Plasma Adiponectin Plays an Important Role in Improving Insulin Resistance With Glimepiride in Elderly Type 2 Diabetic Subjects

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OBJECTIVE — We investigated the effect of glimepiride, a third-generation sulfonylurea hypoglycemic agent, on insulin resistance in elderly patients with type 2 diabetes, in connection with plasma adiponectin and 8-epi-prostagrandin F2α (8-epi-PGF2α), an oxidative stress marker.

RESEARCH DESIGN AND METHODS — A total of 17 elderly patients with type 2 diabetes received 12 weeks of treatment with glimepiride. Homeostasis assessment model of insulin resistance (HOMA-IR), homeostasis assessment model of β-cell function, HbA_{1c}, C-peptide in 24-h pooled urine (urine CPR), and plasma concentrations of 8-epi-PGF2α, tumor necrosis factor-α (TNF-α), plasminogen activator inhibitor type 1, and adiponectin were measured at various times. The metabolic clearance rate of glucose (MCR-g) was also assessed by a hyperinsulinemic-euglycemic clamp.

RESULTS — After 8 weeks of glimepiride treatment, significant reductions were observed in HbA_{1c} (from 8.4 ± 1.9 to 6.9 ± 1.0%), HOMA-IR (from 2.54 ± 2.25 to 1.69 ± 0.95%), and plasma TNF-α concentrations (from 4.0 ± 2.0 to 2.6 ± 2.5 pg/ml). MCR-g was significantly increased from 3.92 ± 1.09 to 5.73 ± 1.47 $mg \cdot kg^{-1} \cdot min^{-1}$. Plasma adiponectin increased from 6.61 ± 3.06 to 10.2 ± 7.14 μg/ml. In control subjects, who maintained conventional treatment, no significant changes were observed in any of these markers.

CONCLUSIONS — Glimepiride remarkably improved insulin resistance, suggested by a significant reduction in HOMA-IR, an increase in MCR-g, and a reduction in HbA_{1c} without changing extrapancreatic β-cell function and urine CPR. Increased plasma adiponectin and decreased plasma TNF-α may underlie the improvement of insulin resistance with glimepiride.

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In elderly diabetic subjects, insulin resistance and obesity increase the risk for arteriosclerosis and related cardiovascular diseases (1–4). In addition to genetic and environmental factors, aging is considered to be a factor that affects insulin resistance. There are several hypotheses for the mechanism of the age-associated increase in insulin resistance (4,5), including *1*) a decrease of glucose uptake in association with reduction of skeletal muscle volume due to reduced daily activities, *2*) a reduction of myocardial blood flow because of a decrease in capillary density, *3*) an increase in abdominal visceral fat, *4*) a decrease in the number of insulin receptors, *5*) a decrease in the number of receptor binding capacity, and 6) an abnormal intracellular signal transduction after the receptor binding (GLUT4 translocation) (6,7).

The administration of insulin or sulfonylurea hypoglycemic (SU) agents to patients with type 2 diabetes elevates blood insulin concentrations and improves glucose metabolism by accelerating cellular glucose uptake. On the other hand, the increase of cellular energy due to excessive insulin secretion is considered to cause weight gain through deposition of body fat. It has also been suggested that the excessive secretion of insulin by SU agents not only incurs a risk of hypoglycemia but also may be related to the development of so-called secondary failure, a problem commonly recognized in the use of SU agents. These phenomena may affect pathophysiology and prognosis in diabetic subjects and thereby progression of atherosclerosis, especially in elderly patients. Because hyperinsulinemia is a risk factor for the onset and progression of large vessel diseases such as coronary arteries, drugs that do not induce hyperinsulinemia would be desirable in treating diabetic patients.

One of the characteristics of glimepiride, a third-generation SU agent, is a mild effect on insulin secretion with the equivalent hypoglycemic effect of glibenclamide (8), although the mechanism for the characteristic has not been well documented (9,10). A previous study using a hyperinsulinemic-euglycemic clamp method in insulin-resistant subjects with a family history of type 2 diabetes and in subjects with normal glucose tolerance

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Abbreviations: 8-epi-PGF2α, 8-epi-prostagrandin F2α; α-GI, α-glucosidase inhibitor; FPG, fasting plasma glucose; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; IRI, immunoreactive insulin; MCR-g, metabolic clearance rate of glucose; PAI-1, plasminogen activator inhibitor type 1; SU agent, sulfonylurea hypoglycemic agent; TNF, tumor necrosis factor; urine CPR, C-peptide in 24-h-pooled urine.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline participant characteristics*

n	29
Ages (years)	67.8 ± 9.9
M/F	19/10
HbA_{1c} (%)	8.1 ± 2.5
BMI (kg/m^2)	21.2 ± 2.2

Data are means ± SD or *n*.

showed that glimepiride improves peripheral insulin sensitivity (11).

