Improvement of Glucose Tolerance in NIDDM by Clofibrate
Randomized Double-Blind Study

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A randomized double-blind study was performed to examine the effect of clofibrate on glucose tolerance in subjects with non-insulin-dependent diabetes mellitus (NIDDM). Clofibrate (1.5 g/day) or placebo was administered to 70 patients and an oral glucose tolerance test (OGTT) was performed before and 12 wk after treatment. Blood glucose levels were significantly improved in clofibrate-treated groups at all time points during OGTT, whereas there was no change in insulin levels. Improvement of fasting glucose levels required 8 wk of clofibrate treatment. Insulin binding to erythrocytes demonstrated no significant change in the clofibrate-treated subjects. These results suggest that clofibrate improves glucose tolerance in NIDDM subjects without a change in insulin receptors and that clofibrate increases insulin sensitivity through an unknown postreceptor mechanism. *Diabetes Care* 11:495–99, 1988

Hypertriglyceridemia is a common finding in patients with non-insulin-dependent diabetes mellitus (NIDDM). It has been reported by several investigators that treatment with clofibrate improves glucose tolerance (1–4), but other investigators reported that clofibrate did not have any effect on glucose tolerance (5,6). However, except for the study on insulin-dependent diabetic (IDDM) subjects reported by Schade et al. (4), these studies were not systematically performed, and the validity is questionable. Furthermore, the mechanism by which the drug improves glucose tolerance has not been clarified. We undertook a double-blind study of the effect of clofibrate in glucose metabolism of subjects with NIDDM and examined insulin-receptor binding.

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MATERIALS AND METHODS

The study was performed following the same protocol in six medical centers in Japan. Seventy patients with NIDDM treated by diet alone were randomly assigned to either placebo or clofibrate treatment by a double-blind method under the supervision of a controller. National Diabetes Data Group diagnostic criteria for diabetes were followed (7). Patients who required insulin therapy or oral-agent administration, had hepatic or renal disorders, were markedly obese (>150% obese), had essential hypertriglyceridemia, required drugs that affected blood glucose and blood lipid levels, showed much change in body weight during the treatment, or were >75 yr old were excluded from the study. Patients were randomized with a computer by use of a table of random numbers. The key codes were made and kept until the end of the trial. Two types of drugs, clofibrate 500-mg soft capsule and an olive oil–containing placebo soft capsule (ICI-Pharma, Osaka, Japan), indistinguishable from each other by appearance, were produced and quality checked. During the study, fasting blood glucose levels, HbA_{1c}, triglyceride, and cholesterol were determined monthly. Oral glucose tolerance testing (75 g; OGTT) was performed before and 12 wk after treatment. Blood from 10 subjects from each group was studied for erythrocyte insulin binding by the method

TABLE 1
Characterization of NIDDM subjects

	Age (yr)	*n* (M/F)	Obesity index (%)	Fasting blood glucose (mg/dl)	HbA_{1c} (%)	Triglyceride (mg/dl)	Cholesterol (mg/dl)
Clofibrate	53.6	22/17	111.9 ± 0.1	143.9 ± 8.6	6.7 ± 0.4	169.8 ± 17.5	223.0 ± 5.4
Placebo	53.8	17/17	113.9 ± 0.1	153.3 ± 12.2	7.2 ± 0.5	190.3 ± 31.8	221.9 ± 7.8
Normal range				60–110	4.0–6.0	55–135	125–240

Values are means ± SE. Differences between groups were not statistically significant.

of Kobayashi et al. (8). The 20 subjects were selected from the Diabetes Center of Tokyo Women's Medical College and were randomly assigned to either placebo or clofibrate treatment by a double-blind method. Clofibrate (Amotril, Atromid-S) 0.5 g/day (1 tablet) or placebo was given three times daily after each meal. The patients with poor compliance were excluded from the study, and all the patients did not suffer any drug side effects. Four patients (2 clofibrate, 2 placebo) were excluded from the study because the patients moved to other clinics. All the patients were instructed to follow the diet regimen, and their body weights before and after the study were not statistically different.

