Bezafibrate Reduces Blood Glucose in Type 2 Diabetes Mellitus

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The clinical efficacy of bezafibrate was examined with special reference to glucose metabolism in patients with type 2 diabetes mellitus (DM2). In protocol 1, 342 patients with DM2 and hyperlipidemias were randomly divided into 2 groups, 16-week bezafibrate treatment (n = 174) and no bezafibrate treatment (n = 168). In protocol 2, 20 DM2 patients were randomly divided into 2 groups, 8-week bezafibrate treatment (n = 10) and no bezafibrate treatment (n = 10), and a meal tolerance test (MTT) was performed. In protocol 1, bezafibrate treatment significantly reduced the fasting levels of triglyceride (TG) by 50% ± 1.6%, total cholesterol (TC) by 12% ± 1.1%, plasma glucose (PG) from 151.3 ± 3.5 to 128.6 ± 3.4 mg/dL, and hemoglobin A_{1c} (HbA_{1c}) from 7.2% ± 0.1% to 6.9% ± 0.1%, and significantly increased high-density lipoprotein cholesterol (HDL-C) by 20% ± 0.8%. In protocol 2, fasting TG, PG, and insulin levels were significantly reduced by bezafibrate treatment. Moreover, in the MTT, postprandial increments of TG were significantly blunted after bezafibrate treatment, whereas postprandial PG and insulin levels were not significantly changed. Leptin levels were significantly decreased, while tumor necrosis factor alpha (TNF-α) levels were not changed. In conclusion, both hyperglycemia and hyperlipidemia can be improved by bezafibrate treatment in DM2.

PATIENTS WITH type 2 diabetes mellitus (DM2) frequently have the complication of dyslipidemia, especially hypertriglyceridemia.[1] Hyperinsulinemia, glucose intolerance, hypertriglyceridemia, and body fat accumulation are also associated with DM2, and are risk factors for the development of atherosclerosis.[2,3] Adipose tissue yields free fatty acids (FFAs) and secretes adipocytokines such as tumor necrosis factor alpha (TNF-α) and leptin that have been shown to affect glucose and lipid metabolism.[4-9]

Recently, it has been reported that the gene transcription factor peroxisome proliferator–activated receptor (PPAR) plays an important role in glucose and lipid metabolism.[10] PPAR-α, an isoform of PPAR, is a receptor of clofibrate, which is primarily expressed in liver, and its activation by derivatives of clofibrate including bezafibrate has been clinically used to improve lipid metabolism especially by reducing triglyceride (TG) levels.[11] On the other hand, PPAR-γ can be bound by thiazolidinediones, which have been shown to enhance muscle glucose consumption, reduce hepatic glucose production, and improve insulin resistance in association with a decrease in TNF-α and leptin levels.[12,13]

A ligand of PPAR-α, bezafibrate, has recently been shown to reduce fasting plasma glucose (FPG) levels.[14,15] However, little is known about the effect of bezafibrate on glucose metabolism or TNF-α and leptin levels. In the present study, we performed an intensive investigation on the effect of bezafibrate on glucose metabolism in DM2 patients.

SUBJECTS AND METHODS

Protocol 1

The study population consisted of 342 DM2 outpatients with hyperlipidemias (Table 1). The age, duration of DM, body mass index (BMI), and other parameters were similar between the control (no bezafibrate) and bezafibrate treatment groups. Patients with renal dysfunction with serum creatinine above 1.5 mg/dL were excluded. The subjects were randomly divided into 2 groups, bezafibrate treatment (group A, n = 174) and no bezafibrate treatment (group B, n = 168). In group A, bezafibrate 400 mg/d was administered for 16 weeks. FPG, hemoglobin A_{1c} (HbA_{1c}), TG, total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) levels were determined at 0, 4, 8, and 16 weeks of the study. Diabetic therapy and other concomitant medications had been continued for 24 weeks and were not changed before and during the study.