It has also been suggested in recent years that some of the cytokines secreted from adipose tissue may be related to insulin resistance. Among the cytokines, adiponectin is considered to increase insulin sensitivity (12), whereas tumor necrosis factor (TNF)-α is considered to reduce it (13). Plasminogen activator inhibitor type 1 (PAI-1) may not directly be involved in insulin resistance but may be involved in the progression of arteriosclerosis by its thromboplastic effect (14).

In this study, we investigated the extrapancreatic effect of glimepiride in elderly patients with type 2 diabetes, in connection with the plasma concentration of adiponectin and TNF-α, factors involved in insulin resistance and plasma concentration of 8-epi-prostagrandin F2α (8-epi-PGF2α), an oxidative stress marker, and PAI-1 as an index for arteriosclerosis.

RESEARCH DESIGN AND METHODS

Patient selection

The patients consisted of 29 elderly subjects (19 men and 10 women, age 67.8 ± 9.9 years) with type 2 diabetes who, at study entry, showed poor blood glucose control (HbA_{1c} 8.1 ± 2.5% [mean ± SD]) despite treatment with oral glibenclamide (7.5–10 mg daily) and acarbose (α-glucosidase inhibitor [α-GI]) (300 mg daily). Clinical profiles of the subjects are shown in Table 1. All subjects were recruited from the geriatric outpatient division of the Nagoya University Hospital. Subjects were not included who already had concomitant large vessel disease (e.g., clinical evidence of coronary artery disease) or were on insulin treatment.

All subjects were randomly assigned to either a group whose medication was changed from glibenclamide to glimepiride (Amaryl) at study entry (glimepiride treatment group, $n = 17$, 11 men and 6 women) or a group whose medication was not changed (control group, $n = 12$, 8 men and 4 women). The oral dose of glimepiride started from 1 mg daily and increased up to 6 mg daily until a fasting glucose level <120 mg/dl or HbA_{1c} level <6.5% was achieved. The treatment with α-GI was continued in all patients. The study was approved by the local ethical committee. Written informed consent was obtained from all subjects after they were given a complete description of the study.

Blood sampling

Blood and urine were sampled at different times (4, 8, and 12 weeks after the start of glimepiride treatment). The following measurements were examined before and 4, 8, and 12 weeks after the start of treatment: BMI [(body weight)/(height)^2], serum total cholesterol, triglyceride, HDL cholesterol, fasting plasma glucose (FPG) and insulin in the morning and 2 h after breakfast, HbA_{1c}, and C-peptide in 24-h pooled urine (urine CPR). Indexes that are considered to reflect insulin resistance were also measured, including homeostasis model assessment of insulin resistance (HOMA-IR) = FPG (mg/dl) × immunoreactive insulin (IRI) (μU/ml)/405, an insulin secretion index, and homeostasis model assessment of β-cell function (HOMA-β) = 360 × IRI/(FPG-63), an index to reflect the ability of endogenous insulin secretion (15–17). At 4 and 8 weeks after the start of treatment, the following indexes, which are considered to be involved in insulin resistance, were also investigated: plasma PAI-1, plasma 8-epi-PGF2α, plasma TNF-α, and plasma adiponectin. As for seven elderly control subjects with type 2 diabetes, who remained on the combination therapy with glibenclamide and α-GI, plasma concentrations of TNF-α and 8-epi-PGF2α were measured at two time points with an interval of 8 weeks for comparison with the results of the glimepiride treatment group. Enzyme-linked immunosorbent assay kits were used for the measurement of concentrations of 8-epi-PGF2α (Oxis International, Portland, ME), TNF-α (Jimro, Takasaki, Japan), PAI-1 (Mitsubishi Chemical and Medical, Tokyo), and adiponectin (Linco Research, St. Charles, MO).

