Long-Term Effects of Fluoxetine on Glycemic Control in Obese Patients With Non–Insulin-Dependent Diabetes Mellitus or Glucose Intolerance: Influence on Muscle Glycogen Synthase and Insulin Receptor Kinase Activity

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Fluoxetine (F) is a specific serotonin-reuptake inhibitor that has been shown to promote weight loss and improve glycemic control in obese diabetic patients. To study its long-term metabolic effect, 40 obese patients with non–insulin-dependent diabetes mellitus (NIDDM) or impaired glucose tolerance (IGT) were included in a 12-month, randomized, placebo-controlled study. Patients were assigned to receive either 60 mg F or placebo (P) daily in conjunction with a 5.0-MJ/d diet (> 50% carbohydrate). Both groups showed a significant weight loss, with a nadir after 6 months without group differences (mean ± SD: F, 10.1 ± 10.0 kg; P, 9.4 ± 11.5 kg). Fifteen patients from the F group and 14 from the P group completed the 12-month study without weight loss differences. Glycemic regulation improved along with the weight loss, but with a larger decline in plasma C-peptide and fasting glucose levels in the F group ($P < .05$). Total skeletal muscle glycogen synthase (GS) activity increased by 31% in the F group ($P < .01$) and by 17% in the P group (nonsignificant) after 6 months of treatment, but was still less than the activity in normal-weight controls (aged 28.0 ± 6.3 years; body mass index, 23.5 ± 2.2). After adjustment for fasting glucose, insulin, weight loss, and diabetic state, a positive effect of F remained on the total GS activity, which accounted for 27% of the variation ($P < .05$). The waist to hip ratio was reduced in P subjects as compared with F subjects ($P < .05$). Fat-free mass (FFM) tended to be more reduced in the F group as compared with P subjects (4.9 *v* 1.9 kg), although the difference did not reach statistical significance. In conclusion, F seems to improve insulin sensitivity beyond the effect mediated through weight loss by a possible effect on GS activity in skeletal muscle tissue.

FLUOXETINE (F) enhances brain serotonergic transmission by selectively inhibiting serotonin reuptake from presynaptic neurons.[1] F has been shown to decrease food intake[2] and cause weight loss in obese patients.[3-5] Besides its anorectic and antidepressant properties,[6] fluoxetine has also been shown to improve glycemic regulation in obese diabetic patients.[7-10] The primary treatment of obese patients with non–insulin-dependent diabetes mellitus (NIDDM) is weight reduction obtained by permanent dietary changes, but it is a rarely achievable goal. Obesity is associated with decreased insulin sensitivity, and in patients with NIDDM obesity aggravates insulin resistance. A persistent effect of F treatment on insulin sensitivity during long periods would therefore be of importance, but so far only studies up to 6 months' duration have been reported.[9] In a recent short-term study, it was shown that F, irrespective of weight loss, improved peripheral and hepatic insulin action as assessed by a hyperinsulinemic-euglycemic clamp in obese insulin-resistant subjects.[8] Studies with another serotonergic agonist, dexfenfluramine,[11,12] have also demonstrated a weight loss–independent, blood glucose–lowering effect and an increased glucose disposal rate in both NIDDM[13-15] and obese patients,[16] but not in normal controls. The mechanism behind this direct effect on insulin action is poorly understood. Skeletal muscle is believed to play an important role in insulin resistance in NIDDM subjects, and interest has focused on glycogen synthesis, which accounts for a major part of nonoxidative glucose disposal during hyperinsulinemia.[17,18] We therefore found it of interest to study the effect of F not only on muscle glycogen synthase (GS) activity but also on insulin receptor kinase, another key enzyme, which has been found to be reduced in obese insulin-resistant patients.[19]

Finally, we wanted to elucidate the long-term effects of F on body composition and body fat distribution, since it has been demonstrated in a recent short-term study using magnetic resonance imaging that F has no effect on the amount of visceral fat, but may even lead to a larger reduction of fat-free mass (FFM) than placebo (P) during weight loss.[20]

SUBJECTS AND METHODS

Patients

The study group consisted of 40 obese patients with NIDDM or impaired glucose tolerance (IGT), according to the World Health Organization's 1985 definition, who participated in a multicenter weight loss study. Patient characteristics are shown in Table 1. Inclusion criteria were as follows: age at least 18 years, body mass index at least 29, confirmed clinical diagnosis of NIDDM with fasting venous plasma glucose greater than 7.8 mmol/L or IGT confirmed by two separate measurements of plasma glucose greater than 7.8 mmol/L 2 hours after an oral 75-g glucose load, and hemoglobin A_{1c} (HbA_{1c}) less than 14%. Criteria for exclusion were as follows: obesity due to endocrine disorders; evidence of severe somatic or psychiatric disorders including alcohol or drug abuse; administration of interfering drugs (monoamine oxidase inhibitors and cyclic antidepressants) 2 weeks before the study; use of anorectics; lactation; pregnancy or desire to be pregnant; weight loss within the 2 preceding months; use of antihypertensive drugs such as guanethidine, reserpine, clonidine, or methyldopa; and severe diabetic complications. None of the patients received insulin therapy.