Protocol 2

Twenty DM2 patients with high TG (fasting TG ≥ 150 mg/dL) were selected from group B, and these 20 patients were randomly divided into 2 groups, 8-week bezafibrate 400 mg/d (group C, n = 10) and no bezafibrate treatment (group D, n = 10). Clinical characteristics of the 2 groups were not significantly different (Table 1). None of the patients were treated with insulin, insulin sensitizers (troglitazone, etc.), or α-glucosidase inhibitors. Six patients in group C and 5 in group D were treated by diet therapy alone. Four patients in group C (2 on gliclazide 40 mg/d, 1 on glibenclamide 0.625 mg/d, and 1 on glibenclamide 1.25 mg/d) and 5 patients in group D (2 on gliclazide 40 mg/d, 2 on glibenclamide 0.625 mg/d and 1 on glibenclamide, 1.25 mg/d) were treated with sulfonylureas which continued to be administered during the study period and were given 15 minutes prior to the meal test. Two patients in group C and 1 in group D had simple diabetic retinopathy. Urinary albumin excretion was negative in all patients.

A meal tolerance test (MTT) was performed after a 12-hour overnight fast. The meal (total, 400 kcal) contained 41.7 g carbohydrate, 22.2 g fat, and 8.2 g protein. Patients were allowed 15 minutes to consume the meal. Blood samples were taken at 0-, 2-, 4-, and 6-hour postprandial points and plasma glucose (PG), insulin, FFA, and TG were determined. Leptin and TNF-α levels were also determined.

Measurements

PG, serum TG, TC, HDL-C, and FFA were determined by standard enzymatic methods. Plasma TNF-α and leptin were determined using commercially available kits, a TNF-α immunoassay kit (Quantikine TMHS; Immuno-Biological Laboratories, Takasaki, Japan) and a human leptin assay kit (JIMRO; Japan Antibody Laboratories, Fujioka, Japan).

Statistical Analysis

All values are expressed as the mean ± SE. Two-tailed ANOVA was used to compare values between the baseline period and the other

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Table 1. Characteristics of the Study Subjects at Baseline (mean ± SE)

Characteristic	Protocol 1		Protocol 2	
	Group A	Group B	Group C	Group D
Bezafibrate treatment 400 mg/d	+	−	+	−
No. of subjects	174	168	10	10
Sex (n)				
Male	71	69	4	4
Female	103	99	6	6
Age (yr)	61.7 ± 4.1	61.4 ± 4.4	61.4 ± 3.7	60.7 ± 3.2
Diabetes duration (yr)	7.8 ± 1.6	7.5 ± 1.4	7.4 ± 1.9	7.9 ± 1.6
BMI (kg/m²)	24.1 ± 0.5	23.9 ± 0.6	24.1 ± 0.3	24.0 ± 0.3
HbA_{1c} (%)	7.2 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1

periods. A 2-tailed *t* test was used to compare values between 2 groups. A *P* level less than .05 was considered statistically significant.

Informed consent was obtained from all subjects before the clinical experiments.

RESULTS

Protocol 1

Bezafibrate treatment significantly decreased fasting TG by 50.1% ± 1.6% and TC by 12.3% ± 1.1% and significantly increased HDL-C by 20.0% ± 0.8% in group A. In contrast, these values were not changed in control group B (Table 2). FPG and HbA_{1c} levels were also significantly decreased from 151.3 ± 3.5 to 128.6 ± 3.4 mg/dL and from 7.2% ± 0.1% to 6.9% ± 0.1%, respectively, after bezafibrate treatment (group A), whereas they were not changed in the untreated group (group B; Table 3). During this study period, no significant changes in the body weight and BMI were observed.

Protocol 2

To further clarify the effects of bezafibrate on glucose and lipid metabolism, we examined the postprandial changes of lipid and glucose levels in DM2 subjects randomly selected from group B and divided into 2 groups, bezafibrate treatment (group C) and no bezafibrate treatment as a control (group D). In group C after the 8-week bezafibrate treatment, fasting TG was significantly decreased. Moreover, postprandial TG was significantly decreased at 2, 4, and 6 hours postprandially. Without bezafibrate treatment (group D), there were no significant differences in fasting or postprandial TG before or after the study period (Fig 1A). No changes in fasting or postprandial FFA levels were observed (Fig 1B).

