq. 1)

where m = mass of water in the tank (g)

c = heat capacity of water (cal/g)

ΔT = difference between the final (measured) and initial (i.e. 34°C) water temperatures in the tank.

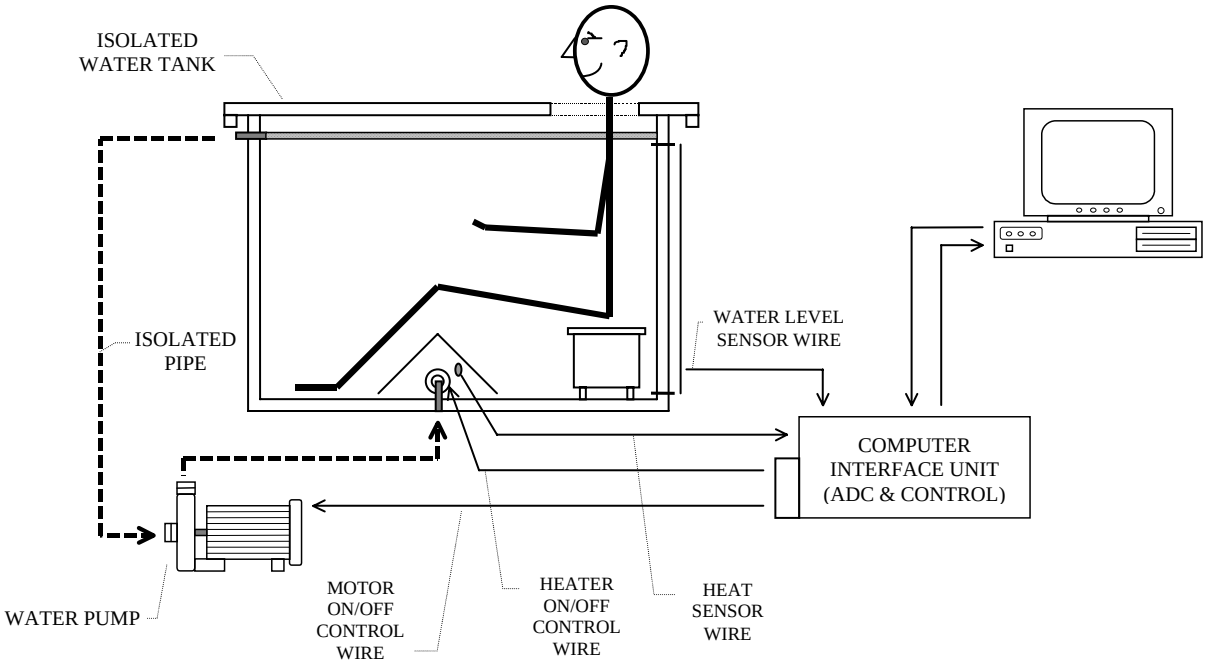

Figure 1. Schematic diagram of the calorimeter and its accessories.