Analytical methods. Blood glucose concentrations were determined by the hexokinase method (9). Serum insulin concentrations were measured as previously described with the radioimmunoassay kit from Midorijuji Radioisotope Laboratory (10). Serum cholesterol and triglyceride were measured by the enzyme method via cholesterol oxidase and glycerol-3-phosphate oxidase, respectively. HbA_{1c} was measured by high-performance liquid chromatography. All these measurements were

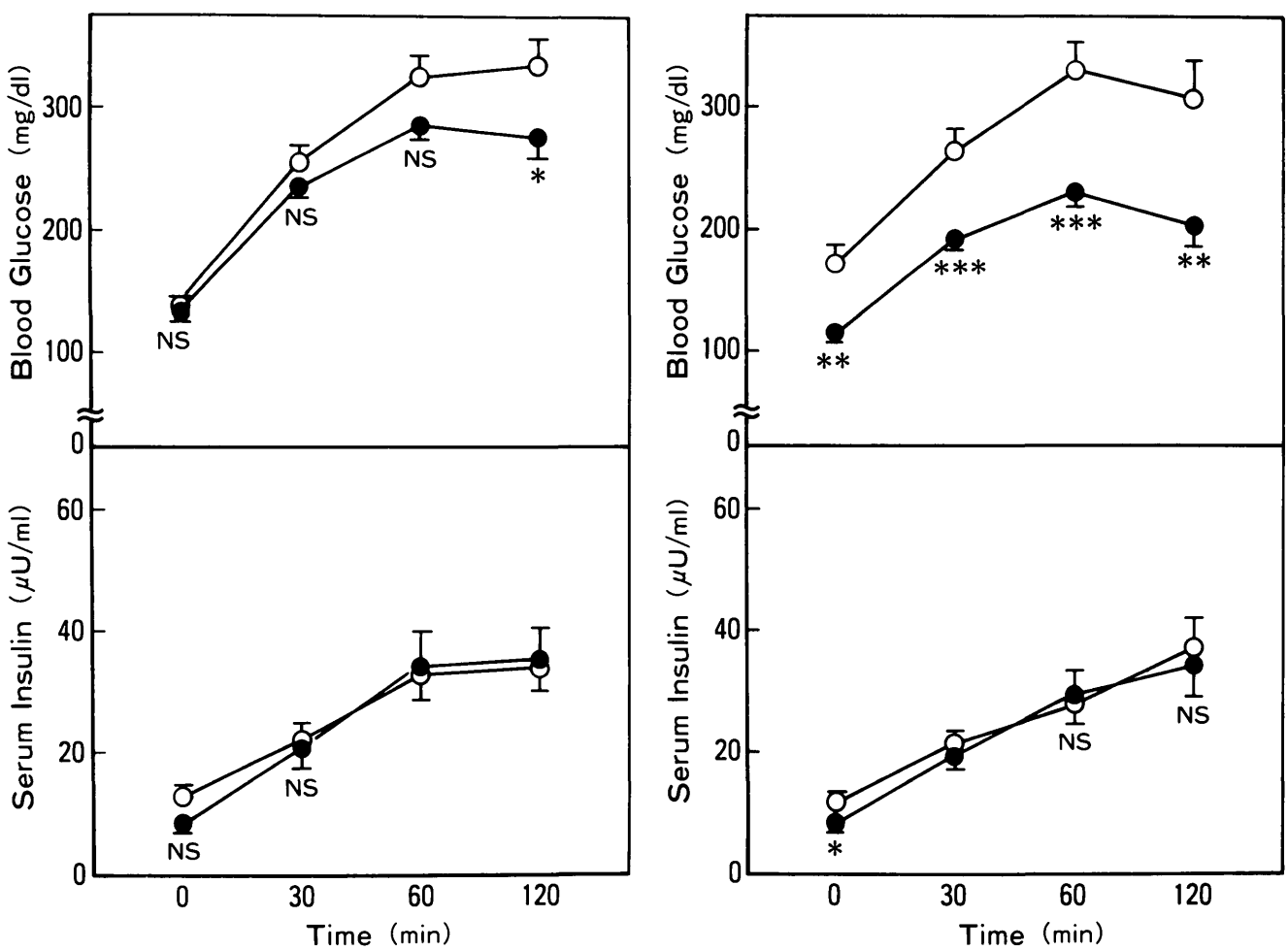

FIG. 1. Change in blood glucose and insulin levels with oral glucose tolerance testing (OGTT) before and after 12 wk treatment by placebo or clofibrate. OGTTs (75 g) were performed before (*left*) and after (*right*) 12 wk of treatment by placebo (○) or clofibrate (●). *Points* are means ± SE. *$P < .05$, **$P < .01$, ***$P < .001$.