FPG and PG at 2 and 4 hours of the MTT were significantly reduced after bezafibrate treatment (group C; Fig 2A). The reduction of PG in the postprandial periods was similar at each time point, and the line indicating PG was shifted downward almost in parallel. Fasting insulin levels were reduced by bezafibrate treatment, but postprandial insulin levels were not significantly changed (Fig 2B). Thus, the insulin to PG ratio tended to increase. In contrast, in group D without bezafibrate treatment, FPG or postprandial PG (Fig 2A) and insulin (Fig 2B) were not changed.

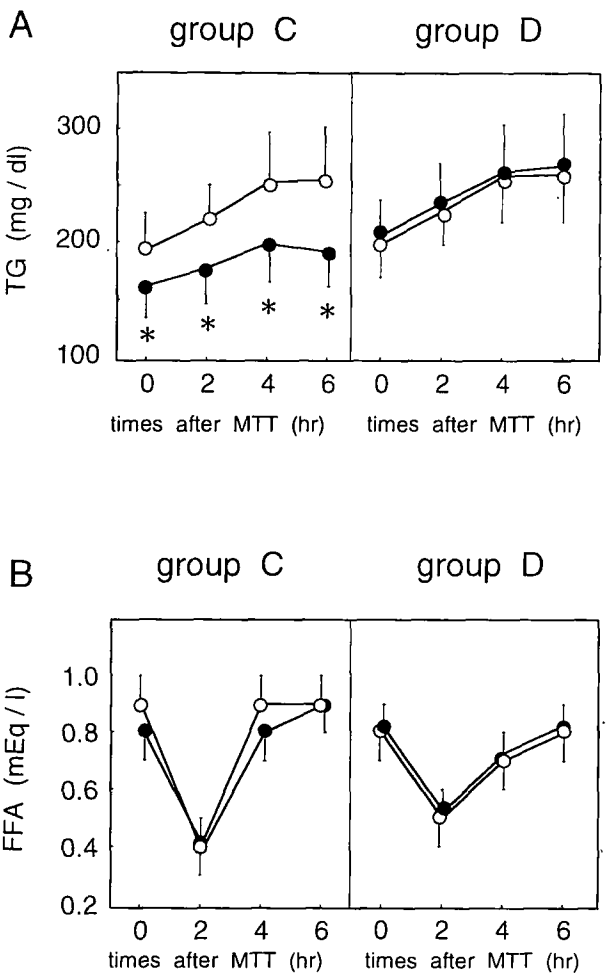

Fig 1. Effect of bezafibrate treatment on plasma lipid levels in patients with DM2 in the MTT. Group C, bezafibrate treatment for 8 weeks; group D, no bezafibrate treatment. (○) Before treatment; (●) after bezafibrate treatment. Each point represents the mean ± SE from 10 DM2 subjects.

Table 2. Serum Lipid Levels (mg/dL) in Group A and Group B (mean ± SE)

Lipid	Group	Treatment Duration (mo)			
		0	1	2	4
Serum triglyceride (mg/dl)	A	264.1 ± 12.2	147.4 ± 7.2*	154.3 ± 11.1*	130.5 ± 8.9*
	B	273.6 ± 12.8	248.9 ± 13.5	287.5 ± 12.3	267.1 ± 11.4
Serum total cholesterol (mg/dl)	A	239.3 ± 4.1	213.7 ± 3.3*	217.5 ± 4.2*	209.8 ± 3.7*
	B	240.5 ± 4.8	245.2 ± 4.5	252.8 ± 5.1	253.7 ± 5.2
Serum high density lipoprotein cholesterol (mg/dl)	A	46.5 ± 1.2	53.8 ± 1.3*	54.1 ± 1.6*	55.7 ± 1.9*
	B	46.8 ± 1.8	45.3 ± 1.5	45.7 ± 1.3	46.6 ± 1.7

*$P < .01$.

Table 3. Fasting PG and HbA_{1c} in Group A and Group B (mean ± SE)

Variable	Group	Treatment Duration (mo) 0	1	2	4
Fasting plasma glucose (mg/dl)	A	151.3 ± 3.5	139.3 ± 3.4†	131.8 ± 4.0†	128.6 ± 3.4†
	B	159.7 ± 3.1	165.4 ± 5.4	168.2 ± 4.8	160.8 ± 4.4
Glycated hemoglobin A1c (%)	A	7.2 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	6.9 ± 0.1*
	B	7.3 ± 0.1	7.3 ± 0.2	7.4 ± 0.2	7.4 ± 0.2

*$P < .05$.
†$P < .01$.