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Submitted November 19, 1994; accepted March 28, 1995.

Supported by a grant from Eli Lilly & Co.

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0026-0495/95/4412-0011$03.00/0

Table 1. Baseline Characteristics of Patients (mean ± SD)

Characteristics	F	P
No. of patients	20	20
Female/male	13/7	15/5
Age (yr)	43.6 ± 9.8	44.3 ± 8.7
Height (cm)	167.8 ± 8.4	165.9 ± 7.4
Weight (kg)	104.1 ± 15.8	108.7 ± 15.4
BMI (kg/m^2)	36.9 ± 4.5	39.5 ± 4.7
NIDDM (n)	9	7
IGT (n)	11	13
Use of oral antidiabetic agents (n)	5	4

Study Design

The investigation was conducted as a 1-year, double-blind, placebo-controlled, randomized study. After initial screening and examination, patients were assigned to either F 60 mg daily or P. The trial medication was dispensed as identical capsules, and patients were asked to take the capsules in the morning. Patients were seen every fourth week in small groups and were instructed by an experienced clinical dietician about a 5.0-MJ/d diet with at least 50% of the energy content from carbohydrates in conjunction with behavior modification. Adverse events and concomitant therapy, including oral hypoglycemic agents, were recorded at each visit. Compliance with the study was evaluated by counting the remaining tablets at each visit. All events were recorded during the study period without trying to distinguish between drug-related adverse reactions and other medical events.

The Helsinki II Declaration was observed, and the study protocol was approved by the Copenhagen Municipal Ethics Committee.

Procedures

At each visit, body weight was measured to the nearest 0.1 kg (with subjects lightly clothed) using an electronic scale (Seca 707; Seca, Naestved, Denmark). Heart rate and blood pressure (supine and erect) were determined using an appropriately sized cuff. Every third month, fasting blood samples were taken for determination of insulin, C-peptide, glucose, HbA_{1c}, thyroid hormones, lipids, and routine laboratory parameters (hematology, urinalysis, liver enzymes, etc.). Before and at the end of the study, a 75-g oral glucose tolerance test was performed. Biochemical data at baseline and at the end of the study are shown in Table 2.

Venous plasma glucose was analyzed by a glucose oxidase method, and capillary blood by reflection photometry (Reflolux II; Boehringer, Mannheim, Germany). Plasma insulin and C-peptide concentrations were measured by radioimmunoassay (Novo-Nordisk, Bagsvaerd, Denmark). Thyroid hormone (triiodothyronine, thyroxine [T_4], thyrotropin [TSH], and triiodothyronine-resin uptake) levels were measured by radioimmunoassay (Farmos, Turku, Finland). HbA_{1c} was analyzed by high-performance liquid chromatography. Plasma triglyceride, total cholesterol, and high-density lipoprotein (HDL) cholesterol were determined enzymatically by semiautomatic methods (Greiner; Boehringer, Mannheim, Germany). Routine analyses were performed at the Department of Clinical Chemistry of Hvidovre University Hospital (Technicon, Tarrytown, NY).

Body Composition and Fat Distribution

The waist to hip ratio was determined every 3 months during the study period. FFM was determined before and at the of the study by bioelectric-impedance analysis[21] (Animeter; HTS Engineering, Odense, Denmark) using the following formulas[22]: for men, FFM = $(0.279 \cdot Ht^2/R) + (0.245 \cdot BW) + (0.231 \cdot Ht) - (0.077 \cdot age) - 14.94$; and for women, FFM = $(0.279 \cdot Ht^2/R) + (0.181 \cdot BW) + (0.231 \cdot Ht) - (0.077 \cdot age) - 14.94$ (with FFM in kilograms, height (Ht) in centimeters, and resistance (R) in Ohms.

