Effects of Dietary Treatment Alone or Diet With Voglibose or Glyburide on Abdominal Adipose Tissue and Metabolic Abnormalities in Patients With Newly Diagnosed Type 2 Diabetes

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OBJECTIVE — To examine the effects of diet and diet with voglibose or glyburide on abdominal adiposity and metabolic abnormalities in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 36 Japanese patients with newly diagnosed type 2 diabetes (50.8 ± 8.6 years of age, BMI 24.5 ± 3.5 kg/m^2) and 273 normal control subjects were studied. The patients were treated for 3 months with diet alone (30 kcal/kg per day) (n = 15), diet with voglibose (n = 12), or diet with glyburide (n = 9). They underwent 75-g oral glucose tolerance testing, assessment of insulin sensitivity (SI), and acute insulin response (AIR) with intravenous glucose tolerance testing based on the minimal model, and measurement of abdominal visceral adipose tissue area (VAT) and subcutaneous adipose tissue area (SAT) by computed tomography before and after treatment.

RESULTS — The diabetic patients had comparable SAT but larger VAT than the control subjects. With a mean weight loss of 2–3 kg, VAT and SAT were decreased similarly in all treatment groups. The VAT-to-SAT ratio was decreased only in the voglibose group. Glycemic control and serum lipid profiles were improved in all groups. Changes in glycemic control after diet were closely correlated with changes in VAT but not with changes in SAT. SI and AIR were unchanged in the diet group but were improved in the voglibose and glyburide groups.

CONCLUSIONS — In Japanese patients with newly diagnosed type 2 diabetes who were relatively lean but had excess VAT, diet with or without voglibose or glyburide effectively reduced VAT. Decrease in VAT was closely associated with improvement of glycemic control with diet. Additional use of voglibose or low-dose glyburide had no detrimental effects on abdominal adiposity and had beneficial effects on SI and AIR.

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Abbreviations: AIR, acute insulin response; FSIVGTT, frequently sampled intravenous glucose tolerance test; SAT, subcutaneous adipose tissue area; SI, insulin sensitivity; TAT, total abdominal adipose tissue area; VAT, visceral adipose tissue area.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Obesity is a major risk factor for type 2 diabetes (1). Over the last two decades, a number of investigators have demonstrated that the anatomical distribution of adipose tissue may play an important role in the pathophysiology of glucose intolerance and other obesity-related metabolic abnormalities (2). Cross-sectional studies have demonstrated increased visceral fat deposition in Caucasian (3) and Japanese-American (4) patients with type 2 diabetes compared with nondiabetic control subjects. More importantly, Boyko et al. (5) recently reported that the amount of visceral fat was a strong predictor of future development of type 2 diabetes, independent of BMI. Problems related to abdominal adipose tissue may not be confined to grossly obese people. The concept of "metabolically obese, normal weight individuals" was proposed by Ruderman et al. (6). Abdominal adipose tissue was an important etiological component of the concept.

Management of obesity is a challenging problem for clinicians. All agree that weight loss is the most effective intervention for an overweight patient with type 2 diabetes (7), but it remains unclear whether loss of fat anywhere is equally effective or whether loss of abdominal adipose tissue has any specific role in metabolic control in patients with type 2 diabetes.

As clearly shown in the U.K. Prospective Diabetes Study (UKPDS) (8), antidiabetic medication may, depending on the drugs chosen, have an adverse effect on body weight. However, very little is known about the effect of antidiabetic drugs on the distribution of abdominal adipose tissue. In this study, we examined the effect of 3-month dietary treatment on abdominal adiposity, insulin resistance, and other metabolic abnormalities in patients with newly diagnosed type 2 diabe-

Table 1—*BMI and abdominal adipose tissue area*

	Diabetic patients		Control subjects	
	Men	Women	Men	Women
n	24	12	250	23
Age (years)	48.7 ± 8.3	55.0 ± 7.8	50.9 ± 6.6	53.7 ± 5.4
BMI (kg/m^2)	24.2 ± 3.9†	25.0 ± 2.8*	22.4 ± 1.7	21.9 ± 1.6
VAT (cm^2)	128.9 ± 47.3†	119.5 ± 27.2*	91.4 ± 36.2	83.8 ± 37.2
SAT (cm^2)	126.4 ± 58.2	219.8 ± 73.6	107.1 ± 36.0	187.5 ± 56.3

Data are means ± SEM. *$P < 0.01$; †$P < 0.001$ vs. respective sex-matched control subjects.

tes. In addition, we compared the effects of addition of voglibose, an α-glucosidase inhibitor, or glyburide to diet with those of dietary treatment alone.

