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Glimepiride increases high-density lipoprotein cholesterol via increasing adiponectin levels in type 2 diabetes mellitus

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Abstract

The aims of the present study are to investigate the effect of glimepiride 1 mg/d on plasma adiponectin and to assess the contribution of adiponectin in changing high-density lipoprotein cholesterol (HDL-c) levels after glimepiride treatment. Forty patients with type 2 diabetes mellitus were included. Plasma adiponectin, fasting plasma glucose, insulin, hemoglobin A_{1c}, and cholesterol were measured at study entry and after 3 months of treatment with glimepiride. Both plasma adiponectin level (7.5 ± 4.5 vs 8.3 ± 4.5 μg/mL, $P = .040$) and HDL-c level increased significantly (50 ± 11 vs 53 ± 10 mg/dL, $P = .041$) in the all-subjects group. In the low-adiponectin group (initial plasma adiponectin level <6 μg/mL), both plasma adiponectin level (4.5 ± 0.9 vs 5.9 ± 2.0 μg/mL, $P = .004$) and HDL-c level increased significantly (44 ± 8 vs 49 ± 9 mg/dL, $P = .011$). There was no significant change in the high-adiponectin group (initial plasma adiponectin level ≥6 μg/mL). Change in plasma adiponectin level was an independent factor for change in HDL-c level after adjustment for other factors ($\beta = .574$, $P = .009$, $R^2 = 0.524$, $P = .036$). In conclusion, glimepiride improved plasma adiponectin level, especially in the subjects with type 2 diabetes mellitus with low adiponectin level before treatment, and may directly contribute to improving HDL-c level.

1. Introduction

Glimepiride, a widely used oral sulfonylurea, exhibits dual activity: stimulation of insulin secretion in pancreatic β-cells and enhancement of insulin action in peripheral tissues. The mechanisms enhancing insulin sensitivity are not yet fully elucidated. A recent in vitro study in cultured adipocytes has shown that glimepiride is a highly potent peroxisome proliferator–activated receptor (PPAR) γ agonist [1]. A PPARγ agonist such as a thiazolidinedione stimulates adiponectin secretion in adipocytes. Adiponectin is an adipocyte-specific protein secreted by adipose tissue that is abundant in the blood and that exerts a protective function for atherosclerosis in addition to insulin-sensitizing effects [2-4]. Subjects with hypoadiponectinemia are reported to have increased risk of coronary artery disease [5,6]. In addition to its direct effects on the endothelium and smooth muscle of vascular cells [7,8], adiponectin is associated with regulating postheparin lipoprotein lipase and hepatic lipase, which play a major role in high-density lipoprotein cholesterol (HDL-c) metabolism and are key enzymes in lipid metabolism. These effects are seen in both nondiabetic and diabetic subjects [9,10]. A significant association exists between plasma adiponectin level and HDL-c in patients with type 2 diabetes mellitus [11], and thiazolidinedione increases HDL-c levels with increasing plasma adiponectin levels [12].

To date, a few studies have reported antiatherogenic effect of glimepiride concerning tumor necrosis factor α or homocysteine [13,14]. However, there are conflicting findings regarding the effect of glimepiride on plasma adiponectin level in diabetic patients [15-18]. The present study was designed to investigate the potential effects of glimepiride on plasma adiponectin level and its possible

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contribution to HDL-c level in patients with type 2 diabetes mellitus in a clinical setting.

2. Methods

2.1. Subjects

Forty subjects with type 2 diabetes mellitus (29 men and 11 women) were enrolled from April 2004 to April 2005 at the Diabetes Center of Osaka City University Hospital and Izumi Municipal Hospital. Patients with type 2 diabetes mellitus aged between 40 and 70 years who have insufficient glycemic control (hemoglobin A_{1c} [HbA_{1c}] >6.5%) despite diet, exercise, and/or hypoglycemic agents except for thiazolidinediones and insulin were sequentially included. Patients with type 2 diabetes mellitus with severe heart, renal, or liver diseases and other acute medical illness were excluded. The protocol was approved by the university institution's ethics committee (approval no. 560), and written informed consent from all patients was obtained before the entry. The subjects were given 1 mg/d of glimepiride for 3 months. Before treatment, 4 subjects were treated with α-glucosidase inhibitor, 5 with metformin, 1 with a combination of α-glucosidase inhibitor and metformin, and 30 with diet and exercise alone. Pharmacologic treatment regimens were maintained without change in doses throughout the study.

