Effects of Bezafibrate on Insulin Sensitivity and Insulin Secretion in Non-Obese Japanese Type 2 Diabetic Patients

Ataru Taniguchi, Mitsuo Fukushima, Masahiko Sakai, Kumpei Tokuyama, Itaru Nagata, Akiko Fukunaga, Hiroyuki Kishimoto, Kentaro Doi, Yukio Yamashita, Toshifumi Matsuura, Naomi Kitatani, Takahide Okumura, Shoichiro Nagasaka, Shigeo Nakaishi, and Yoshikatsu Nakai

The aim of the present study was to investigate the effect of bezafibrate on insulin sensitivity and insulin secretion in 30 non-obese Japanese type 2 diabetic patients with hypertriglyceridemia (serum triglycerides > 150 mg/dL). Insulin sensitivity was measured with homeostasis model assessment insulin resistance (HOMA-IR) proposed by Matthews et al. HOMA–B-cell function, proposed by Matthews et al validated against minimal model-derived insulin secretion, was used to assess pancreatic insulin function. Twenty-two patients were treated with glibenclimide and the rest were treated with diet alone. All patients were treated with bezafibrate (400 mg/d) for 3 months. There were no changes in diet and the dose of any medications used throughout the study. Fasting glucose, insulin, triglycerides, HDL cholesterol, and total cholesterol levels were measured before and after treatment of bezafibrate. After treatment of bezafibrate for 3 months, serum triglyceride levels significantly decreased from 277 ± 30 to 139 ± 9 mg/dL ($P < .001$) and serum HDL cholesterol levels increased significantly from 45 ± 2 to 52 ± 2 mg/dL ($P = .003$). Serum cholesterol level was unchanged during the study (198 ± 7 *v* 201 ± 7 mg/dL, $P = .383$). Fasting glucose (163 ± 8 *v* 139 ± 6 mg/dL, $P = .006$) significantly decreased after the treatment with bezafibrate. HbA1c levels decreased, although not statistically significant (7.50 ± 0.25 *v* 7.17% ± 0.19%, $P = .147$). On the other hand, fasting insulin (9.3 ± 0.7 *v* 7.3 ± 0.5 μU/mL, $P = .010$) and HOMA-IR (3.61 ± 0.24 to 2.53 ± 0.20, $P < .001$) levels decreased significantly after the treatment with bezafibrate. In contrast, HOMA-B-cell function did not change during the study (41.4 ± 5.5 *v* 41.8 ± 4.7, $P = .478$). There was no significant difference in body mass index (BMI) levels before and after the therapy (23.0 ± 0.4 *v* 23.1 ± 0.4 kg/m^2, $P = .483$). From these results, it can be concluded that bezafibrate reduces serum tiglycerides, insulin resistance, and fasting blood glucose levels in non-obese Japanese type 2 diabetic patients.

TYPE 2 DIABETES IS A heterogeneous disorder characterized by insulin resistance and/or defective insulin secretion.[1,2] Japanese type 2 diabetic patients are unique in that they are divided into 2 variants: one with insulin resistance and the other with normal insulin sensitivity.[3-5] We very recently disclosed that Japanese type 2 diabetic patients with insulin resistance are characterized by higher body mass index (BMI) and higher triglyceride levels as compared with those with normal insulin sensitivity.[6,7] Furthermore, we showed that insulin resistance observed in non-obese Japanese type 2 diabetic patients is positively correlated with serum triglyceride levels, but not with BMI.[6,8]

There are some data suggesting that pharmacologic therapy to lower triglycerides is associated with an improvement in glucose tolerance in type 2 diabetic patients. Triglyceride-lowering drugs such as bezafibrate[9,10]or clofibrate,[11]are shown to reduce plasma glucose level in type 2 diabetic patients. It is not yet known, however, whether or not the triglyceride-lowering effect by bezafibrate is associated with an improvement in insulin sensitivity or insulin secretion. To accomplish this, we recruited 30 non-obese Japanese type 2 diabetic patients with hypertriglyceridemia and investigated the effect of bezafibrate on insulin sensitivity and insulin secretion.

