Effects of Dexfenfluramine on Resting Metabolic Rate and Thermogenesis in Premenopausal Obese Women During Therapeutic Weight Reduction

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To investigate whether a serotoninergic drug such as dexfenfluramine (dF) may have some beneficial effects on energy expenditure (EE) during therapeutic weight reduction, a 3-month study was conducted in a double-blind, placebo-controlled trial. Thirty-two obese, premenopausal women received either dF or placebo (P) in addition to a very-low-calorie diet (VLCD) prescription. All patients started—when hospitalized at the metabolic ward—with a 500-kcal regimen and fulfilled the 3-month trial on a ±760-kcal protein-sparing modified fast. Although not statistically significant, women receiving dF lost more weight (16.0 ± 1.4 *v* 12.8 ± 1.3 kg, $P = .111$) over the 3-month study period. Resting metabolic rate (RMR) decreased significantly by 5% in the dF group (4.79 to 4.53 kJ/min) and by 9% in the P group (5.09 to 4.63 kJ/min). When expressed per kilogram body weight, RMR significantly increased from 0.050 to 0.057 kJ/min/kg in the dF group ($P < .001$), versus 0.053 to 0.056 in the P group (NS). When expressed per kilogram fat-free mass (FFM), RMR remained stable in the dF group, whereas it significantly decreased in the P group ($P = .024$). No significant differences could be found between groups. Glucose-induced thermogenesis (GIT), expressed as percent increase above RMR, did not show significant differences between groups. When expressed per kilogram body weight, mean GIT increased in the dF group from 0.14% to 0.16% above RMR, with a significant decrease from 0.15% to 0.13% in the P group. Only during the first hour did GIT per kilogram body weight significantly ($P = .038$) increase in the dF group during the outpatient period (between day 16 and day 90). These results show that a serotoninergic drug seems capable of limiting the weight reduction–associated decrease in RMR and dietary-induced thermogenesis (DIT), certainly when expressed on a per-kilogram-weight basis.

OVER THE PAST 50 YEARS, obesity has increasingly become a major risk factor for a large number of clinical conditions. Overweight is associated with an increased risk for morbidity and mortality in both men and women.[1] The most important prospective evidence is derived from the Framingham cohort: these data indicate that after more than 20 years of follow-up study, it finally emerged that obesity could be considered an independent risk factor for coronary artery disease.[2] Although (fat) overeating can be considered the major determinant for the development of obesity, the definite reasons remain unclear.

If low energy output by obese individuals cannot be held totally accountable for the physiopathology behind the problem, then energy input must play a significant role.[3] Our actual understanding of the physiology of weight control in man and the factors that can influence it is increasing, and effective pharmacologic and nonpharmacologic forms of treatment are being developed.

Dietary therapy—from "healthy food" in moderately overweight subjects to very-low-calorie diet (VLCD) in the more obese—remains the cornerstone of long-term weight reduction success. Dexfenfluramine (dF), a specific serotoninergic food-intake regulator,[4-6] has been shown to be effective in addition to dietary therapy in long-term weight reduction.[7] Besides the specific central anorectic effects of the drug, more peripheral effects (energy metabolism and insulin sensitivity) may also play a role in the effects on weight loss and/or weight maintenance.

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In human subjects, resting metabolic rate (RMR) decreases during weight reduction; however, the effects of weight loss on dietary-induced thermogenesis (DIT) are not so uniform.[8] In animal and human studies, it was demonstrated that dF may have a positive influence on energy expenditure (EE), DIT in particular. In animal studies, an enhancement of the thermic effect of food,[9-10] a higher postprandial thermogenesis in rats,[11] and an increased oxygen consumption were reported previously.[12]

In human subjects, challenging results have been reported with regard to the effects of dF on EE.[13-19] These different effects, both in obese and non-obese subjects, are listed in Table 1. The other possible peripheral effects of dF (insulin sensitivity and glucose disposal) have been included in this series.[15-16]

During VLCD, changes in RMR and DIT can occur,[20] paralleling the considerable weight loss during such therapy. If the decrease in RMR and DIT could be limited during therapeutic weight reduction, a longer-lasting energy deficit could be the favorable consequence during weight-reducing programs.

To investigate whether the use of dF during a VLCD and protein-sparing modified fast may have such an additional effect on long-term weight loss and EE parameters, a double-blind, placebo-controlled study was performed.

SUBJECTS AND METHODS

Subjects

Thirty-two obese premenopausal women aged 18 to 52 years were selected for this protocol. Only women with abdominal obesity were included, because of the earlier recognition that women with an upper-body fat predominance seem to have more clinical benefits from dF treatment.[21]

Only patients with a body mass index (BMI) greater than 30 were included. Patients were not included if they showed any of the following conditions: obesity of clear endocrine origin, pregnancy, lactation, renal or hepatic disease, depression, and treatments that might interfere with dF activity and/or with sex hormone behavior.