RESEARCH DESIGN AND METHODS

Subjects and protocol

The study subjects were 36 patients with newly diagnosed type 2 diabetes (12 women, 24 men). Age was 50.8 ± 8.6 years (31–68) and BMI was 24.5 ± 3.5 kg/m^2 (19.3–39). They were diagnosed between 1995 and 1997 at Kizawa Memorial Hospital, which is situated in an urban area of Gifu, Japan. They were invited and entered the study after giving informed consent. The study was approved by the Ethics Committee of the hospital. A total of 32 patients were randomly assigned to one of the following three treatment groups. They were treated on an outpatient basis for 3 months with diet alone ($n = 11$), diet plus voglibose ($n = 12$), or diet plus glyburide ($n = 9$). Energy intake was 30 kcal/kg of ideal body weight per day. They consumed 60% of total energy as carbohydrate, 20% as fat, and 20% as protein. They underwent counseling on diet twice before treatment and monthly thereafter. Voglibose, an α-glucosidase inhibitor, at a dose of 0.9 mg/day was taken immediately before each meal, and glyburide (1.25 mg/day) was administered after breakfast. Each patient underwent a series of examinations at baseline and repeated them after 3 months of treatment. After completing the randomized phase of the study, four patients were consecutively assigned to the diet group to facilitate analysis of correlations between the changes in abdominal adipose tissue and glycemic control with diet. They were not included in any other analyses that compared three different treatment groups. These four patients were treated and evaluated in a fashion similar to the other patients in the diet group.

Abdominal subcutaneous adipose tissue area (SAT) and visceral adipose tissue area (VAT) were measured by computed tomography with a HiSpeed Advantage ZE (General Electric Medical Systems, Milwaukee, WI) at the level of the umbilicus. The window was set between −30 and −190 Hounsfield Units (9). For reference, computed tomography measurements of VAT and SAT were performed in men ($n = 250$) and women ($n = 23$) who participated in a periodic health check program conducted at Matsunami General Hospital (10) and had normal weight (BMI 18.5–24.9) and normal glucose tolerance on a 75-g oral glucose tolerance test. Age was matched between the study subjects and the control subjects. Insulin sensitivity and acute insulin response (AIR) were estimated by frequently sampled intravenous glucose tolerance test (FSIVGTT). Patients who fasted overnight received an intravenous bolus of 0.3 g glucose per kg body wt. Human regular insulin (0.05 units per kg body wt) was administered intravenously 20 min after the glucose bolus. Plasma glucose and insulin were measured for 29 samples obtained between −15 and 180 min. The control subjects were included solely for the purpose of comparison of VAT and SAT. FSIVGTT was not performed in the control subjects. Insulin sensitivity (SI) was calculated based on Bergman's minimal model (11). Incremental insulin area over the basal level from 0 to 6 min was calculated and defined as AIR. A blood sample was obtained after an overnight fast for measurements of serum total cholesterol, HDL cholesterol, triglycerides, and free fatty acids. Plasma glucose and insulin levels were measured by the glucose oxidase method and double-antibody radioimmunoassay, respectively.

Statistical methods

Values are expressed as means ± SD. Statistical analyses were performed with StatView for Windows, Version 5.0 (SAS Institute, Cary, NC). Normalization of distribution was performed for SI and AIR by square root transformation (12) and for triglycerides by logarithmic transformation. The resultant means were root

Table 2—*Changes in BMI and abdominal adipose tissue after 3-month treatment*

	Diet alone	Voglibose	Glyburide
n (women/men)	11 (4/7)	12 (3/9)	9 (3/10)
Body weight (kg)			
Before	62.2 ± 6.5	62.9 ± 5.2	66.4 ± 14.4
After	59.5 ± 6.4†	60.4 ± 4.6†	63.3 ± 13.1†
BMI (kg/m^2)			
Before	24.0 ± 2.2	24.7 ± 3.1	24.3 ± 2.3
After	22.9 ± 2.0†	23.6 ± 2.8†	23.2 ± 2.0†
VAT (cm^2)			
Before	119.2 ± 32.7	128.3 ± 42.5	127.6 ± 41.6
After	91.5 ± 38.4†	88.9 ± 33.8‡	88.8 ± 36.5†
Changes	27.7 ± 20.1	39.4 ± 20.4	38.8 ± 27.4
SAT (cm^2)			
Before	124.7 ± 41.6	165.1 ± 95.0	167.7 ± 66.1
After	103.7 ± 42.8†	135.8 ± 79.4*	138.7 ± 75.2*
Changes	20.9 ± 21.8	29.3 ± 32.8	29.0 ± 29.1
VAT-to-SAT ratio			
Before	1.12 ± 0.73	0.98 ± 0.50	0.86 ± 0.37
After	0.99 ± 0.48	0.81 ± 0.38*	0.76 ± 0.41