SUBJECTS AND METHODS

Thirty Japanese type 2 diabetic patients who visited our clinics were employed for the present study. Type 2 diabetes was diagnosed based on the criteria of the World Health Organization (WHO).[12] They all had either a fasting serum glucose greater than 140 mg/dL and/or 2-hour postglucose level greater than 200 mg/dL. The duration of the diagnosis of diabetes was 12.3 ± 1.3 years (mean ± SE; range, 1 to 33 years). They all were treated with bezafibrate for 3 months. During the therapy, the dose of bezafibrate (400 mg/d) was unchanged. Twenty-two patients were treated with an oral hypoglycemic agent (glibenclimide), but the same doses were continued during the study. None of the patients had received insulin therapy. All subjects had ingested at least 150 g of carbohydrate throughout the study. None of the subjects had significant renal, hepatic, or cardiovascular disease. The blood was drawn in the morning after a 12-hour fast before and after treatment of bezafibrate for 3 months.

Plasma glucose was measured in duplicate with an automatic analyzer (Kyoto-Daiichi-Kagaku, Kyoto, Japan) by a glucose oxidase method. Plasma insulin was measured in duplicate using 2-site immunoradiometric assay (Insulin Riabead II, Dainabot, Osaka, Japan). Coefficients of variation (CVs) were 4% for insulin greater than 25 μU/mL and 7% for insulin less than 25 μU/mL, respectively. The total cholesterol, HDL cholesterol, and triglycerides were measured by standard enzymatic methods.[13] The estimate of insulin resistance by homeostasis model assessment insulin resistance (HOMA-IR) was calculated with the formula fasting serum insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5, as described by Matthews et al.[14] Insulin secretion was calculated with the formula fasting serum insulin

From the Division of Diabetes, Kansai-Denryoku Hospital, Osaka: Department of Metabolism and Clinical Nutrition, Graduate School of Medicine, Kyoto University, Kyoto; Laboratory of Biochemistry of Exercise and Nutrition, Institute of Health and Sports Science, Tsukuba University, Ibaraki; Kyoto University Graduate School of Medicine, Kansai Health Management Center, Osaka; the Division of Endocrinology and Metabolism, Jichi Medical School, Tochigi; Nakaishi Clinic, Osaka; and the Division of the Science of Nursing, College of Medical Technology, Kyoto University, Kyoto, Japan.

Submitted July 11, 2000; accepted September 29, 2000.

Address reprint requests to Ataru Taniguchi, MD, First Department of Internal Medicine, Kansai-Denryoku Hospital, 2-1-7 Fukushima, Fukushima-ku, Osaka-City, Osaka 553-0003, Japan.

0026-0495/01/5004-0028$35.00/0
doi:10.1053/meta.2001.21028

(μU/mL) $\times$ 20/(fasting plasma glucose [mmol/L] 3.5) proposed by Matthews et al.[14] We very recently showed that this index, HOMA–B-cell function, is validated against minimal model-derived insulin secretion in non-obese Japanese type 2 diabetic patients.[15]

Statistical Analysis

The statistical analysis was performed with the StatView 5 system (Statview, Berkeley, CA). The differences of mean were determined by the Student's *t* test. Data are expressed as the mean $\pm$ SEM unless otherwise stated.

RESULTS

The subjects studied were all Japanese type 2 diabetic patients (21 men and 9 women) with an age range of 42 to 75 years (61.6 $\pm$ 1.4) and a BMI of 16.6 to 26.7 kg/m^2 (23.0 $\pm$ 0.4). They all were non-obese.[16] The fasting plasma glucose was 163 $\pm$ 8 mg/dL (range, 100 to 278) and glycosylated hemoglobin (HbA1c) was 7.50% $\pm$ 0.25% (range, 5.2% to 11.3%). The fasting plasma insulin level was 9.3 $\pm$ 0.7 μU/mL (range, 4.0 to 19.0). Serum triglycerides, cholesterol, and HDL cholesterol levels were 287 $\pm$ 30 mg/dL (range, 152 to 907), 198 $\pm$ 7 mg/dL (range, 135 to 298), and 45 $\pm$ 2 mg/dL (range, 24 to 66), respectively.

Table 1 illustrates the individual parameters before and after the treatment of bezafibrate (400 mg/day) for 3 months. There was no significant difference in BMI levels before and after the treatment. After the treatment, fasting triglyceride levels decreased significantly from 287 $\pm$ 30 to 139 $\pm$ 9 mg/dL. HDL cholesterol significantly increased, but the total cholesterol level was unchanged during the study. On the other hand, fasting plasma glucose and fasting insulin levels decreased significantly. HbA1c decreased, but was not statistically significant. HOMA-IR levels significantly decreased from 3.61 $\pm$ 0.24 to 2.53 $\pm$ 0.20 after the therapy. In contrast, bezafibrate therapy did not affect HOMA–B-cell values in our patients.