At study entry and at the end of 3 months of treatment, plasma adiponectin, fasting plasma glucose (FPG), insulin (IRI), HbA_{1c}, total cholesterol (TC), HDL-c, and triglyceride (TG) levels were measured. During the 3-month treatment period, body weight, blood pressure, presence of adverse effects, and drug compliance were checked every 1 or 2 months by clinical diabetologists.

2.2. Assay of plasma adiponectin and biochemical analysis

Fasting plasma adiponectin levels were measured using an enzyme-linked immunosorbent assay kit (Otsuka Pharmaceuticals, Tokyo, Japan). High-density lipoprotein cholesterol levels were measured using enzymatic methods (Cholestest N HDL; Daiichi Pure Chemical, Tokyo, Japan). Fasting plasma glucose levels were measured using the glucose oxidase method; HbA_{1c}, by high-pressure liquid chromatography (reference range, 4.0%-5.8%); and IRI, by immunoradiometric assay (ARCHITECT Insulin; Abbott, Chicago, IL). Serum TC and TG levels were measured using enzymatic methods adapted to an autoanalyzer (Hitachi 7450; Hitachi, Tokyo, Japan). The homeostasis model assessment of insulin resistance (HOMA-IR) and HOMA-β, the indexes of insulin resistance and secretion by the homeostasis model assessment, respectively, were calculated using the following formulas [19]:

$$\text{HOMA}-\text{IR} = \text{IRI}(\text{in milliunits per liter}) \times \text{FPG}(\text{in milligrams per deciliter})/405$$

$$\text{HOMA}-\beta = \text{IRI}(\text{in milliunits per liter}) \times 360/[\text{FPG}(\text{in milliliters per deciliter}) - 63]$$

It has been well documented that these simple indexes are good surrogate markers for insulin resistance and secretion assessed by the glucose clamp technique, the criterion standard, in type 2 diabetes mellitus [20-22].

2.3. Statistical analysis

Values are presented as means ± SD unless otherwise indicated. Statistical analyses were performed with StatView 5.0 software (SAS Institute, Cary, NC). Change of clinical variables after glimepiride treatment was evaluated using paired *t* tests. Difference of baseline clinical variables between the low- and high-adiponectin (LAD and HAD) groups was evaluated using unpaired *t* test. To explore the effects of plasma adiponectin level on HDL-c, simple and multiple linear regression analyses were performed. On the multiple regression analysis, change of HDL-c was adopted as dependent variable; and age, sex, duration of diabetes, HDL-c level before treatment, change of body mass index (BMI), change of TG, change of HOMA-IR, change of HbA_{1c}, and change of plasma adiponectin level after treatment were used as independent variables. *P* values less than .05 were considered significant. Sample size was estimated based on the data of previous reports [16,23] that the difference of the mean plasma adiponectin levels before and after treatment was 3.0 μg/mL with the standard deviation of 7.0 μg/mL, using a 2-sided paired *t* test with 80% power and 10% type 1 error.

3. Results

The treatments of glimepiride for 3 months were continued in all 40 subjects, and none were dropped out.

Table 1
Clinical characteristics at baseline and after 3 months of glimepiride treatment

	Baseline	After treatment
Age (y)	63 ± 11	–
Sex (M/F)	29/11	–
Duration (y)	9 ± 9	–
BMI (kg/m^2)	24.3 ± 3.7	24.1 ± 3.1
SBP (mm Hg)	130 ± 16	128 ± 17
DBP (mm Hg)	74 ± 9	74 ± 11
FPG (mg/dL)	189 ± 111	135 ± 35**
HbA_{1c} (%)	8.6 ± 1.8	7.1 ± 1.1***
IRI (mU/L)	8.4 ± 7.1	10.4 ± 7.9*
HOMA-IR	3.5 ± 3.3	3.5 ± 3.2
HOMA-β	33.6 ± 23.6	63.0 ± 57.6**
TC (mg/dL)	195 ± 31	190 ± 24
TG (mg/dL)	129 ± 84	112 ± 68
HDL-c (mg/dL)	50 ± 11	53 ± 10*
Adiponectin (μg/mL)	7.5 ± 4.5	8.3 ± 4.5*

Values are means ± SD or the number of subjects. SBP indicates systolic blood pressure; DBP, diastolic blood pressure.
*$P < .05$, **$P < .01$, and ***$P < .001$ vs baseline data.