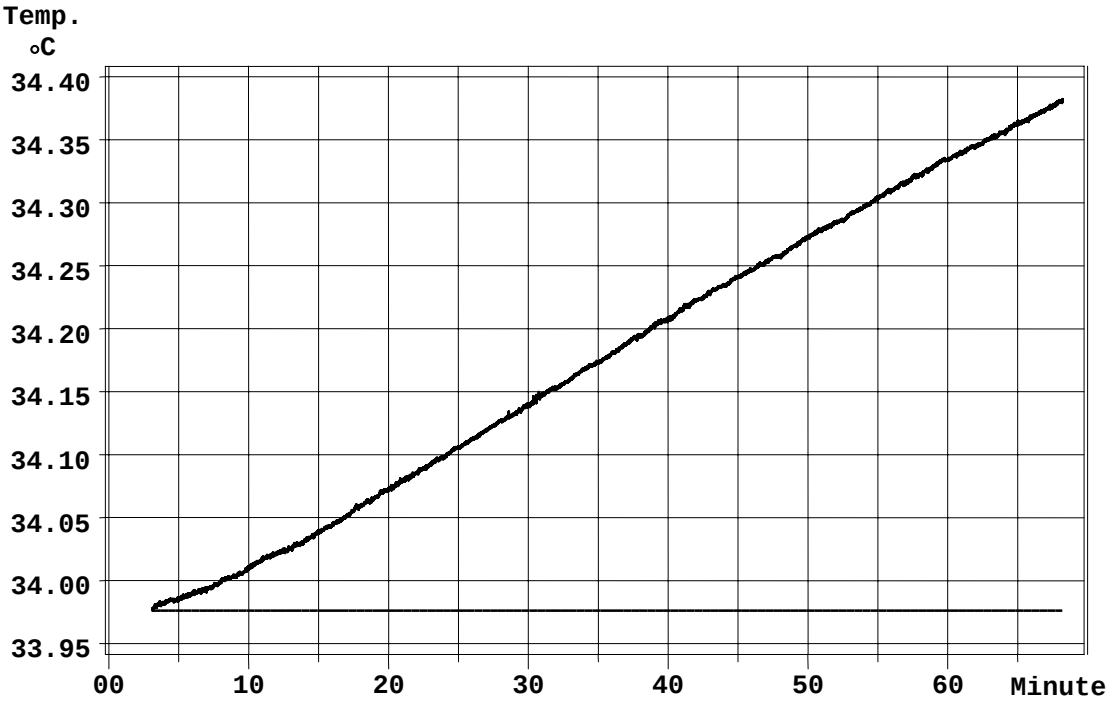

Figure 2. Rise of calorimeter water temperature with time.

The law of conservation of energy dictates that in a living system;

Food intake = Work done by the system + Energy stored + Heat loss

When food intake is 0 as is the case in a fasting individual and work done is zero as in a resting individual heat generated by the body comes from the stored energy only. Under these conditions in a calorimeter such as the one described here, heat *lost* by the patient, is nearly equal to heat *gained* by the tank water. Therefore, Q is a measure of heat generation (thermogenic response) by the subject and can be expressed in kcal per hour per

unit mass of the patient (kcal/h/kg). It should be noted that Q does not include heat loss from the patient by respiration and from the skin in the head region that is outside the water. But these losses are minimal as will be explained in the subsequent paragraphs.

The above procedure is repeated for each patient. The water tank is emptied, disenfected and made ready for the next patient. Measurements are made before medication and 15 days after treatment with sibutramine.

Statistical Analysis: Mean thermogenic response, mean BMI and anthropometric parameters of patients were compared by the two- tailed t-test before and after treatment with sibutramine (10 mg/day) for 15 days. A p-value >0.05 was considered significant. SPSS program version 6.1 was used for all statistical analyses. Data which were not normally distributed were analyzed by the Mann-Whitney U test.

Results

Anthropometric data and blood profiles of patients are given in Table 1 and Table 2 respectively, in the results.

Table 1. Average values of subject characteristics before and after treatment

	Before	After
Body weight (kg)	84.63± 8.26	82.40± 8.61
Systolic BP* (mmHg)	129.7± 13.4	125.5± 8.0
Diastolic BP* (mmHg)	62.0± 12.6	61.5± 6.6
Heart Rate (pulse/min)	79.34± 21.12	80± 13.24
BMI (kg/m^2)	33.15± 3.03	32.22± 3.17
Waist circumference (cm)	89.91± 11.09	87.76± 3.65

*BP Blood pressure

Table 2. Blood profiles of patients

Triglyceride (mg/dl)	124.2± 39.80
LDL-Cholesterol (mg/dl)	123.0± 28.70
HDL-Cholesterol (mg/dl)	50.33± 11.20
Fasting blood glucose (mg/dl)	90.9± 6.23
Post prandial glucose (mg/dl)	119.4± 17.20
SGOT (U/l)	24.0± 5.50
SGPT (U/l)	28.4±8.60
Total protein (g/dl)	7.2± 0.29
Na (mEq/l)	143.2± 3.00
K (mEq/l)	4.3± 0.50
Ca (mg/dl)	9.0± 0.40
Üre (mg/dl)	28.5± 2.67
Creatinine (mg/dl)	0.98± 0.30
Haematocrit (%)	37.5± 3.90
Leucocyt ($x10^3/mm^3$)	8.5± 1.80
Platelet ($x10^3/mm^3$)	380.0± 75.20