Muscle Biopsies and Enzymes

Before and after 6 months of treatment, muscle biopsies were performed during fasting conditions in a subgroup of 16 patients consisting of eight patients from the F group (of whom four were

Table 2. Metabolic Variables Before and After 12 Months' Treatment With F or P in Combination With a 5.0-MJ/d Diet (mean ± SD)

Variable	Baseline		12 Months	
	F	P	F	P
Glycemic regulation				
HbA_{1C} (%)	7.4 ± 2.2	6.8 ± 1.8	6.1 ± 1.8†	6.0 ± 1.6*
OGGT (mmol/L)				
0 min	10.1 ± 4.4	8.7 ± 2.3	7.5 ± 3.6	7.3 ± 2.5
120 min	15.2 ± 6.6	14.5 ± 4.5	9.7 ± 5.0*	11.0 ± 4.2*
Lipids (mmol/L)				
Cholesterol	6.8 ± 0.9	6.5 ± 2.2	6.9 ± 1.3	6.1 ± 1.2
HDL	1.05 ± 0.2	1.07 ± 0.3	1.1 ± 0.3*	1.2 ± 0.3*
Triglycerides	2.7 ± 2.0	2.7 ± 2.2	2.4 ± 1.4	2.3 ± 1.0
Thyroid function				
TSH (mU/L)	1.6 ± 1.3	1.8 ± 2.0	1.6 ± 0.6	1.7 ± 1.2
Free-T_4 index (nmol/L)	105.0 ± 23.5	116.0 ± 26.4	96.8 ± 14.7	103.5 ± 16.7*
Body composition				
Waist to hip ratio	0.98 ± 0.06	0.99 ± 0.04	0.97 ± 0.05	0.95 ± 0.04†‡
Lean body mass (kg)	60.3 ± 10.2	60.5 ± 9.2	55.4 ± 7.2†	58.6 ± 7.4*
Cardiovascular system				
Systolic BP (mm Hg)	141.5 ± 19.1	146.0 ± 26.1	140.0 ± 14.4	138.9 ± 18.6*
Diastolic BP (mm Hg)	90.0 ± 11.7	91.8 ± 15.5	83.3 ± 9.2	85.4 ± 16.1*
Heart rate (beats per min)	78.6 ± 11.4	77.4 ± 13.7	76.7 ± 11.7	73.1 ± 14.2

*$P < .005$ *v* baseline.

†$P < .001$ *v* baseline.

‡$P < .05$, F *v* P (Δ0-12 months).

women and five were subjects with IGT) and eight patients from the P group (of whom six were women and five were subjects with IGT). This point in time was chosen in order to have a sufficient number of patients, since not all patients were expected to participate in this procedure. Biopsies were taken under local anesthesia (1% lidocaine) using a Bergstrom biopsy needle through a small incision in the skin and muscle sheath above the vastus lateralis muscle. The biopsies, which contained 200 to 250 mg muscle tissue, were immediately (within 15 seconds) frozen in liquid nitrogen and stored at −80°C until analyses were performed. The defrosted biopsies were homogenized in an ice-cold buffer (1 mL/100 mg muscle) with a motor-driven nylon pestle (2,000 rpm). The homogenate was then centrifuged for 10 minutes at 3,200 × *g* at 4°C. The buffer contained 25 mmol/L HEPES, 4 mmol/L EDTA, 10 mmol/L NaF, 1 mmol/L benzamidine, 2 mmol/L phenylmethylsulfonyl fluoride, 900 KIU/mL aprotinin, and 1% Triton X-100, pH 7.4. Insulin receptors were solubilized and purified by wheat germ agglutination chromatography as described previously.[23]

Insulin receptor binding was measured as previously described, and the number of insulin-binding sites was determined with a Scatchard plot.[24] Insulin receptor kinase activity was measured as the ability of wheat germ agglutination–purified insulin receptors to phosphorylate the exogenous substrate poly(Glu^{4}Tyr^1) (Sigma Chemical, St Louis, MO). Insulin receptor kinase activity was adjusted for the number of insulin-binding sites in the eluate and expressed as femtomoles of phosphate per femtomoles of receptor per minute. GS activity is expressed as the concentration of the allosteric activator, glucose-6-phosphate (G6P), necessary to obtain half-maximal activation of the enzyme ($A_{0.5}$ for G6P).[23] Total GS activity is defined as the activity of the enzyme in the presence of a saturating concentration of G6P (6.7 mmol/L), and is expressed as nanomoles of uridine diphosphate glucose incorporated into glycogen per minute per milligram soluble protein in the homogenate.

Statistics

A two-sample *t* test was used for comparison of treatment groups, and a one-sample *t* test was used for comparison of differences between time periods. *P* values less than .05 were considered significant.

Data are presented as the mean ± SD unless otherwise stated. Stepwise multiple regression analyses were used to assess the relationship between the change in muscle enzymes and independent variables. Adverse drug events were evaluated by chi-square test with Yates correction. Statgraphics software (Graphic Software Systems, Rockville, MD) was used for the analyses.