Data are means ± SEM. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$ after vs. before.

Table 3—*Changes in metabolic parameters after 3-month treatment*

	Diet alone	Voglibose	Glyburide
n (women/men)	11 (4/7)	12 (3/9)	9 (3/6)
Fasting glucose (mmol/l)			
Before	8.4 ± 1.3	10.7 ± 3.9	9.9 ± 2.8
After	7.5 ± 1.1*	7.4 ± 0.9*	7.1 ± 1.6*
Fasting insulin (pmol/l)			
Before	60.8 ± 44.5	51.4 ± 12.2	50.3 ± 17.8
After	39.4 ± 13.3	36.0 ± 10.2†	46.7 ± 14.8
HbA_{1c} (%)			
Before	8.3 ± 1.3	8.0 ± 1.7	9.1 ± 2.5
After	6.6 ± 0.7‡	6.3 ± 0.9‡	6.1 ± 1.3†
Total cholesterol (mmol/l)			
Before	5.2 ± 0.9	5.6 ± 1.3	5.3 ± 1.5
After	4.7 ± 1.0*	4.4 ± 0.9‡	4.0 ± 1.1*
HDL cholesterol (mmo/l)			
Before	1.4 ± 0.5	1.6 ± 0.4	1.4 ± 0.3
After	1.6 ± 0.4	1.4 ± 0.5	1.4 ± 0.5
Triglyceride (mmol/l)			
Before	1.9 (1.5–2.5)	2.0 (1.2–3.1)	1.8 (1.2–2.5)
After	1.3 (0.9–2.0)	1.2 (0.9–1.7)†	1.3 (0.8–1.9)†
Free fatty acids (μmol/l)			
Before	741 ± 186	736 ± 127	870 ± 292
After	544 ± 145†	575 ± 140‡	664 ± 272*

Data are means ± SEM. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$ after vs. before.

transformed or antilogarithmically transformed and expressed with the 25th and 75th percentiles. Values before and after treatment within each group were analyzed by the paired Student's *t* test. Comparisons between groups were performed using ANOVA with Tukey-Kramer post hoc testing.

RESULTS

BMI and abdominal adipose tissue area before and after treatment

As shown in Table 1, the patients with newly diagnosed type 2 diabetes had significantly higher BMI and larger VAT than the control subjects with respective gender. The patients had ~40% larger VAT than the control subjects. There was no difference in SAT between the patients and the control subjects.

Changes in body weight, BMI, VAT, and SAT after 3-month treatments are shown in Table 2. After treatment, the three groups of patients had similar weight losses (diet group 2.7 ± 2.8, voglibose group 2.6 ± 2.2, glyburide group 3.1 ± 2.4 kg). Percent reductions of VAT were 25.8 ± 20.7% for the diet group, 30.7 ± 12.5% for the voglibose group, and 30.2 ± 20.1% for the glyburide group. There were no differences between the groups. Similarly, the percent reduction of SAT in the diet-only group (17.2 ± 24.0%) was comparable to the value in the voglibose group (16.3 ± 19.6%) and the glyburide group (19.3 ± 16.9%). In separate analyses for men, there were no differences in the percent reduction of VAT and SAT among the three groups (data not shown). The number of female patients in each group was too small for statistical analysis. The patients treated with voglibose had a significantly lower VAT-to-SAT ratio after treatment than before treatment. The other two groups exhibited similar trends, but their changes did not reach statistical significance. When the three groups of patients were considered together as a whole group and compared with the control subjects, the mean values of BMI (22.7 ± 2.1 kg/m^2) and VAT (91.1 ± 39.9 cm^2) for the group of all male patients ($n = 24$) after 3 months of treatment were no longer different from those of male control subjects.