Table 1. Literature Data on the Effect of dF on EE in Human Subjects (OB, N-OB, and NIDDM)

Study	Effect
Short-term effects	
Munger et al, 1987[13]	↑ Postprandial thermogenesis in N-OB
Troiano et al, 1990[14]	↑ Late postprandial thermogenesis in N-OB
Scheen et al, 1991[15]	↑ Insulin-induced glucose disposal in NIDDM
Andersen et al, 1993[16]	↑ Glucose disposal in OB
Scalfi et al, 1993[17]	↑ RMR and thermogenesis in OB
Long-term effects	
Breum et al, 1990[18]	No change in 24-hour EE in OB
Lafrenière et al, 1993[19]	No change in RMR and DIT in OB

Abbreviations: OB, obese; N-OB, non-obese; NIDDM, non–insulin-dependent diabetes mellitus.

To exclude any possible influence of sex hormones on EE, only premenopausal women without secondary amenorrhea were accepted. No oral contraceptives were allowed, and to avoid a possible pregnancy during the trial, only women who underwent a tubal ligature or hysterectomy (without ovariectomy) or who were using an intrauterine device could participate in this protocol. All patients had a stable body weight for at least 2 to 3 months before entering the study. Estimation of fat distribution was based on measurement of the waist to hip ratio (WHR), performed in standardized (duplo) conditions by the same investigator. Upper-body obesity was considered present when WHR was greater than 0.80, as previously reported.[22]

All patients were euthyroid, as demonstrated by normal plasma free thyroid hormone and thyrotropin levels. No biochemical abnormalities were found for peripheral blood cell count and liver and kidney function.

None of the women had diabetes, based on an oral glucose tolerance test and according to the National Diabetes Data Group criteria.[23] However, some of them showed impaired glucose tolerance.

Protocol

Thirty-two obese women received in a double-blind, placebo-controlled, randomized trial dF 30 mg (15 mg twice daily) or placebo (P) throughout a 3-month period. All patients were initially admitted to the metabolic ward of the University Hospital. After a run-in period of 3 days during which they consumed an equicaloric diet, they started with a VLCD preparation of 500 kcal (2,100 kJ) daily for the initial period of 12 days. After 16 days, at the time of discharge from the hospital, patients switched to a protein-sparing modified-fast preparation of ±760 kcal daily to be followed throughout the study period of 3 months. They were intermittently seen by the treating doctor and several times by a dietician. All patients were rehospitalized after 3 months for reevaluation. Blood analysis and measurements of body composition (impedance technique) and EE (indirect calorimetry) were performed at the start, after 16 days of the inpatient program, and after 10 weeks of outpatient treatment.

The study was approved by the Ethics Committee of the University Hospital, and all patients gave their informed consent.

Indirect Calorimetry and Laboratory Tests

EE was measured by indirect calorimetry using the ventilated-hood system. The open-circuit ventilated-hood system uses a 30-L canopy to measure EE continuously. Validation of the whole analyzing system was performed periodically by the ethanol-combustion method. Conditions for the measurement of EE were carefully standardized. Each subject slept the night before the experiment at the metabolic ward to ensure perfect basal conditions. They fasted overnight and remained supine until the measurement in the metabolic test room, where ambient temperature was between 24° and 26°C.

EE was measured in the basal state for approximately 30 minutes and throughout a 3-hour period after a 100-g glucose load. Glucose-induced thermogenesis (GIT) was expressed as the percent increase above RMR and as a percentage of the metabolizable energy (ME) content of the glucose load. Differences in RMR, expressed as a percentage of ME intake, are excluded from GIT evaluation, which gives a more absolute estimate of the thermogenic effect of glucose.

Assessment of body composition, important in the evaluation of EE, was performed by bioelectrical impedance measurements.[24] This recently developed method is regarded as a valid technique to measure body composition; it is also less time-consuming than classic techniques such as hydrodensitometry. We used the bioelectrical tetrapolar impedance technique (BIA-101, RJL Systems, Detroit, MI), measuring the resistance of a weak current of 800 μA at a signal frequency of 50 kHz.

To calculate fat-free mass (FFM), we used a specific regression equation for an obese population with resistance, sex, and body weight as the included variables.[24]

All patients were asked to refrain from smoking at least 12 hours before the test procedure.