RESULTS

Course

The patients were well matched at baseline, without significant differences between F and P groups regarding anthropometric characteristics (Table 1) or biochemical variables (Table 2), although glucose and HbA_{1c} levels were higher in the F group (nonsignificant). Patients with NIDDM had the same mean age and body weight as patients with IGT. There was no difference between treatment groups with regard to family history of NIDDM, nor were there any differences in smoking habits or alcohol consumption at baseline (data not shown).

During the course of the study, 11 patients dropped out (Table 3). Only two patients, one from each group, were withdrawn due to adverse drug events. A number of events were reported in both groups. Well-known serotonergic side effects such as asthenia and nausea occurred more frequently in the F group, but none of the differences in incidence between F and P groups were significant.

Table 3. Dropouts and Adverse Treatment Events During the Study

Parameter	F	P
Dropouts (n)		
Not showing up at visits	1	4
Patient's decision	3	1
Halitosis		1
Rash	1	
Adverse treatment events (n ≥ 3)		
Rhinitis	10	8
Asthenia	7	3
Nausea	7	4
Headache	4	1
Diarrhea	3	2
Gastroenteritis	3	
Tremor	3	
Vertigo	2	3
Injuries and accidents	3	3
Infections	10	11
Nervousness	1	3
Myalgia	1	2
Menstrual disorders	3	2
Sweating	3	

NOTE. There were no significant differences between treatment groups (chi-square test).

Weight Loss, Fat Distribution, and Body Composition

Both treatment groups lost a considerable amount of weight, with a nadir at 6 months (Fig 1). Weight loss was almost identical in both groups, and none of the differences were significant. After 6 months of treatment, weight loss was 11.4 ± 9.9 kg in the F group and 11.3 ± 9.5 kg in the P group. After 12 months, the F group had lost 10.1 ± 10.0 kg and the P group 9.4 ± 11.5 kg. When expressing the weight

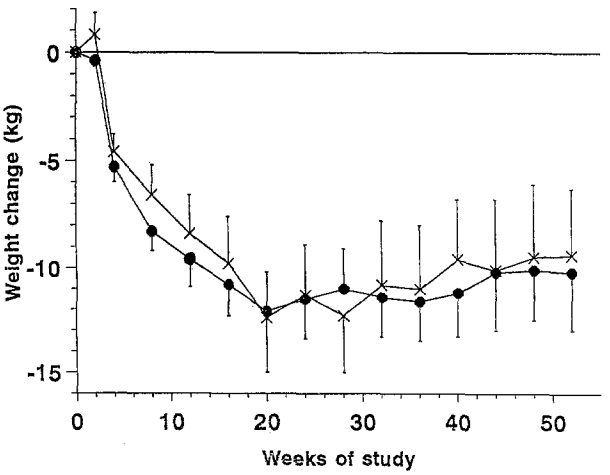

Fig 1. Body weight changes (mean ± SEM) in 40 obese patients with NIDDM or IGT during 52 weeks' treatment with (●) F 60 mg/d or (x) P in conjunction with a 5.0-MJ/d diet. Differences between treatment groups were all nonsignificant (*t* test).

change as a reduction in the overweight percentage, similar nonsignificant results were obtained (16.4% ± 9.1% *v* 14.8% ± 12.7%, F *v* P, respectively). During the study, waist to hip ratio declined significantly in the P group ($P < .05$), whereas the ratio was unchanged in the F group (Table 2). FFM tended to be more reduced in F subjects than in P subjects (4.9 *v* 1.9 kg), but the difference was not statistically significant (Table 2).

Glycemic Regulation

Glycemic regulation improved significantly in both treatment groups (Fig 2 and Table 2). In the F group, there was a tendency for a larger decline in HbA_{1c} and insulin levels ($P < .07$), but the difference only reached statistical significance for C-peptide levels at the 12-month visit (F, 0.5 ± 0.5 nmol/L; P, 0.1 ± 0.8 nmol/L; $P < .05$). Fasting glucose levels declined significantly in the F group during the study period (2.1 ± 3.6 mmol/L, $P < .05$), whereas levels were unchanged in the P group (0.8 ± 1.2 mmol/L, NS). The improvement in glucose tolerance also tended to be more pronounced in F patients, but the differences were not significant (Table 3). There were no significant differences between IGT and NIDDM patients with respect to changes in glucose, insulin, or C-peptide levels.