On the other hand, the female patients ($n = 12$) still had higher BMI (24.4 ± 2.3 kg/m^2) than the control subjects, even after treatment. Nonetheless, VAT in these patients (86.8 ± 22.1 cm^2) was not significantly different from the value for female control subjects.

Metabolic changes after treatment

Fasting plasma glucose and HbA_{1c} were significantly reduced after treatment in each group (Table 3). There were no significant differences in posttreatment gly-

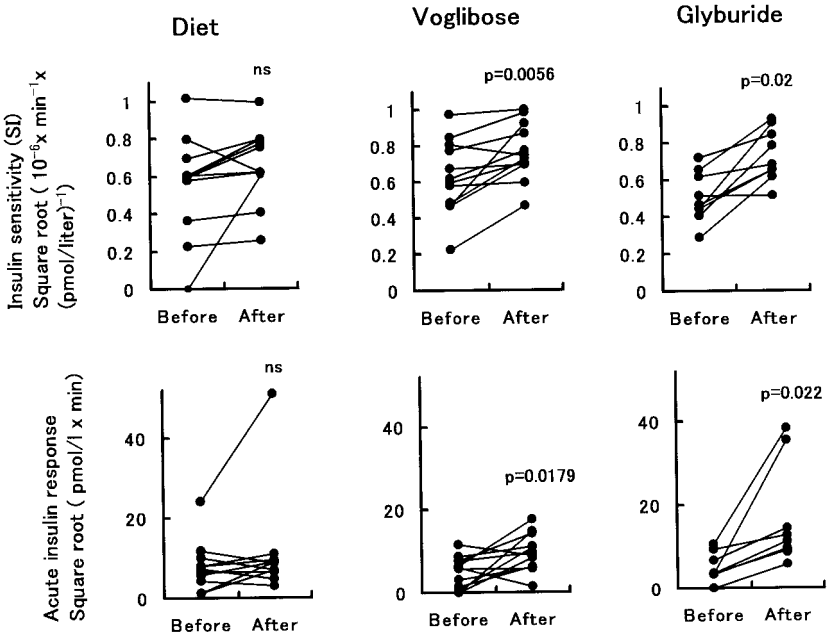

Figure 1—*Changes in SI* (top) *and AIR* (bottom) *before to after treatment in each group of patients. SI and AIR were normalized by square root transformation.*

cemic control levels among the three groups.

As shown in Fig. 1, both SI and AIR were improved by treatment with either voglibose or glyburide. Although the patients treated with diet alone also exhibited similar trends in changes in these parameters, their differences did not reach statistical significance.

The levels of serum total cholesterol and free fatty acids were decreased in all groups of patients, regardless of treatment modalities. Serum triglyceride levels were significantly decreased by treatment with voglibose or glyburide but not by diet alone. HDL cholesterol did not change significantly in any of the three treatment groups.

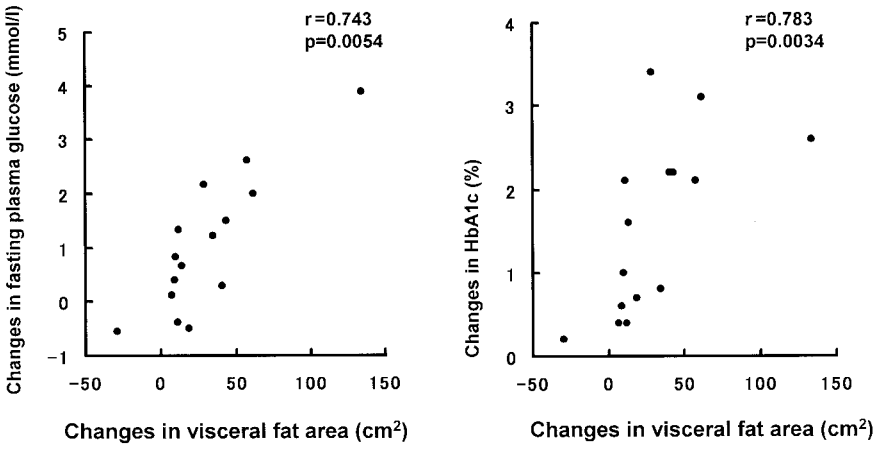

Figure 2—*Association between changes in VAT and changes in fasting plasma glucose* (left) *and in* HbA_{1c} (right) *in the group of patients treated with diet alone.*

Correlations between metabolic improvements and changes in abdominal adiposity in patients treated with diet alone