On the same day that EE was measured, blood was taken from an antecubital vein for determination of glucose, insulin, and thyroid hormone levels. Glucose tolerance parameters were consequently measured every 30 minutes after the oral glucose load. Plasma glucose determinations were performed at the routine laboratory using the hexokinase method. Free triiodothyronine (coefficient of variation 2.8%) and thyroxine (coefficient of variation 4.1%) levels were determined using Amersham kits (Amerlex-M free T_4, -M free T3, Amersham), and thyrotropin levels were measured using the radioimmunoassay from Behring (Marburg, Germany).

Statistical Analysis

Comparability of groups was assessed using a two-tailed Student's *t* test for independent samples. Change over time for parameters of clinical examination and EE was compared between groups using a two-way (group × time) ANOVA with repeated measures on time. Moreover, change over time in each group was evaluated using a one-way ANOVA with repeated measures on time, completed by a Neuman-Keuls test. Total weight loss was compared between groups using a Student's *t* test for independent samples. The type I error level was set at .05.

RESULTS

Both groups (17 dF and 15 P) were comparable at baseline for anthropometric measurements, as well as for RMR and GIT expressed as the percentage increase above RMR (Table 2).

No significant differences were observed at baseline for mean caloric intake and percent nutrient intake between both groups (mean carbohydrate intake, 38.4 ± 2.3% in the dF group *v* 39.5 ± 2.0% in the P group).

Twenty-six patients (15 dF and 11 P) completed the 3-month study. After 2 weeks, weight loss (mean ± SEM) was almost identical in both groups (5.5 ± 0.5 with dF *v* 5.0 ± 0.6 kg with P).

After 3 months, patients receiving dF lost 16.0 ± 1.4 kg, versus 12.8 ± 1.3 in the P group; these changes are

Table 2. Patient Characteristics for Body Weight and Fat Indices and EE According to the Double-Blind Treatment With dF (n = 17) and P (n = 15)

	dF	P
Age (years)	33.9 ± 1.8	35.0 ± 2.7
Obesity duration (years)	17.6 ± 2.9	15.5 ± 2.5
Body weight (kg)	96.6 ± 2.6	94.5 ± 2.7
BMI (kg · m^{-2})	37.4 ± 1.2	35.9 ± 0.9
WHR	0.86 ± 0.01	0.85 ± 0.01
FFM (kg)	46.3 ± 1.0	46.9 ± 1.5
Fat mass (%)	51.3 ± 1.2	49.7 ± 1.3
RMR (kJ/min)	4.88 ± 0.15	4.94 ± 0.18
Mean 3-hour GIT (% above RMR)	12.6 ± 1.3	13.5 ± 1.4

NOTE. Results are the mean ± SEM.

significant ($P < .001$) for both groups, with a significance of $P = .111$ between groups (Table 3). WHR, the sum of four skinfolds, and waist circumference decreased significantly ($P < .001$) after 3 months of therapy. Between groups, results showed a significantly higher decrease in the dF group versus P group for the sum of four skinfolds (98.1 ± 5.1 to 62.2 ± 4.8 mm *v* 97.9 ± 7.3 to 73.6 ± 5.8, $P = .027$) and for waist circumference (103.1 ± 3.1 to 87.0 ± 2.9 cm *v* 101.3 ± 2.8 to 90.1 ± 2.8).

RMR decreased significantly by 5% in the dF group (from 4.79 to 4.53 kJ/min) and by 9% in the P group (from 5.09 to 4.63). No significant difference occurred between groups.

When expressed per kilogram body weight, RMR significantly increased from 0.050 to 0.057 kJ/min/kg in the dF group ($P < .001$), versus 0.053 to 0.056 in the P group (NS). When expressed per kilogram FFM, RMR remained stable in the dF group, whereas it significantly decreased in the P group ($P = .024$). No significant differences could be found between groups (Table 4).

After 3 months, GIT, expressed as the percent increase above RMR, did not show significant differences between groups; however, in the dF group, it increased by 10% after the first hour from 13.4% to 14.8%, whereas it decreased by 20% (from 16.6% to 13.1%) in the P group. Mean GIT did not change substantially between and within groups.

When expressed per kilogram weight, mean GIT increased in the dF group from 0.14% to 0.16%, with a decrease from 0.15% to 0.13% in the P group.

Only during the first hour did GIT (expressed per kilogram body weight) significantly increase in the dF group between day 16 and 3 months ($P = .038$), with a parallel decrease in the P group. However, when GIT is expressed as percent ME (GIT-ME), a slight reduction of GIT was observed in both groups: 10% decrease in the dF group and 20% in the P group (Table 5).