Muscle Enzymes

The influence of weight loss and the trial medication on basal insulin receptor kinase activity and GS activity is shown in Fig 3. Total GS activity increased significantly in the F group after 6 months of treatment by 31% (from 28.5 ± 2.2 to 41.4 ± 3.7 nmol/min/mg protein, $P < .01$), whereas the increase in the P group was much less and nonsignificant (Fig 3). However, the activities were still less than levels for normal controls (45.7 ± 3.2 nmol/min/mg protein). Differences between F and P groups did not reach statistical significance (*t* test), whereas drug treatment was found to be the only significant factor ($R^2 = .27, P < .05$) in a multiple regression analysis with diabetic state (NIDDM or IGT), weight loss, and changes in plasma insulin and glucose levels included. Sensitivity of GS to its allosteric activator G6P ($A_{0.5}$ for G6P) was not influenced by the drug treatment (Fig 3). In a multiple regression analysis, weight loss and change in fasting glucose from baseline to 6 months explained more than 78% of the variation in the change of GS activity ($P < .005$). Basal insulin receptor kinase activity was not affected by the weight loss, and no difference was found between treatment groups.

Other Measurements

The lipid profile was not improved during the study period, except for a small increase in HDL in both groups (Table 2). Thyroid function, as estimated by plasma TSH and the free-T_4 index, was not affected by the drug. Systolic and diastolic blood pressures declined only in the P group ($P < .05$). Heart rate was not significantly reduced in either group.

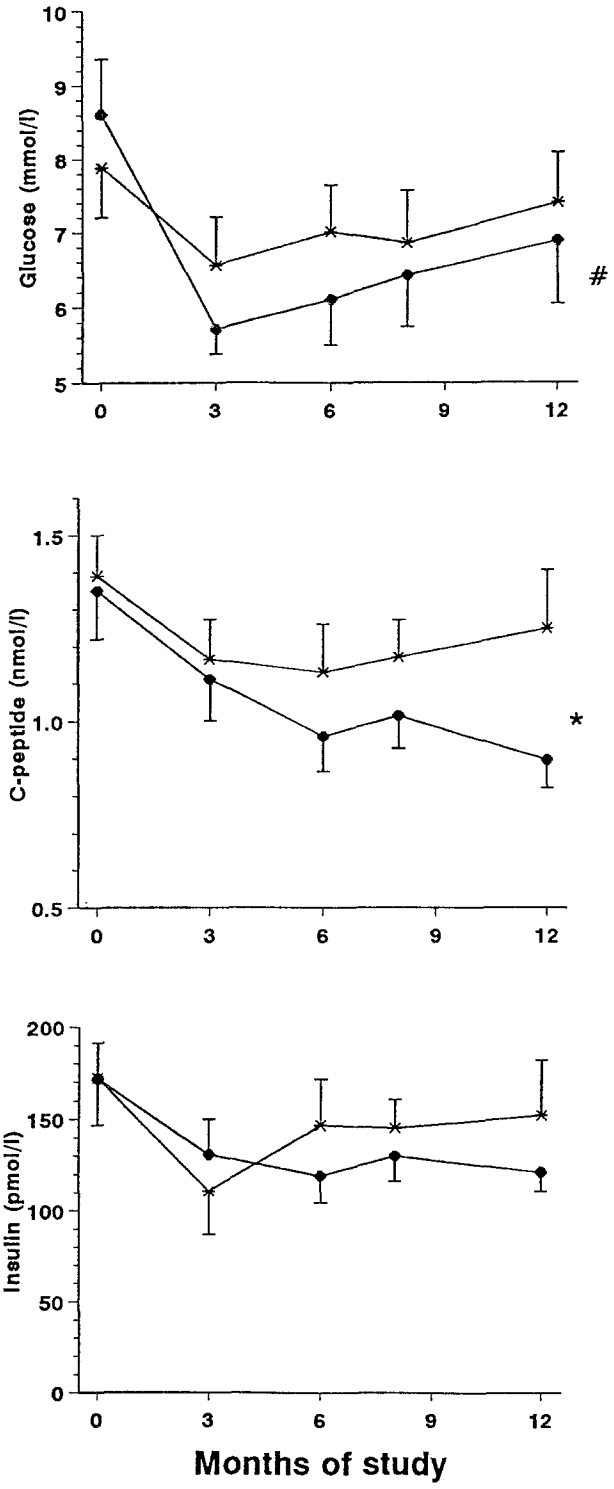

Fig 2. Change in fasting levels (mean ± SEM) of plasma glucose, C-peptide, and insulin during 52 weeks' treatment with (●) F or (x) P in obese patients with NIDDM or IGT. *$P < .05$, P *v* F. #$P < .05$, pretreatment *v* 12 months.