DISCUSSION

Type 2 diabetes is a syndrome characterized by insulin resistance and/or defective insulin secretion.[1,2] There seems to be ethnic differences in insulin resistance in type 2 diabetes. Haffner et al[17] recently disclosed that 92% of type 2 diabetic patients are insulin-resistant in white populations. In contrast, Chaiken et al[18] previously showed that 60% of type 2 diabetic patients are insulin-resistant in black Americans with a BMI less than 30 kg/m^2. Using the minimal model approach shown by Bergman et al,[19] we previously showed that non-obese Japanese type 2 diabetic patients are divided into 2 variants: one with primary insulin resistance and the other with normal insulin sensitivity.[3-5] Japanese subjects with impaired glucose tolerance had also 2 discrete forms: insulin resistance and normal insulin sensitivity.[20]

Table 1. Clinical Characteristics Before and After Treatment With Bezafibrate

Characteristic	Before	After	*P*
BMI (kg/m^2)	23.0 $\pm$ 0.4	23.1 $\pm$ 0.4	.483
Triglycerides (mg/dL)	287 $\pm$ 30	139 $\pm$ 9	$<$.001
HDL cholesterol (mg/dL)	45 $\pm$ 2	52 $\pm$ 2	.003
Cholesterol (mg/dL)	198 $\pm$ 7	201 $\pm$ 7	.383
Fasting glucose (mg/dL)	163 $\pm$ 8	139 $\pm$ 6	.006
Fasting insulin (μU/mL)	9.3 $\pm$ 0.7	7.3 $\pm$ 0.5	.01
HbA1c (%)	7.50 $\pm$ 0.25	7.17 $\pm$ 0.19	.147
HOMA-IR	3.61 $\pm$ 0.24	2.53 $\pm$ 0.20	$<$.001
HOMA–B-cell	41.4 $\pm$ 5.5	41.8 $\pm$ 4.7	.478

We later disclosed that non-obese type 2 diabetic patients with insulin resistance had significantly higher triglyceride levels as compared with those with normal insulin sensitivity.[6,7] Moreover, we showed that insulin resistance observed in non-obese Japanese type 2 diabetic patients is positively correlated with serum triglyceride levels, but not with BMI.[6,8] Thus, it might be speculated that non-obese type 2 diabetic patients with high triglyceride levels are resistant to the effects of insulin on glucose utilization. The mechanism responsible for the insulin resistance seen in hypertriglyceridemia has not yet been fully clarified. Incubating IM-9 lymphocytes with very low-density lipoprotein has been reported to downregulate the cell's insulin receptors.[21] Insulin binding to erythrocytes in the blood of the patients with hypertriglyceridemia is reported to be low, but the improvement of hypertriglyceridemia did not correct insulin-binding abnormalities.[22] Irrespective of the mechanism of insulin resistance observed in hypertriglyceridemia, these previous studies, including ours, suggest that the pharmacologic therapy that lowers serum triglyceride levels is associated with an improvement in insulin sensitivity and glucose levels in non-obese Japanese type 2 diabetic patients. This idea is supported from our very recent report that physical exercise lowers triglycerides, fasting glucose, and HOMA-IR levels in Japanese type 2 diabetic patients without affecting BMI.[23]

In the present study, we showed that bezafibrate not only lowers triglycerides, but also fasting glucose levels in diabetic patients. Two research groups recently reported similar results in diabetic patients.[9,10] However, the mechanism by which bezafibrate lowers glucose levels in diabetic patients is not yet clarified. The reduction in plasma glucose level is caused by an enhancement in insulin sensitivity, insulin secretion, or both. For that reason, we simultaneously evaluated insulin sensitivity and insulin secretion in the present study.

With regard to insulin sensitivity, Emoto et al[24] and Bonora et al[25] recently showed that the HOMA-IR value is closely correlated with the insulin resistance index assessed by the euglycemic clamp in diabetic patients. Our team[26] and Hermans et al[27] recently showed that the HOMA-IR value is highly correlated with insulin resistance calculated by the minimal model approach in subjects with varying degrees of glucose tolerance. In contrast, we very recently showed that HOMA–B-cell proposed by Matthews et al[14] is highly correlated with insulin secretion calculated by the minimal model approach in non-obese Japanese type 2 diabetic patients.[15] Using the hyperglycemic clamp, Stumvoll et al[28] thereafter disclosed that HOMA–B-cell proposed by Matthews et al[14] provides an accurate estimate of B-cell function in white patients with type 2 diabetes. Miettinen and Haffner et al[29] previously showed that HOMA–B-cell function is positively correlated with the ratio of change in insulin and glucose over 30 minues of an oral glucose tolerance test in type 2 diabetic patients. These findings favor the use of HOMA-IR and HOMA–B-cell in the assess-

ment of insulin sensitivity and insulin secretion in non-obese Japanese type 2 diabetic patients, respectively. HOMA-IR and HOMA–B-cell is a simple and non-invasive method. We therefore used HOMA-IR and HOMA–B-cell in the present study.