Baseline (before medication) mean thermogenic response was found to be 0.97±0.03 kcal/h/kg. It increased to 1,26±0.17 kcal/kg/h at the end of the 15-day sibutramine treatment ($p<0.05$). The difference was significant. BMI which was 33.15±3.03 kg/m^2 before treatment decreased to 32.22±3.1 kg/m^2 after treatment. Thermogenic responses of patients before and after treatment with sibutramine are given in Table 3. Sibutramine treatment had no adverse effects. Mean waist circumference changed from 89.91± 11.09 to 87.76± 3.65. No changes were observed in routine blood parameters.

Table 3. Thermogenic responses of patients

	Sibutramine (n=30)			
	Before		After 15 days	
Pat. No	Weight (kg)	Therm Resp. (kcal/kg/hr)	Weight (kg)	Therm Resp. (kcal/kg/hr)
1	84	0.88	82	0.92
2	86	0.90	85	0.99
3	79	0.98	75	1.70
4	75	1.00	76	0.90
5	76	1.00	75	1.00
6	74	0.90	76.1	1.70
7	86	1.00	83	1.50
8	89	0.90	88.1	1.87
9	87	1.40	85	1.32
10	90	1.20	90.1	1.60
11	87	1.20	86	1.21
12	86.5	1.00	85	1.17
13	86	1.20	86.2	1.48
14	89	1.10	85.7	1.10
15	88	1.00	87.4	1.00
16	87.3	1.04	86.2	1.05
17	85.1	1.00	84	1.26
18	86.3	0.60	85.2	1.14
19	79	0.80	77	1.16
20	81	1.18	80	1.48
21	87	0.70	86	1.25
22	85.2	0.80	84	0.99
23	83.2	0.90	80	0.90
24	88	0.70	89.5	1.40
25	88.1	1.00	80	1.50
26	78	1.00	75	1.10
27	79.2	0.90	79	1.30
28	90	0.83	89	1.30
29	92.3	0.94	88	1.20
30	94	1.00	90	1.40

Discussion

In this study baseline mean thermogenic response was found to be 0.97±0.03 kcal/kg/h but it increased to 1.26±0.17 kcal/kg/h at the end of the 15-day sibutramine treatment ($p<0.05$) meaning that sibutramine treatment at a dose of 10 mg/day elevates body heat generation as early as 15 days after the beginning of treatment. This is consistent with the efferent sympathetic effects that elevate heat generation. Previously, RMR using indirect calorimetry was not changed at 3 hours after the first dose of drug was administred, and at the end of the 8-week period [9]. Our findings suggested that thermogenic response was increased at two weeks period. Thermogenic response was measured using direct water immersion calorimetry in our study.

Some technical comments should be made about the water immersion calorimetry method introduced in the present study and what it actually measures. We believe that this type of calorimetry is superior to other methods measuring metabolic heat production such as spirometry which is based on O_2 consumption, and ventilated hood indirect calorimetry which involves three types of heat transfer (i.e. conduction, radiation and convection) from the body to its surroundings. Water immersion calorimetry eliminates heat transfer by convection because the skin temperature is always nearly equal to the water temperature because the two are in contact at all times. Heat transfer by radiation and conduction occurs directly into the surrounding water.

Normally, heat loss from the body occurs in two stages at equal rates: the first is heat transfer from the core of the body to the skin (largely by the blood supply to the skin), the second stage is heat transfer from the skin to the surroundings by radiation, conduction and convection. Our calorimeter provides a shorter and more efficient heat transfer route from the body core to the surroundings (i.e. tank water) by eliminating convection and radiation.