DISCUSSION

In the present 12-month, double-blind study, we have shown that long-term treatment with F results in an improvement of glycemic control, since fasting levels of

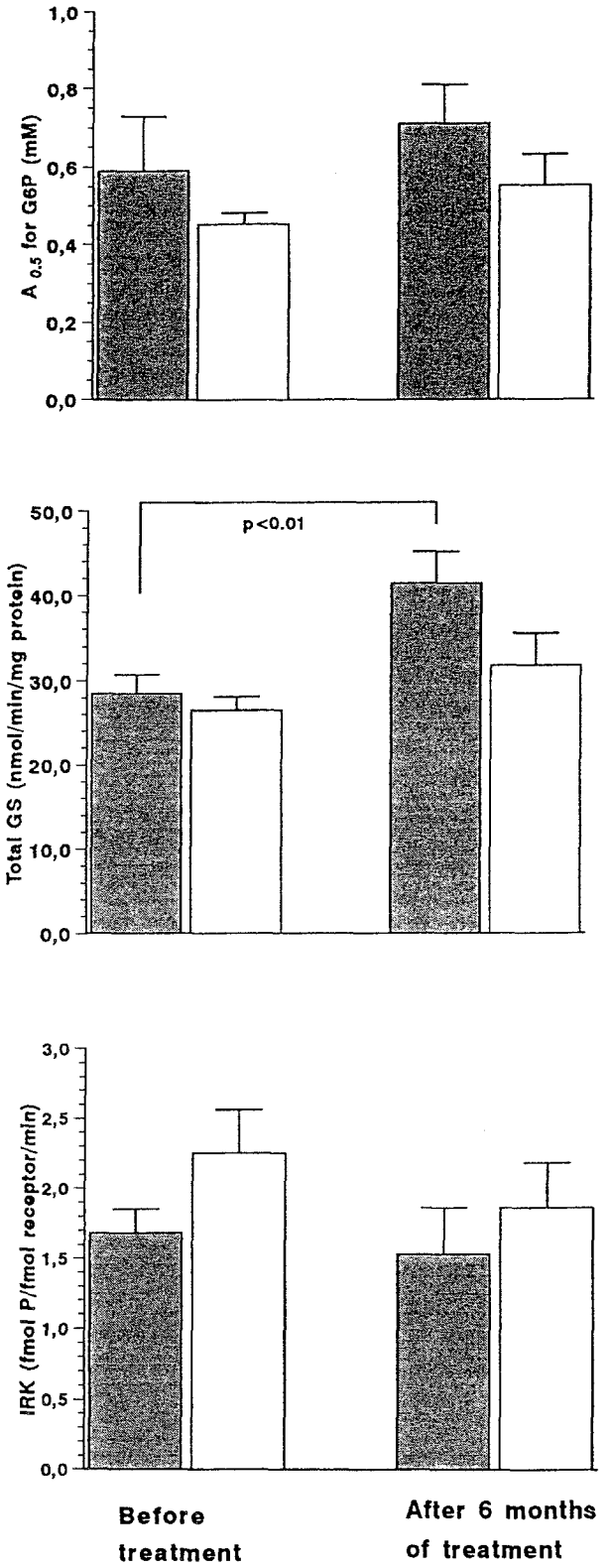

Fig 3. Basal GS activity and insulin receptor kinase (IRK) activity (mean ± SEM) in skeletal muscle tissue from obese patients with NIDDM or IGT before and at the end of 6-month treatment with (■) F (n = 8) or (□) P (n = 8). *$P < .01$ for difference between pretreatment and 6 months.