In the present study, we first showed that the treatment of bezafibrate reduced insulin resistance and fasting insulin levels without affecting insulin secretion in non-obese Japanese type 2 diabetic patients. In this context, a major problem is that HOMA–B-cell function is reflective of early phase insulin secretion to glucose only, because a positive correlation exists between HOMA–B-cell function and acute insulin response to intravenous glucose stimuli.[15] Thus, it may be considered that the glucose-lowering effect by bezafibrate is associated with an improvement of insulin sensitivity, but not associated with an improvement in the early phase of insulin secretion. It is unknown, however, whether or not bezafibrate affects endogenous insulin secretion in non-obese Japanese type 2 diabetic patients.

The mechanism by which bezafibrate improves insulin sensitivity in non-obese Japanese type 2 diabetic patients remains to be clarified. There is no evidence that it is the reduction in triglycerides that directly results in an increase in insulin sensitivity. There may be an effect of bezafibrate on insulin action of some other metabolic phase in diabetic patients. Alternatively, the changes in triglycerides and insulin action may cosegregate in response to the drug.

As an assessment of glucose tolerance, we used HbA1c and glucose levels on the fasting state. Bezafibrate lowered fasting glucose, but did not improve HbA1c levels. The reason for the discrepancy between fasting glucose and HbA1c is not known at present. The daily glucose profile might affect HbA1c levels, but we did not measure the daily profile. Alternatively, the treatment duration of bezafibrate might affect the results of HbA1c. Ogawa et al[10] reported that the HbA1c level significantly decreased after the 4-month bezafibrate treatment.

In summary, although our present study is performed among the limited number of patients ($n = 30$), it can be concluded that bezafibrate not only lowers serum tiglycerides and glucose levels, but also reduces insulin resistance in non-obese Japanese type 2 diabetic patients. In this respect, the finding that thazolidinediones, which are being developed for the treatment of insulin resistance and type 2 diabetes, also profoundly reduces triglyceride levels in type 2 diabetes is very interesting.[30] A larger population study should be undertaken to clarify whether or not the triglyceride-lowering effect of bezafibrate is associated with an improvement in insulin sensitivity and fasting glucose concentration in non-obese Japanese type 2 diabetic patients.

ACKNOWLEDGEMENT

We are very grateful to the Department of Biochemistry, Kansai-Denryoku Hospital and Shionogi Biomedical Laboratory, Osaka, Japan for encouraging this study.

REFERENCES

1. DeFronzo RA: Lilly Lecture 1987: The triumvirate: Beta-cell, muscle, liver: A collusion responsible for NIDDM. Diabetes 37:667-687, 1988

2. Gerich JE: The genetic basis of type 2 diabetes mellitus: Impaired insulin secretion versus impaired insulin sensitivity. Endocr Rev 19: 491-503, 1998

3. Taniguchi A, Nakai Y, Fukushima M, et al: Pathogenic factors responsible for glucose intolerance in patients with NIDDM. Diabetes 41:1540-1546, 1992

4. Nagasaka S, Tokuyama K, Kusaka I, et al: Endogenous glucose production and glucose effectiveness in type 2 diabetic subjects derived from stable-labeled minimal model approach. Diabetes 48:1054-1060, 1999

5. Taniguchi A, Fukushima M, Sakai M, et al: Insulin secretion, insulin sensitivity, and glucose effectiveness in nonobese individuals with varying degrees of glucose tolerance (letter). Diabetes Care 23: 127-128, 2000

6. Taniguchi A, Fukushima M, Sakai M, et al: The role of the body mass index and triglyceride levels in identifying insulin-sensitive and insulin-resistant variants in Japanese non-insulin-dependent diabetic patients. Metabolism 49:1001-1005, 2000

7. Taniguchi A, Fukushima M, Sakai M, et al: Remnant-like particle cholesterol, triglycerides, and insulin resistance in nonobese Japanese type 2 diabetic patients. Diabetes Care (in press)