Measurement of the metabolic clearance rate of glucose

In 6 of the 17 patients who were randomly selected from the glimepiride treatment group, a hyperinsulinemic-euglycemic clamp was carried out by using an artificial pancreas (STG-22; Nikkiso, Tokyo) (18) before and at 8 weeks after the start of the treatment to assess insulin resistance in the peripheral tissue, especially in the skeletal muscle. The subjects were kept in a fasting state by not having any food intake for >10 h before the trial. Intravenous injection of insulin was made with a constant infusion rate (insulin infusion rate = 1.12 mU · kg^{-1} · min^{-1}) to suppress the secretion of endogenous insulin. Then, glucose was injected to maintain the fasting blood glucose within the normal range (100–110 mg/dl). When the dose of glucose injection became constant, the constant glucose infusion rate, given as the *M* value, was recorded as an index to reflect insulin resistance in skeletal muscle. The metabolic clearance rate of glucose (MCR-g) was obtained from the following formula: MCR-g = *M*/fasting blood glucose × 100. Because the glucose release from the liver into the bloodstream is almost completely inhibited when peripheral insulin concentrations are at the physiological upper limit, the injection volume of glucose and peripheral glucose, mainly taken up by the skeletal muscle, are considered to be in an equilibrium state. Therefore, glucose uptake of the skeletal muscle is estimated from the amount of glucose injected into the body (18,19).

Statistical analysis

Data are means ± SD, and all variables were normally distributed. The paired Student's *t* tests was applied, and a *P* value of <0.05 was considered significant. Statistical analyses were performed using Stat View software (version 5.01; SAS Institute, Cary, NC).

RESULTS — Clinical profiles of the patients are shown in Tables l and 2. Age, sex, BMI, lipid profiles (total cholesterol, triglycerides, and HDL cholesterol), and HbA_{1c} did not differ between the group treated with glimepiride and the control group. Eight weeks of treatment with glimepiride significantly reduced HbA_{1c} and HOMA-IR (Table 1). No significant changes were observed in urine CPR and HOMA-β in the glimepiride treatment

Table 2—*HbA_{1c}, BMI, urine CPR, HOMA-R, HOMA-β, plasma lipids, plasma glucose, and plasma insulin at baseline and at 4, 8, and 12 weeks after treatment*

	Baseline	4 weeks	8 weeks	12 weeks
HbA_{1c} (%)	8.4 ± 1.9	7.5 ± 1.2	6.9 ± 1.0*	6.5 ± 1.0*
BMI (kg/m^2)	21.2 ± 2.2	21.2 ± 2.3	21.4 ± 2.1	20.9 ± 1.6
Urine CPR (μg/day)	68.9 ± 61.3	63.3 ± 76.4	65.0 ± 44.4	53.2 ± 39.5
HOMA-IR	2.54 ± 2.25	2.45 ± 1.90	1.69 ± 0.95*	1.49 ± 0.71*
HOMA-β	35 ± 31	48 ± 37	44 ± 31	53 ± 35
Total cholesterol (mg/dl)	197 ± 52	183 ± 48	173 ± 44	163 ± 38
Triglycerides (mg/dl)	138 ± 61	124 ± 64	108 ± 59	124 ± 47
HDL cholesterol (mg/dl)	47 ± 18	44 ± 15	43 ± 14	40 ± 13
FBS (mg/dl)	157 ± 50	130 ± 36*	118 ± 30*	110 ± 39*
IRI (μU/ml)	6.5 ± 4.6	7.4 ± 5.1	5.8 ± 2.9	5.5 ± 2.0
2-h FBS (mg/dl)	272 ± 93	204 ± 68*	192 ± 78*	178 ± 73*
2-h IRI (U/ml)	15.2 ± 20.8	20.8 ± 20.9	15.9 ± 10.6	12.2 ± 4.9

Data are means ± SD. *$P < 0.05$. FBS, fetal bovine serum.

group (Table 2), whereas those indexes were increased in the control group (data not shown). Meanwhile, a significant increase in the MCR-g was observed in all subjects, whose insulin resistance was examined by the hyperinsulinemic-euglycemic clamp test (Table 3). The blood glucose levels during fasting and 2 h after breakfast became significantly lower than the baseline levels at 4, 8, and 12 weeks after glimepiride treatment; however, those levels tended to increase in the control group (Table 2).