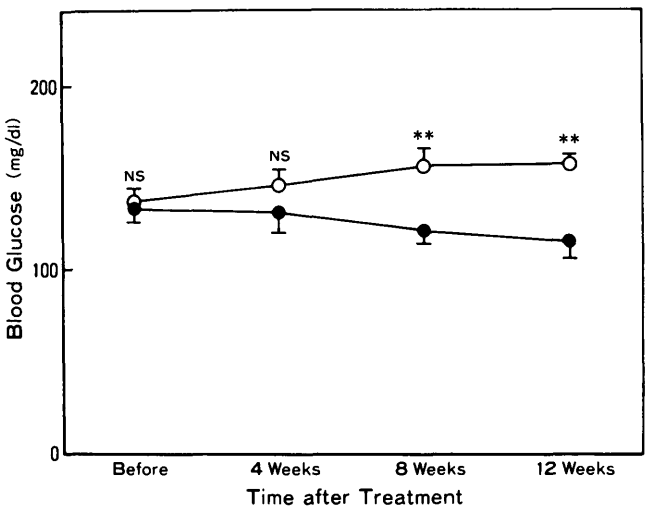

FIG. 2. Change in fasting blood glucose levels after treatment with placebo (○) or clofibrate (●). *Points* are means ± SE. *$P < .01$.

checked or approved for quality control in six centers by the Japan Medical Association.

Statistical methods. The two-tailed Student's *t* test was used to analyze the significant differences. All data are expressed as means ± SE.

RESULTS

Table 1 shows the characteristics of the subjects in this study. There was no difference between the two groups in age and severity of diabetes. Figure 1 shows glucose and insulin levels during the OGTT before and 12 wk after the treatment. Glucose levels improved at all time points in the clofibrate-treated group, whereas there was no difference in the placebo group (Fig. 1). Insulin concentrations during the OGTT were comparable before and after the study in both groups. When the change in fasting blood glucose levels during the treatment with clofibrate or placebo was examined, the difference between control and clofibrate treatment was obvious (Fig. 2). Time required to reach the statistical difference between the two groups was 8 wk. However, HbA_{1c} failed to show statistically significant improvement after clofibrate administration (Fig. 3). Triglyceride levels were significantly decreased after 12 wk of clofibrate treatment, but cholesterol levels were unchanged (Fig. 4).

Insulin binding to erythrocytes was performed to investigate the mechanism of insulin action in the patients treated with clofibrate. Insulin binding was not increased by the treatment, although there was some tendency toward increased affinity at 4 wk after the treatment (Fig. 5). Furthermore, after 12 wk, insulin binding decreased compared with the result before treatment, but there was no difference in insulin binding between the two groups. Thus, insulin-receptor binding may not play an important role in improvement of glucose tolerance in the patients treated with clofibrate.

DISCUSSION

It has been known that clofibrate may improve glucose tolerance in diabetic subjects (1–4). However, most of these studies were not performed systematically on NIDDM subjects, and the effect of diet therapy may cause improvement of glucose metabolism. Our studies used the more objective double-blind method. The effect of diet therapy or other intervention on these patients may be excluded, and more objective results can be expected.

When the placebo and clofibrate-treated groups were compared, the baseline values of glucose levels and HbA_{1c} were comparable. In the treated group, fasting blood glucose levels started to decrease at 8 wk, but in the placebo group they were elevated at 8 wk. These results suggest that clofibrate improves glucose levels and does not merely prevent worsening. After 12 wk, the OGTT showed significant improvement both before and after glucose loading. Insulin levels were comparable before and after clofibrate treatment. HbA_{1c} levels failed to show a statistical improvement in the clofibrate group. Barnett et al. (2) reported that 4 wk of treatment improves glucose tolerance in NIDDM subjects treated with diet alone or with oral agents. Schade et al. (4) reported a similar effect of clofibrate after 3 wk of treatment. Taken together, the glucose-lowering effects of clofibrate may require 3–8 wk of treatment.