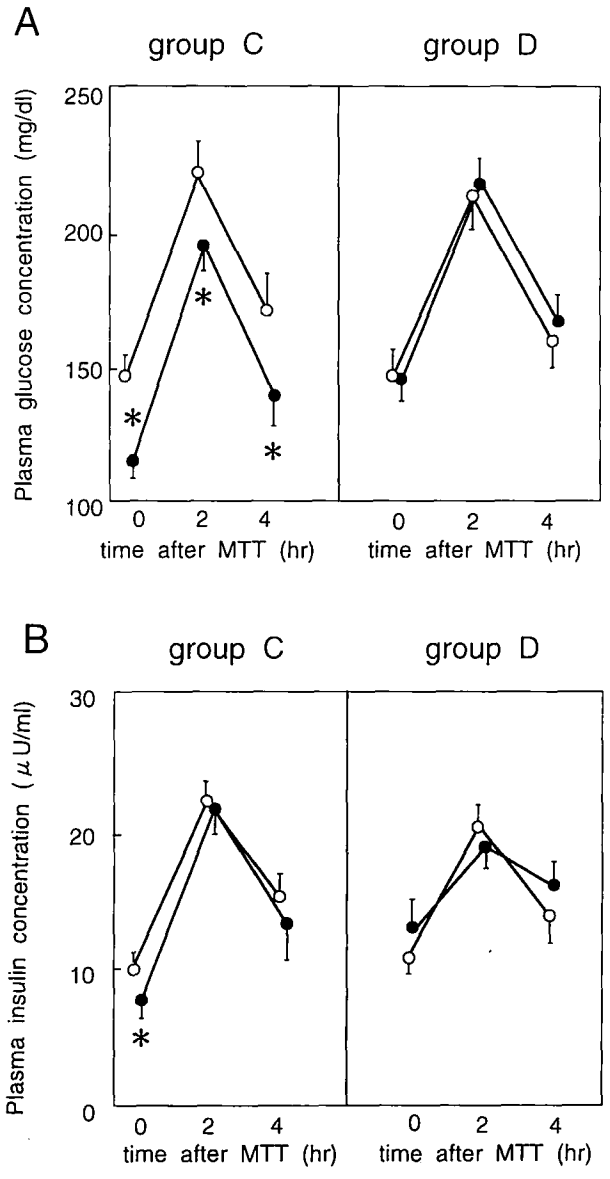

Fig 2. Effect of bezafibrate treatment on PG and insulin levels in DM2 patients in the MTT. Group C, 8-week bezafibrate treatment; group D, no bezafibrate treatment (control). (○) Before treatment; (●) after bezafibrate treatment. Each point represents the mean ± SE from 10 DM2 subjects.

Fasting levels of TNF-α and leptin were also determined. Plasma leptin levels were significantly reduced by bezafibrate treatment (group C), but no change was observed without treatment (group D) (Fig 3A). On the other hand, no significant changes in TNF-α levels were observed in subjects with or without bezafibrate (Fig 3B). The BMI did not change in both groups.

DISCUSSION

Bezafibrate has been used to improve lipid metabolism specifically by reducing TG. As expected, we observed de-