Plasma 8-epi-PGF2α, TNF-α, PAI-1, and adiponectin concentrations

There was a highly significant elevation in plasma adiponectin concentration by 8 weeks of glimepiride treatment (Fig. 1). A significant decrease in plasma TNF-α concentration was also observed (Table 3) in the glimepiride treatment group. However, plasma adiponectin and TNF-α concentrations did not change in the control group (adiponectin: from 11.5 ± 4.1 to 10.5 ± 4.0 μg/ml; TNF-α: from 0.14 ± 0.10 to <0.05 pg/ml in 8 weeks). After 8 weeks of glimepiride treatment, plasma concentrations of 8-epi-PGF2α and PAI-1 tended to decrease, and the trend did not reach statistical significance (8-epi-PGF2α: $P = 0.07$; PAI-1: $P = 0.06$, Table 3), whereas those of the control group did not change over the period of observation.

CONCLUSIONS — The results of this study indicate that glimepiride may improve not only glucose metabolism but also insulin resistance in elderly diabetic subjects. They are demonstrated by reductions in HbA_{1c} and blood glucose levels at fasting and 2 h after breakfast, in concert with a significant increase of MCR-g and a reduction in HOMA-IR. By contrast, the control group did not show change in any of those indexes. BMI and plasma lipid profile tended to improve by glimepiride treatment, not by the control treatment using glibenclamide. These results may suggest that glimepiride not only improves blood glucose metabolism and insulin resistance in peripheral tissues, but also may improve factors related to the insulin resistance syndrome, such as plasma lipid profile and BMI. Eventually, glimepiride may be expected to retard the progression of arteriosclerosis, which is one of the major complications in elderly diabetic subjects.

Table 3—*MCR-g, plasma adiponectin, TNF-α, PAI-I, and 8-epi-PGF2α/TP at baseline and at 4 and 8 weeks after treatment*

	Baseline	4 weeks	8 weeks
Adiponectin (μg/ml)	6.61 ± 3.06	8.19 ± 3.33	10.2 ± 7.14*
MCR-g (mg · kg^{-1} · min^{-1})	3.92 ± 1.09	—	5.73 ± 1.47*
TNF-α (pg/ml)	4.0 ± 2.0	3.0 ± 3.0	2.6 ± 2.5*
PAI-I (ng/ml)	29.5 ± 12.0	28.2 ± 12.8	23.6 ± 8.24
8-epi-PGF2α/TP (ng · ml^{-1} · mg protein^{-1})	898.7 ± 234.3	858.7 ± 434.6	881.5 ± 182.2

Data are means ± SD. *$P < 0.05$. TP, total protein.

Alterations of plasma adiponectin concentration and plasma TNF-α concentration in response to glimepiride are intriguing. In both diabetic groups examined, average plasma adiponectin level was significantly lower than that of five nondiabetic elderly subjects (20.6 ± 7.7 μg/ml), which implicates that adiponectin level is decreased in type 2 diabetic subjects, as suggested by Hotta et al. (20). The results of this study are in keeping with those of a previous report (21), showing that blood adiponectin concentration correlates with MCR-g, an index of insulin resistance. It was confirmed that thiazolidine improves insulin resistance by increasing plasma adiponectin (22). Therefore, a similar mechanism may underlie the findings we observed. Recently, attention has been paid to the anti-arteriosclerotic effect of adiponectin in connection with coronary artery disease. Several reports suggest that reduction in plasma adiponectin level may be related to the elevation of insulin resistance (12,23). Adiponectin is a specific plasma glycoprotein, contained in adipose tissue, with various homologies to collagen, complement proteins, and hibernation-associated proteins. In vitro studies have shown anti-atherogenic, anti-inflammatory, and apoptotic effects of adiponectin. The presence of adipocytes is essential for the onset of the normal insulin action. It is noteworthy that secretion factors, such as free fatty acid, TNF-α, and resistin, are involved in insulin resistance resulting from the hypertrophy of adipocytes. In particular, TNF-α is known to induce insulin resistance by inhibiting the activity of insulin receptor tyrosine kinase and the expression and translocation of GLUT4, and adiponectin specifically inhibits the expression of TNF-α among the inflammatory cytokines secreted from macrophages (24–27). Therefore, the observed changes in plasma adipocytokine levels may account for the improvement of insulin resistance by glimepiride.