C-peptide and glucose were reduced after 1 year of treatment ($P < .05$). Furthermore, there was a tendency for a larger reduction in fasting insulin and HbA_{1c} levels and an improved glucose tolerance in the F group as compared with the P group. These changes are probably not secondary to alterations in the diet, since dietary intakes obtained from food records before and after 6 months of treatment were similar in F and P groups (data not shown). In opposition to other long-term treatment studies with obese diabetic subjects,[15] the interpretation of this study is not biased by differences in weight loss between treatment groups. Furthermore, it should be emphasized that patients were weight-stable when muscle biopsies were taken at the 6-month visit. The mechanisms behind the improvement in insulin action are still not understood. In a 4-week study with obese subjects with and without NIDDM, it was shown that F improved peripheral and hepatic insulin action during a hyperinsulinemic-euglycemic clamp.[8] Studies with dexfenfluramine[14-16] have confirmed these results, but the mechanisms are still not elucidated. In the present study, we found a larger increase in fasting GS in F patients, which might be of importance since glycogen storage is a quantitatively important pathway for nonoxidative glucose metabolism.[18] The lack of effect of both diet and drug treatment on basal muscle insulin receptor kinase activity has also been described in other studies after dietary[24] or antidiabetic pharmacological[23] therapy, whereas an improvement was seen after weight loss in isolated adipocytes.[25] The levels found in this study are comparable to levels in normal controls. The weight losses obtained in the actual study are larger than described in previous short-term studies with similar types of patients,[7,9] but are consistent with two long-term studies of nondiabetic obese patients[4,26] in which dietary counseling and behavior modification were emphasized as important parts of the program. In contrast to these studies, both the weight loss obtained in the P group and the adherence to the program were significantly greater in our study, despite repeated invasive procedures such as muscle biopsies. This was probably due to the efficient program, which includes continuous instruction in diet and behavioral modification in small, uniform groups. Similar results concerning P patients have been obtained in other weight loss studies from our center.[27,28] It should be noted that maximal weight loss was reached and stabilized after 6 months of treatment. The drug was well tolerated, since only two patients withdrew from the study due to suspected adverse drug reactions (Table 3). Adverse treatment events were within acceptable limits and comparable to those described in other studies.[4,10] The effect of F treatment on body composition has been studied in a group of abdominally obese male subjects by nuclear magnetic resonance imaging.[20] Treatment with F resulted in a greater weight loss than with P, but also in a greater loss of FFM (40%) than P (9%). Our results showed the same tendency, although the differences did not reach statistical significance. In the P group, loss of FFM was similar to what has been described in other studies using bioelectrical-impedance analysis.[29] The larger decline in waist to hip ratio

found in P patients versus F patients ($P < .05$) has not been described previously, but is in accordance with the changes in visceral fat found in the nuclear magnetic resonance study.[20] The lack of effect of F on visceral adipose tissue might also explain the lack of influence on the lipid profile. The mechanisms behind these changes in body composition and fat distribution are unknown, but it is possible that they may be attributed to the diminished effect of the drug during long-term weight control.

It has been shown that dexfenfluramine, independent of energy restriction, can decrease blood pressure in obese, normotensive subjects through a diminished sympathetic nervous system activity.[30,31] Our results do not confirm these results during long-term treatment with F, since no reduction was found in blood pressure, either supine or erect, or in heart rate. The weight-reducing effect of F found in other studies has been suggested to be due to an increased thermogenesis or lipid oxidation, but only one study[32] has addressed this question, without being able to confirm this hypothesis.

In conclusion, long-term treatment with F seems to improve glycemic regulation in obese patients with NIDDM or IGT, possibly by an increase in total GS activity in skeletal muscle tissue, independent of weight loss.

ACKNOWLEDGMENT

We are grateful to Professor Flemming Quaade, MD, for valuable support in initiation of the study, and to clinical dieticians Lis Kristoffersen and Hanne Foged and laboratory technician Inge Timmermann for their skillful assistance.

REFERENCES

1. Garattini S, Buczko W, Jori A, et al: The mechanism of action of d-fenfluramine. Postgrad Med J 51:27-32, 1975 (suppl)

2. Pijl H, Koppeschaar PF, Willekens FLA, et al: Effect of serotonin reuptake inhibition by fluoxetine on body weight and spontaneous food choice in obesity. Int J Obes 15:237-242, 1991

3. Levine LR, Enas GG, Thompson WL, et al: Use of fluoxetine, a selective serotonin-uptake inhibitor, in the treatment of obesity: A dose-response study. Int J Obes 13:635-645, 1989

4. Darga LL, Carrol-Michals L, Botsford SJ, et al: Fluoxetine's effect on weight loss in obese subjects. Am J Clin Nutr 54:321-325, 1991

5. Goldstein DJ, Rampey AH Jr, Dornseif BE, et al: Fluoxetine: A randomized clinical trial in the maintenance of weight loss. Obes Res 1:92-98, 1993

6. Byerley WF: Fluoxetine, a selective serotonin reuptake inhibitor for the treatment of major depression. J Clin Psychopharmacol 8:12-115, 1988

7. Kutnowski M, Daubresse JC, Friedman H, et al: Fluoxetine therapy in obese diabetic and glucose intolerant patients. Int J Obes 16:S63-S66, 1992

8. Potter van Loon BJ, Radder JK, Frolich M, et al: Fluoxetine increases insulin action in obese nondiabetic and in obese non–insulin-dependent diabetic individuals. Int J Obes 16:79-85, 1992

9. Gray DS, Fujioka K, Devine W, et al: Fluoxetine treatment of the obese diabetics. Int J Obes 16:193-198, 1992

10. Wise SD: Clinical studies with fluoxetine in obesity. Am J Clin Nutr 55:181S-184S, 1992

11. Guy-Grand B, Apfelbaum M, Crepaldi G, et al: International trial of long-term dexfenfluramine in obesity. Lancet 2:1142-1145, 1989