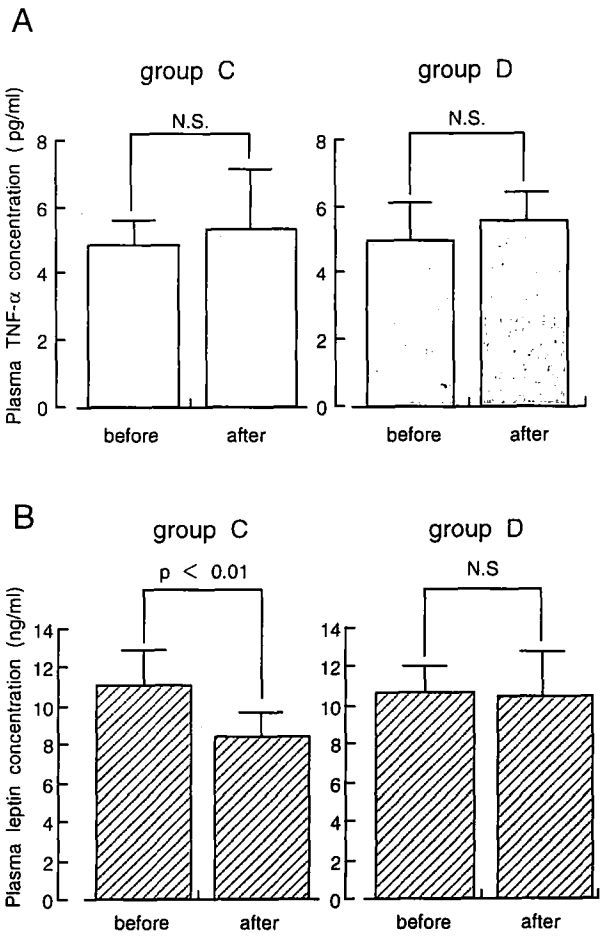

Fig 3. Effect of bezafibrate treatment on plasma TNF-α and leptin levels in DM2 patients. Group C, bezafibrate treatment for 8 weeks; group D, no bezafibrate treatment. Each bar represents the mean ± SE from 10 DM2 subjects. N.S., not significant.

creases in TG in DM2 patients. The MTT in protocol 2 has shown that increments of TG are blunted by bezafibrate treatment. The reduction of lipid levels is thought to be due to a decrease in hepatic lipid synthesis and induction of lipoprotein lipase.[16,17] Moreover, we examined the effect of bezafibrate on glucose metabolism in DM2 patients. As reported previously,[15] we observed significant decreases in FPG and HbA_{1c} with bezafibrate treatment in protocol 1. However, it was unclear how bezafibrate improved glucose metabolism in DM2. We therefore performed a MTT in protocol 2 including a control study (although not a placebo-controlled and double-blind study) to examine the possible mechanism underlying the beneficial effect of bezafibrate on glucose metabolism. The MTT showed that 8-week bezafibrate treatment reduced not only FPG but also postprandial PG, thus indicating that the increments of postprandial PG before and after bezafibrate treatment were similar. The decrease in postprandial PG is therefore suggested to be primarily due to the reduced FPG levels. Since basal insulin levels were also decreased by bezafibrate treatment, an enhancement of fasting pancreatic insulin secretion is ruled out as a cause. However, the ability of the pancreas to secrete insulin may be increased, because the insulin to glucose ratio tended to increase after bezafibrate treatment (Fig 2). It may be speculated that bezafibrate increases fasting hepatic glucose uptake or decreases fasting hepatic glucose release. The resultant decrease in FPG is most likely responsible for the decrease in fasting insulin. Since no change was observed in fasting or postprandial FFA levels, the improvement of fasting glucose metabolism does not appear to be due to an alteration in FFA release from adipose tissue, which is a major source of FFA. However, as FFA has been shown to inhibit hepatic glucose uptake[18] or to increase hepatic glucose release,[19] bezafibrate may decrease hepatic FFA via FFA oxidation,[17] leading to enhanced hepatic glucose uptake, although a change in FFA was not detected in the present study.

Bezafibrate significantly decreased plasma leptin in DM2 patients. The adipocytokine leptin is synthesized in adipocytes[20] and affects hepatic lipid and glucose metabolism. Bezafibrate is known to be a ligand of PPAR-α,[11] which is primarily present in liver.[17] It is therefore unlikely that bezafibrate directly decreases leptin synthesis in adipocytes. Improved hepatic glucose metabolism with bezafibrate may lead to a decrease in leptin via an unknown mechanism. On the other hand, there was no change in TNF-α levels with bezafibrate treatment. TNF-α is postulated to inhibit glucose uptake in muscles by interfering with insulin signaling, thereby causing insulin resistance.[5,6,9] An improvement of insulin resistance was not observed with bezafibrate treatment in the present study.

In conclusion, bezafibrate not only reduces TG and TC but can also decrease FPG, probably by improving hepatic lipid metabolism, and may increase the ability of the pancreas to secrete insulin in DM2 patients.

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