Improved glucose tolerance with unchanged insulin levels suggests that insulin sensitivity may be improved in the clofibrate group. Increased affinity of insulin receptors has been reported (11). We tested 10 subjects before and after either placebo or treatment with clofi-

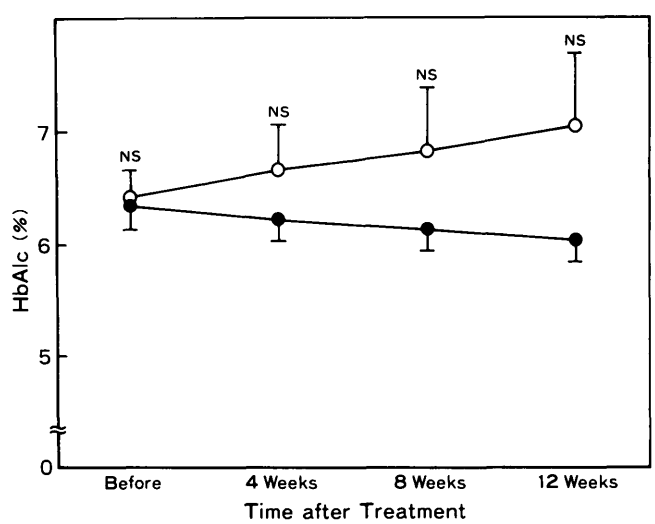

FIG. 3. Change in HbA_{1c} levels after treatment with placebo (○) or clofibrate (●). Values indicate means ± SE. Difference between groups was not significant.

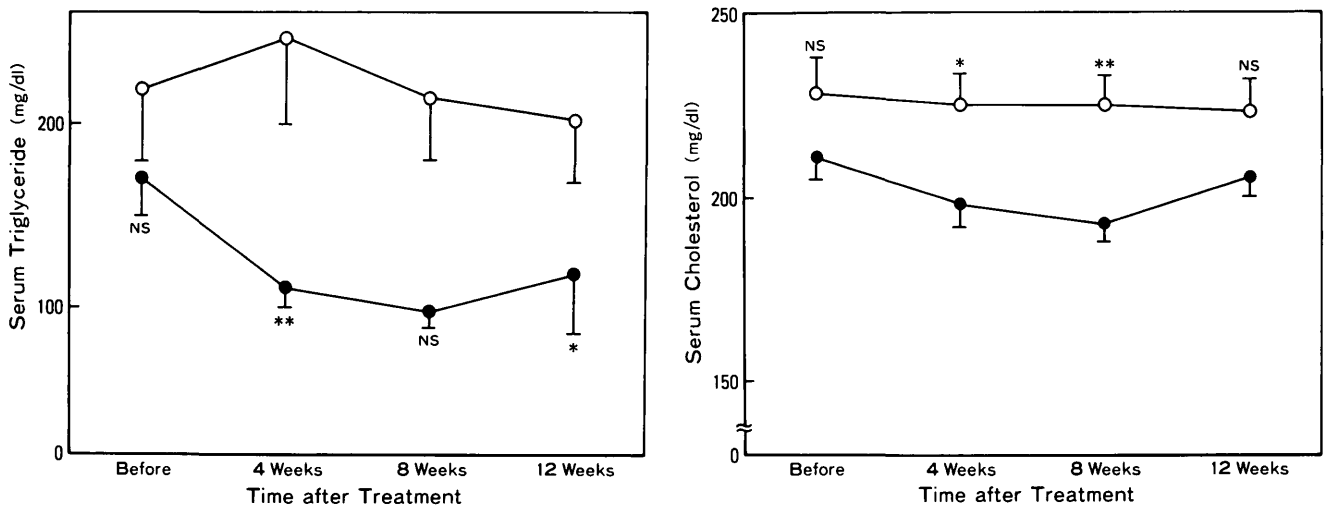

FIG. 4. Change of serum triglyceride levels (*left*) and serum cholesterol levels (*right*) before and after placebo (○) or treatment with clofibrate (●). *$P < .05$, **$P < .01$.

brate. After 4 wk, insulin binding to erythrocytes tended to increase in both groups, but the increase was not statistically significant. The binding decreased after 12 wk, but the change may not have been significant, because the binding data of the two groups after 12 wk were comparable. Why the binding decreased after 12 wk is not clear. The different batches of iodinated insulin may be one of the factors that caused the change. However, the difference between the two groups could be compared at the indicated time points. Because erythrocyte insulin binding may not reflect the binding of the insulin-sensitive tissues, insulin binding to these tissues, i.e., muscles or adipocytes, may be necessary to prove these results. Clofibrate did not significantly change insulin binding in erythrocytes in these subjects. A similar finding was reported by Ip et al. (12), who studied insulin binding in fat cells from rats treated with clofibrate. Weis et al. (13) reported that increased insulin sensitivity was observed in the fat pad from rats treated with clofibrate. However, we found that clofibrate failed to change