Reductions of urine CPR and HOMA-β implicate that glimepiride does not stimulate endogenous insulin production, unlike other SU agents. Eight weeks of treatment with glimepiride did not change plasma concentrations of 8-epi-PGF2α, known as a free radical ox-

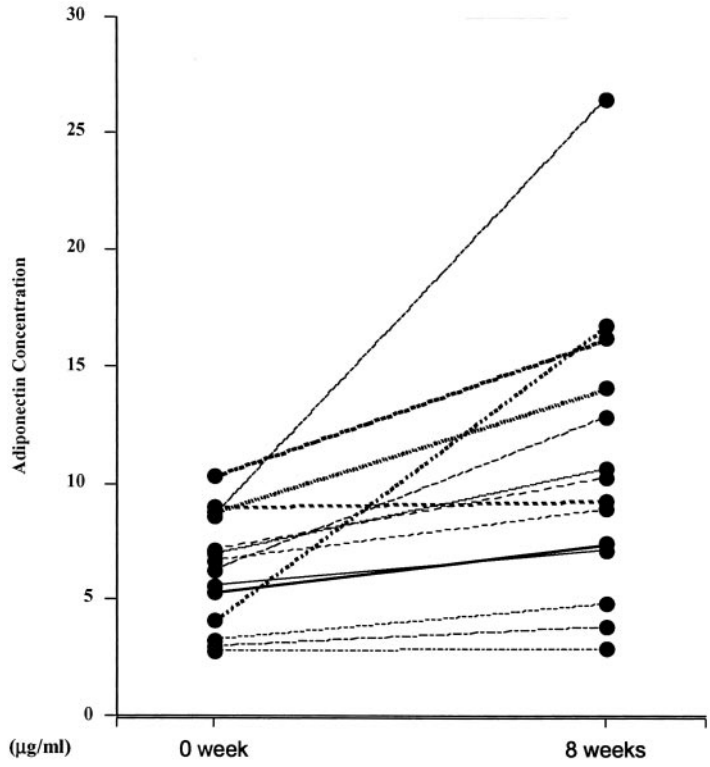

Figure 1—*Change in plasma adiponectin concentration from glimepiride treatment for 8 weeks in each patient.*

idative stress marker, which may suggest that glimepiride has no such short-term effect regarding oxidative stress as the one observed in our previous study using cerivastatin (28). Sampson et al. (29) suggested that acute rather than fasting hyperglycemia may be associated with macrovascular risk in type 2 diabetes by demonstrating a significant rise in plasma 8-epi-PGF2α concentrations when the patients underwent a 75-g glucose tolerance test. Therefore, the same test would have been necessary to assess the effect of glimepiride on reducing oxidative stress because we measured 8-epi-PGF2α concentrations only in fasting conditions. Also, longer periods of observation may be necessary to assess the chronic effect of glimepiride on macrovascular risk.

PAI-1 is considered a risk factor for the development of type 2 diabetes, independent of insulin resistance (14). Observed reduction of PAI-1 by glimepiride, although it did not achieve statistical significance, may implicate a diverse effect of the SU agent other than improvement of insulin sensitivity. The improvement of lipid profile we observed suggests that glimepiride may also have some effect on lipid metabolism. An in vitro experiment investigating oxidative denaturation of LDL in coronary artery endothelial cells has shown that glimepiride inhibits oxidation of LDL in a dose-dependent manner and also lowers plasma LDL (30). To our knowledge, there has been no adequate report conclusively answering the question of whether SU agents have a direct effect on preventing the onset and progression of macrovascular disease. We also found that 8 weeks of glimepiride treatment tended to increase the concentration of plasma NOx (sum of NO_2^- and NO_3^-, data not shown), which implicates that glimepiride may improve nitric oxide availability in vascular endothelial cells, thus retarding the progression of arteriosclerosis when insulin resistance is increased. The extrapancreatic effect of glimepiride needs to be clarified in further investigations.

In summary, the present study demonstrates that glimepiride improves insulin resistance, probably by its extrapancreatic effects, in elderly patients with type 2 diabetes. The mechanism for the improvement may involve a decrease in plasma TNF-α, presumably induced by increased plasma adiponectin. HbA_{1c} and blood glucose levels were improved, whereas the extrapancreatic β-cell function (HOMA-β) and urine CPR remained unchanged. Thus, the observed improvement of glucose metabolism without stimulating extrapancreatic insulin secretion may indicate the advantage of glimepiride over other SU agents in the management of elderly patients with type 2 diabetes.

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