To assess the heat absorbing properties of the calorimeter we calculated the heat input into the tank water (443 kg without the subject) from its 2100 watt electrical heater. The heater rated at 2100 watts delivered 2100x3600/4.18 = 1808.612 kcal per hour into the tank water and water temperature increased by 4.90 C° during the hour. Using these data in Eq. 1 we calculated the heat gain of the tank water to be 1836 kcal per hour, a value very close to the 1808 kcal/h delivered by the heater. The fact that heat gain of the tank water was slightly higher than that delivered by the heater may be accounted for by the additional frictional heat contributed by the circulation pump.

It may be wondered why the initial temperature of the tank water was set to 34°C, some 2-2.5 degrees below normal core temperature. The rationale behind this was that normal skin temperature is 34°C (11). This temperature stimulates neither the warmth nor cold receptors on the skin. That this temperature was comfortable for the subjects was evident from their reports of feeling relaxed during measurements. Since the water tank was a large heat sink its temperature never rose to a level high enough to stimulate thermal receptors. This was important as regards the constancy of the core temperature (37°C) because water temperature did not cause activation of the hypothalamic temperature sensitive neurons where would otherwise activate temperature regulation mechanisms. Yet, the tank water temperature rose to instrumentally measurable levels (about 34°C in one hour) high enough to allow calculation of the heat absorbed by the water. As such the tank water was acting to keep the skin temperature nearly constant and in a way facilitating heat transfer from the core to the skin and hence from the skin to the surrounding water. Therefore, it would not be appropriate to denote such heat transfer rate as the *resting metabolic rate* (RMR) or *resting energy expenditure* (REE) although other conditions of its measurement were identical with those of RMR or REE measurements. Rather, it should perhaps be defined as *enhanced resting metabolic rate* (eRMR). Indeed, the values measured in the present study are considerably higher compared to values measured in other studies or predicted from patient characteristics using various prediction equations. Therefore, by virtue of their methodological differences our measurements could not be compared with other types of measurements such as ventilated hood indirect calorimetry or spirometry.

Several prediction equations have been developed to calculate basal metabolic rate (BMR), resting

metabolic rate (RMR) and basal energy expenditure (BEE) from combinations of weight, height and age for different subject groups such as children, adolescents, normal and obese man and women. In most of these studies while a given equation yielded values consistent with measured values for one group of subjects it failed to do so for other groups (11-16).

The above view appears to have found support also from the more recent conclusions of Schofield (17) who have questioned the validity of the equations used to predict basal metabolic rate (BMR) in the obese. These authors state that the Schofield equations are unsuitable for obese populations; because current Western populations exhibit prevalences of obesity many times greater than those in the Schofield database, pointing to the need for further study of suitable predictors for these individuals (17).

For example, in a study by Frankenfield et al. (18) predicted RMR was found to be more than 10% different from the measured in 22% of subjects using the Mifflin equation, in 33% of subjects using the Harris-Benedict equation and in 35% of subjects using the Owen equation.

On the other hand, even if prediction equations developed by several authors were assumed to be reliable estimators of RMR in the obese it would not be legitimate to use them as tools to test the results of our study. Because, in the present study thermogenic response promoting effect of a drug has been investigated. Sibutramine administration is expected to decrease weight and when reduced weight is used in the above equations they would yield lower RMR values. In other words, weight reducing and thermogenesis promoting effects of the drug can not be reflected in the RMR values calculated by prediction equations.

As to heat losses from the patient by way of respiration and from the exposed head skin have not been taken into account in this study, these losses besides being very difficult if not impossible to measure they are small. For example, heat loss by insensible evaporation of water from the whole body skin and lungs of the human body is in the range of 12-16 kcal/h (19). This quantity is even smaller on the basis of heat loss *per kg of body mass* and can therefore be neglected. Furthermore, since heat loss due to insensible evaporation from the head skin and lungs would be the same during pre- and post- treatment measurements, comparisons of pre- and post-treatment values neglecting these small losses in both measurements should not invalidate our conclusions.

Conclusions

The following conclusions have been reached from the results of the present study:

1. Sibutramine is capable of promoting thermogenesis after a treatment period of 15 days (early effect).
2. Thermogenic response increased (statistically significantly) ($p<0.05$) at the end of a 15-day treatment period.

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