To determine the relation between abdominal adipose tissue and the effects of diet on glycemic control, correlations between metabolic improvements and the amounts of reduction in abdominal adipose tissue area were analyzed for the patients treated with diet alone. To this end, changes in VAT, SAT, and total abdominal adipose tissue area (TAT) (TAT = VAT + SAT) before and after diet were calculated, and correlations between them and changes in glycemic control were analyzed. Eleven randomized and four nonrandomized patients were analyzed together. Changes in TAT were correlated with changes in fasting plasma glucose (0.714, $P = 0.0075$) as well as those in HbA_{1c} (0.633, $P = 0.018$). Notably, changes in VAT were associated with the changes in fasting plasma glucose and HbA_{1c} (Fig. 2), but changes in SAT were not associated with changes in either fasting plasma glucose (0.421, NS) nor HbA_{1c} (0.227, NS).

CONCLUSIONS — We found that relatively lean Japanese patients with newly diagnosed type 2 diabetes had increased deposition of VAT. Through diet with or without voglibose or glyburide for 3 months, which resulted in a mean weight loss of 3.2 ± 3.4 kg, VAT in the patients became comparable to that in normal-weight control subjects. Therefore, 3-month dietary treatment with small to moderate weight loss was very effective in decreasing excess VAT in this patient population.

Although there is much concern regarding the effect of antidiabetic medications on body weight, little is known about their effects on abdominal adipose tissue. Several investigators have demonstrated that thiazolidinediones, a new class of insulin-sensitizing antidiabetic drugs, increase SAT with decrease or no change in VAT (13,14). In our study, neither voglibose, an α-glucosidase inhibitor, nor glyburide adversely affected either diet-induced weight loss or reduction in VAT. Although α-glucosidase inhibitors may, in large doses, cause malabsorption and thus aid weight reduction, they do not affect body weight in clinical doses (7). In our study, although changes in VAT and SAT themselves did not differ among the three groups of patients, VAT-to-SAT ratio decreased only in the voglibose group. This may suggest preferential loss of VAT in the voglibose-treated patients. It may be that long-term treatment with this drug significantly decreases VAT. The explanation of this effect is unknown. It is often argued that sulfonylurea leads to weight gain. We found no detrimental effects of glyburide on either body weight or abdominal adipose tissue. This may be related to the fact that we used low doses of glyburide for a short period of time while patients had just started diet, and their adherence to it should have been better than on later occasions. The dose of glyburide was determined according to the design of the study, which intended to compare the effects of diet alone and diet plus glyburide in treatment-naïve patients. In clinical practice, glyburide is generally used much later and at a higher dose; our results cannot be applied to such a clinical situation.

Three-month treatment with diet alone or with voglibose or glyburide effectively improved glycemic control, with a mean decrease in HbA_{1c} of ~2%. Interestingly, improvement in glycemic control after diet was closely correlated with decrease in VAT. Markovic et al. (15) previously demonstrated that the effect of 4W energy restriction on glycemic control was mediated by decrease in abdominal adipose tissue as measured by dual-energy X-ray absorptiometry. Their methodology did not enable them to differentiate VAT from SAT. We extended their findings. Loss of VAT but not SAT was an important determinant of metabolic control with dietary treatment.

We demonstrated that diet supplemented with voglibose or glyburide improved both insulin resistance and β-cell dysfunction, two major abnormalities of type 2 diabetes. Because the patients treated with diet alone had no statistically significant changes in SI and AIR, it is likely that voglibose and glyburide had additive effects with diet in improving SI and AIR. Decrease in glucose toxicity due to improved glycemic control is a possible explanation for the observed improvements. However, because posttreatment glycemic control levels were similar among the three groups of patients, other mechanisms may be involved. For example, increased release of glucagon-like peptide 1 after voglibose treatment has

been reported (16). Glucagon-like peptide 1 has been reported to enhance insulin secretion (17) and SI (18). This may explain the increase in SI and AIR in the voglibose-treated patients. On the other hand, extrapancreatic action of sulfonylureas (19) may contribute to the increased SI in the glyburide group.

In conclusion, relatively lean Japanese patients with newly diagnosed type 2 diabetes had increased VAT. Improvement in glycemic control by diet was closely associated with decrease in VAT. Supplement with voglibose or low-dose glyburide had no detrimental effects on abdominal fat and had beneficial effects on SI and AIR.

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