Table 3. Evolution of Body Weight and BMI Throughout the 3-Month Trial Period in 26 Patients (15 dF and 11 P) Who Completed the Study

	Start	2 Weeks	3 Months
Body weight (kg)			
dF	96.1 ± 3.2	90.6 ± 3.2	80.1 ± 2.7
P	95.4 ± 3.1	90.4 ± 3.4	82.7 ± 3.3
BMI (kg · m^{-2})			
dF	37.0 ± 1.4	34.9 ± 1.3	30.8 ± 1.1
P	36.2 ± 1.1	34.3 ± 1.2	31.3 ± 1.1
Weight loss (kg)			
dF	—	5.5 ± 0.5	16.0 ± 1.4
P	—	5.0 ± 0.6	12.8 ± 1.3

NOTE. Results are the mean ± SEM. Within groups, all parameters were significant at the .001 level; between groups, the significance for weight loss at 3 months reached $P = .111$.

Table 4. Indices of RMR (kJ/min) in Absolute Terms and Expressed Per Kilogram Body Weight and Per Kilogram FFM (15 dF and 11 P)

	Start	3 Months	Time Effect
RMR (kJ/min)			
dF	4.79 ± 0.15	4.53 ± 0.15	$P = .013$
P	5.09 ± 0.21	4.63 ± 0.17	$P = .002$
RMR (kJ/min)/kg weight			
dF	0.050 ± 0.002	0.057 ± 0.002	$P < .001$
P	0.053 ± 0.002	0.056 ± 0.002	NS
RMR (kJ/min)/kg FFM			
dF	0.103 ± 0.003	0.103 ± 0.004	NS
P	0.106 ± 0.004	0.099 ± 0.004	$P = .024$

NOTE. Results are the mean ± SEM.

DISCUSSION

It has been shown that serotoninergic agonists such as dF are capable of increasing RMR and DIT.[13-19] Most of these previous reports were based on short-term observations, and the longer-term studies reported hitherto—the 1-year trial by Breum et al[18] and that recently published by Lafrenière et al[19]—showed no effects of dF on RMR, DIT, and overall EE.

There exists some controversy as to whether GIT will be

Table 5. GIT After 100 g Glucose, Expressed as the Mean Value, GIT%RMR (mean and after each hour), and GIT-ME (15 dF and 11 P)

	Start	3 Months
Mean GIT (%RMR)		
dF	12.8 ± 1.5	12.7 ± 1.6
P	13.4 ± 1.8	11.0 ± 2.1
GIT 60 minutes		
%RMR		
dF	13.4 ± 1.7	14.8 ± 1.6
P	16.6 ± 2.5	13.1 ± 2.3
%RMR/kg		
dF	0.14 ± 0.02	0.19 ± 0.02
P	0.18 ± 0.03	0.16 ± 0.03
GIT 120 minutes (%RMR/kg)		
dF	0.17 ± 0.02	0.20 ± 0.03
P	0.17 ± 0.02	0.16 ± 0.03
GIT 180 minutes (%RMR/kg)		
dF	0.09 ± 0.02	0.10 ± 0.02
P	0.09 ± 0.02	0.07 ± 0.02
GIT-ME		
dF	6.65 ± 0.81	6.02 ± 0.76
P	7.10 ± 0.93	5.64 ± 1.18

NOTE. Results are the mean ± SEM.

Abbreviations: GIT %RMR, GIT expressed as the percent increase above RMR; GIT-ME, GIT as a percent of ME.

reduced during major weight reduction.[20] We previously reported such an observation, and this trial seems to confirm a ±20% reduction of GIT after significant weight loss by VLCD.[25]

This double-blind study with dF attempted to elucidate whether a serotoninergic drug can limit or even reverse the before-mentioned decrease in EE during VLCD. As proven by most of the previous studies, dF did not have any effect on RMR either in absolute term or when expressed per kilogram body weight or per kilogram FFM. When dF is given to premenopausal obese women maintained on a 760-kcal diet over a 10-week period, it seems to prevent the decrease in GIT, at least during the first hour after the glucose load.

On a per-kilogram-body-weight basis, mean GIT increased with dF administration, but not with P. However, when expressed as the percent ME, no effect of dF was observed when compared with P.

It is not easy to speculate about possible mechanisms behind these findings. Insulin sensitivity, which is known to influence negatively DIT,[26] not only decreases during weight reduction but also seems to be influenced by dF.[15] Although Scheen et al[15] reported this finding only in non–insulin-dependent diabetic subjects, Andersen et al[16] described an improvement in whole-body insulin-stimulated glucose disposal in nondiabetic obese subjects independently of weight loss.[16] It is plausible that an enhanced insulin sensitivity induced by major weight loss and administration of dF can partly explain the effects on DIT.

One could speculate that without major weight loss—ranging from 9 to approximately 25 kg in this study, due to the importance of diet restriction in both groups—the effects of dF on GIT would have been more clear.

However, serotoninergic drugs such as dF can be considered a useful adjunct in limiting the adaptive decrease in EE that accompanies marked weight loss.

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