8. Taniguchi A, Fukushima M, Sakai M, et al: Insulin-sensitive and insulin-resistant variants in nonobese Japanese type 2 diabetic patients. The role of triglycerides in insulin resistance (letter). Diabetes Care 22:2100-2101, 1999

9. Jones IR, Swai A, Taylor R, et al: Lowering of plasma glucose concentrations with bezafibrate in patients with moderately controlled NIDDM. Diabetes Care 13:855-863, 1990

10. Ogawa S, Takeuchi K, Sugimura K, et al: Bezafibrate reduces blood glucose in type 2 diabetes mellitus. Metabolism 49:331-334, 2000

11. Kobayashi M, Shigeta Y, Hirata Y, et al: Improvement of glucose tolerance in NIDDM by clofibrate: Randomized double- blind study. Diabetes Care 11:495-499, 1988

12. World Health Organization: Diabetes mellitus: Report of a WHO study group. WHO Tech Rep Ser no.727, 1985

13. Nakamura M, Kishi K, Watazu Y: Evaluation of three total cholesterol methods. Clin Chem 43:S260, 1997

14. Matthews DR, Hosker JP, Rudenski AS, et al: Homeostasis model assessment: Insulin resistance and B-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28: 412-419, 1985

15. Taniguchi A, Nagasaka S, Fukushima M, et al: Assessment of insulin sensitivity and insulin secretion from the OGTT in nonobese Japanese type 2 diabetic patients: Comparison with minimal model approach (letter). Diabetes Care 23:1439-1440, 2000

16. Taniguchi A, Nakai Y, Doi K, et al: Insulin sensitivity, insulin secretion, and glucose effectiveness in obese subjects: A minimal model analysis. Metabolism 44:1397-1400, 1995

17. Haffner SM, D'Agostino R Jr, Mykkanen L, et al: Insulin sensitivity in subjects with type 2 diabetes. Relationship to cardiovascular risk factors: The Insulin Resistance Atherosclerosis Study. Diabetes Care 22:562-568, 1999

18. Chaiken R, Banerji MA, Huey H, et al: Do blacks with NIDDM have an insulin-resistance syndrome? Diabetes 42:444-449, 1993

19. Bergman RN: Toward physiological understanding of glucose tolerance: minimal-model approach. Diabetes 38:1512-1527, 1989

20. Taniguchi A, Nakai Y, Doi K, et al: Glucose effectiveness in two subtypes within impaired glucose tolerance. A minimal model analysis. Diabetes 43:1211-1217, 1994

21. Steiner G: Insulin and hypertriglyceridemia, in Waldhausl WK (ed): Diabetes. Amsterdam, The Netherlands, Excerpta Medica, 1979, pp 590-593

22. Bieger WP, Michel G, Barwich D, et al: Diminished insulin

receptors on monocytes and erythrocytes in hypertriglyceridemia. Metabolism 33:982-987, 1984

23. Taniguchi A, Fukushima M, Sakai M, et al: Effect of physical training on insulin sensitivity in Japanese type 2 diabetic patients: Role of serum triglyceride level (letter). Diabetes Care 23:857-858, 2000

24. Emoto M, Nishizawa Y, Maekawa K, et al: Homeostasis model assessment as a clinical index of insulin resistance in type 2 diabetic patients treated with sulfonylureas. Diabetes Care 22:818-822, 1999

25. Bonora E, Targher G, Alberiche M, et al: Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity. Studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care 23:57-63, 2000

26. Fukushima M, Taniguchi A, Sakai M, et al: Homeostasis model assessment as a clinical index of insulin resistance: Comparison with the minimal model analysis. Diabetes Care 22:1911-1912, 1999 (letter)

27. Hermans MP, Levy JC, Morris RJ, et al: Comparison of insulin sensitivity tests across a range of glucose tolerance from normal to diabetes. Diabetologia 42:678-687, 1999

28. Stumvoll M, Mitrakou A, Pimenta W, et al: Assessment of insulin secretion from the oral glucose tolerance test in white patients with type 2 diabetes (letter). Diabetes Care 23:1440-1441, 2000

29. Miettinen H, Haffner SM: The homeostasis model (HOMA) in Mexican Americans and non-Hispanic whites in the San Antonio Heart Study. Diabetologia 391:A159, 1996 (suppl 1)

30. Schoonjans K, Auwerx J: Thazolidinediones: An update. Lancet 355:1008-1010, 2000