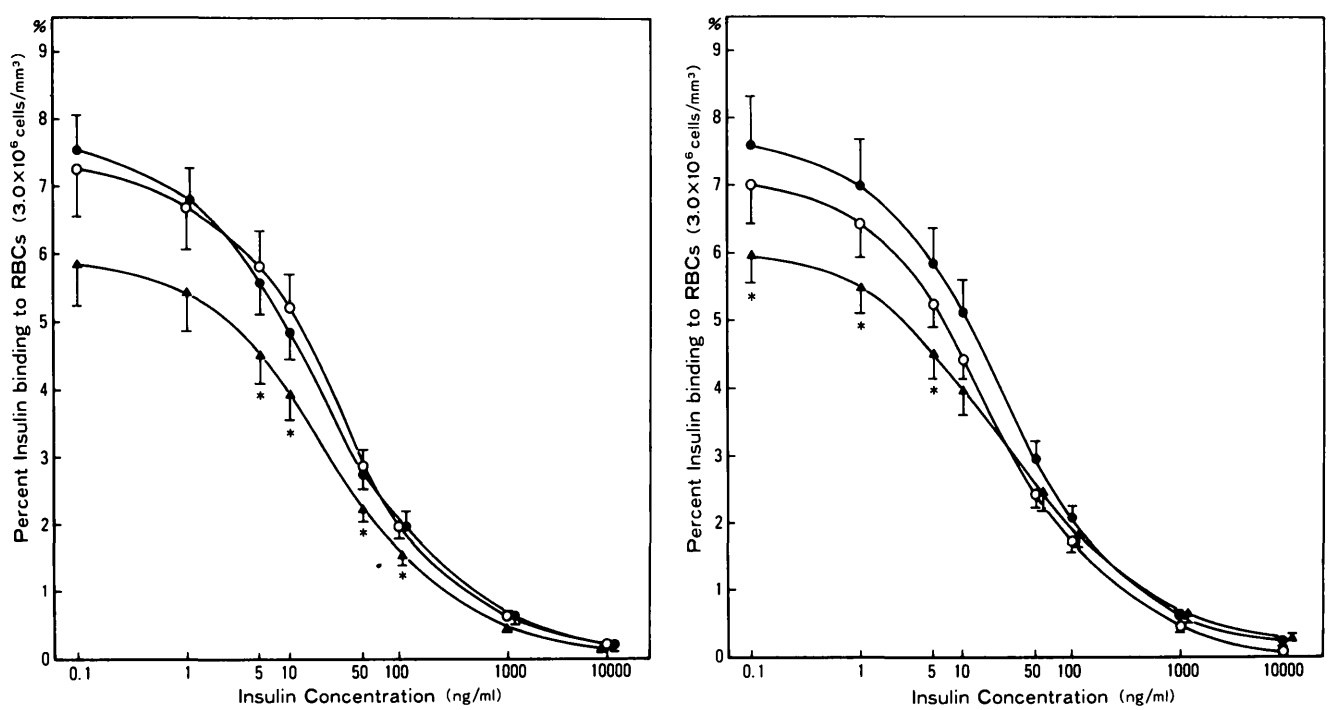

FIG. 5. Insulin binding to erythrocytes before and after treatment with placebo (*left*) or clofibrate (*right*). Insulin binding was performed before (○) and 4 wk (●) and 12 wk (▲) after treatment *$P < .05$.

insulin sensitivity in vitro and in vivo in rats (14), but our studies were done over a relatively short period (7 days of treatment), and more time may be required to improve glucose tolerance. Because insulin binding did not change in the treated group, postreceptor steps may be affected by clofibrate treatment. Clarification of the mechanism may require examining postreceptor steps, e.g., kinase activity of β-subunit of insulin receptor, in relation to insulin action, e.g., glucose transport.

Several investigators reported that a rise in the level of plasma fatty acids caused insulin insensitivity (15,16) and that a positive correlation existed between very-low-density lipoprotein triglyceride production rate or plasma triglyceride level and insulin resistance (17). Therefore, a hypoglycemic effect of clofibrate may be induced by decreased triglyceride level or free–fatty acid level but not by the direct effect of clofibrate on insulin action. A long-term culture of insulin-sensitive cells with clofibrate may be necessary to prove these possibilities. In conclusion, our results suggest that clofibrate may be a good adjunct treatment in addition to diet therapy for patients with mild NIDDM and hypertriglyceridemia.

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