12. Mathus-Vliegen EMH, Van de Vorde K, Kok AME, et al: Dexfenfluramine in the treatment of severe obesity: A placebo-controlled investigation of the effects on weight loss, cardiovascular risk factors, food intake and eating behaviour. J Int Med 232:119-127, 1992

13. Turtle JR, Burgess JA: Hypoglycemic action of fenfluramine in diabetes mellitus. Diabetes 22:858-867, 1973

14. Scheen AJ, Paolisso G, Salvatore T, et al: Improvement of insulin-induced glucose disposal in obese patients with NIDDM after 1-wk treatment with d-fenfluramine. Diabetes Care 14:325-332, 1991

15. Damsbo P, Madsbad S, Henriksen JE, et al: Effect of weight loss and dexfenfluramine on glycemic control and glucose metabolism in obese NIDDM patients. Diabetes 40:307A, 1991 (suppl 1, abstr)

16. Andersen PH, Richelsen B, Bak J, et al: Influence of short-term dexfenfluramine therapy on glucose and lipid metabolism in obese non-diabetic patients. Acta Endocrinol (Copenh) 128:251-258, 1993

17. Bogardus C, Lillioja S, Stone K, et al: Correlation between muscle glycogen synthase activity and in vivo insulin action in man. J Clin Invest 73:1185-1190, 1984

18. Shulmann GI, Rothman DL, Jue T, et al: Quantitation of muscle glycogen synthesis in normal subjects and subjects with non–insulin-dependent diabetes by ^{13}C nuclear magnetic resonance spectroscopy. N Engl J Med 322:223-228, 1989

19. Caro JF, Sinha MK, Raju SM, et al: Insulin receptor kinase in human skeletal muscle from obese subjects with and without noninsulin dependent diabetes. J Clin Invest 79:1330-1337, 1987

20. Visser M, Seidell JC, Koppeschaar HPF, et al: The effect of fluoxetine on body weight, body composition and visceral fat accumulation. Int J Obes 17:247-253, 1993

21. Lukaski HC, Johnson PE, Bolonchuck WW, et al: Assessment of fat-free mass using bioelectrical impedance measurements of the human body. Am J Clin Nutr 41:810-817, 1985

22. Heitmann BL: Prediction of body water and fat in adult Danes from measurement of electrical bioimpedance. A validation study. Int J Obes 14:789-802, 1990

23. Bak JF, Schmitz O, Schwartz Sørensen N, et al: Postreceptor effects of sulfonylurea on skeletal muscle glycogen synthase activity in type II diabetic patients. Diabetes 38:1343-1350, 1989

24. Bak JF, Møller N, Schmitz O, et al: In vivo insulin action and muscle glycogen synthase activity in type 2 (non–insulin-dependent) diabetes mellitus: Effects of diet treatment. Diabetologia 35:777-784, 1992

25. Freidenberg GR, Suter SL, Henry RR, et al: Reversibility of defective adipocyte insulin receptor kinase activity in non–insulin-dependent diabetes mellitus. Effect of weight loss. J Clin Invest 80:1398-1406, 1988

26. Marcus MD, Wing RR, Ewing L, et al: A double-blind, placebo-controlled trial of fluoxetine plus behaviour modification in the treatment of obese binge-eaters and non–binge-eaters. Am J Psychiatry 147:876-881, 1990

27. Andersen T, Astrup A, Quaade F: Dexfenfluramine as adjuvant to a low-calorie formula diet in the treatment of obesity: A randomized clinical trial. Int J Obes 16:35-40, 1992

28. Astrup A, Breum L, Toubro S, et al: The effect and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine and placebo in obese subjects on an energy restricted diet. A double blind trial. Int J Obes 16:269-277, 1992

29. Saunders NH, Al-Zeibak S, Ryde SJS, et al: The composition of weight loss in dieting obese females by electrical methods. Int J Obes 17:317-322, 1993

30. Andersson B, Zimmermann ME, Hedner T, et al: Haemodynamic, metabolic and endocrine effects of short-term dexfenfluramine treatment in young, obese women. Eur J Clin Pharmacol 40:249-254, 1991

31. Kolanowski J, Younis LT, Van Butsele, et al: Effect of dexfenfluramine treatment on body weight, blood pressure and noradrenergic activity in obese hypertensive patients. Eur J Clin Pharmacol 42:599-606, 1992

32. Stinson JC, Murphy CM, Andrews JF, et al: An assessment of the thermogenic effects of fluoxetine in obese subjects. Int J Obes 16:391-395, 1992