Table 2
Comparison between LAD group and HAD group

	LAD		HAD	
	Baseline	After treatment	Baseline	After treatment
n	20	–	20	–
Age	60 ± 11	–	65 ± 10	–
Sex (M/F)	16/4	–	13/7	–
Duration	7 ± 6	–	10 ± 11	–
BMI	24.2 ± 2.8	24.3 ± 3.0	24.3 ± 4.4	23.8 ± 3.3
FPG	184 ± 53	138 ± 33†††	161 ± 53	134 ± 37†††
HbA_{1c}	9.2 ± 1.7	7.2 ± 0.8†††	8.0 ± 1.7*	7.0 ± 1.4†††
HOMA-IR	4.2 ± 3.7	4.2 ± 3.7	2.9 ± 2.9	2.9 ± 2.6
HOMA-β	29.1 ± 18.5	62.1 ± 40.9††	37.7 ± 35.2	63.8 ± 71.1
TC	187 ± 29	184 ± 31	202 ± 32	196 ± 14
TG	146 ± 103	118 ± 74	113 ± 58	107 ± 63
HDL-c	44 ± 8	49 ± 9†	56 ± 11***	57 ± 9
Adiponectin	4.5 ± 0.9	5.9 ± 2.0††	10.5 ± 4.8	10.7 ± 5.1

Values are means ± SD or the number of subjects.
*P < .05 and ***P < .001 vs baseline in LAD group; $^{\dagger}P$ < .05, $^{\dagger\dagger}P$ < .01, and $^{\dagger\dagger\dagger}P$ < .001 vs baseline in each LAD or HAD group.

Table 1 shows clinical characteristics before and after glimepiride treatment for 3 months in the all-subjects group. Mean age and duration of diabetes were 63 ± 11 (SD) and 9 ± 9 years, respectively. Body mass index was 24.3 ± 3.7 kg/m^2. There were no significant changes in BMI, systolic blood pressure, HOMA-IR, TC, or TG during glimepiride treatment. Neither hypoglycemic episodes nor adverse effects of glimepiride were seen throughout the 3-month treatment period. After glimepiride treatment, FPG and HbA_{1c} significantly decreased; and IRI and HOMA-β significantly increased. Both plasma adiponectin levels (7.5 ± 4.5 vs 8.3 ± 4.5 μg/mL, P = .040) and HDL-c levels increased significantly (50 ± 11 vs 53 ± 10 mg/dL, P = .041) in the all-subjects group (Table 1).

The median plasma adiponectin level of all subjects before treatment was 6 μg/mL. To evaluate the effect of initial plasma adiponectin level on plasma adiponectin level after glimepiride treatment, patients were divided into 2 groups according to the initial level: LAD group (initial plasma adiponectin level <6 μg/mL) and HAD group (initial plasma adiponectin level ≥6 μg/mL). Table 2 shows the comparison of clinical parameters before and after treatment between the LAD group and the HAD group. In the LAD group, HbA_{1c} before treatment was significantly higher and HDL-c level before treatment was significantly lower than those in the HAD group. There were no differences in the other initial clinical parameters between the 2 groups. We analyzed change of adiponectin and HDL-c after glimepiride treatment in each group. In the LAD group, both plasma adiponectin level (4.5 ± 0.9 vs 5.9 ± 2.0 μg/mL, P = .004) and HDL-c level increased significantly (44 ± 8 vs 49 ± 9 mg/dL, P = .011). In the HAD group, neither of them significantly changed (adiponectin: 10.5 ± 4.8 vs 10.7 ± 5.1 μg/mL, P = .810; HDL: 56 ± 11 vs 57 ± 9 mg/dL, P = .683) (Fig. 1).

On the simple linear regression analyses, plasma adiponectin level before treatment was positively correlated with HDL-c level before treatment in the all-subjects group (r = 0.365, P = .021) (Fig. 2A); and change in plasma adiponectin level was positively correlated with increase in HDL-c level in the all-subjects group (r = 0.411, P = .008) (Fig. 2B). The change in plasma adiponectin level after treatment was inversely correlated with the decrease in HbA_{1c} level in the all-subjects group (r = −0.473, P = .002)

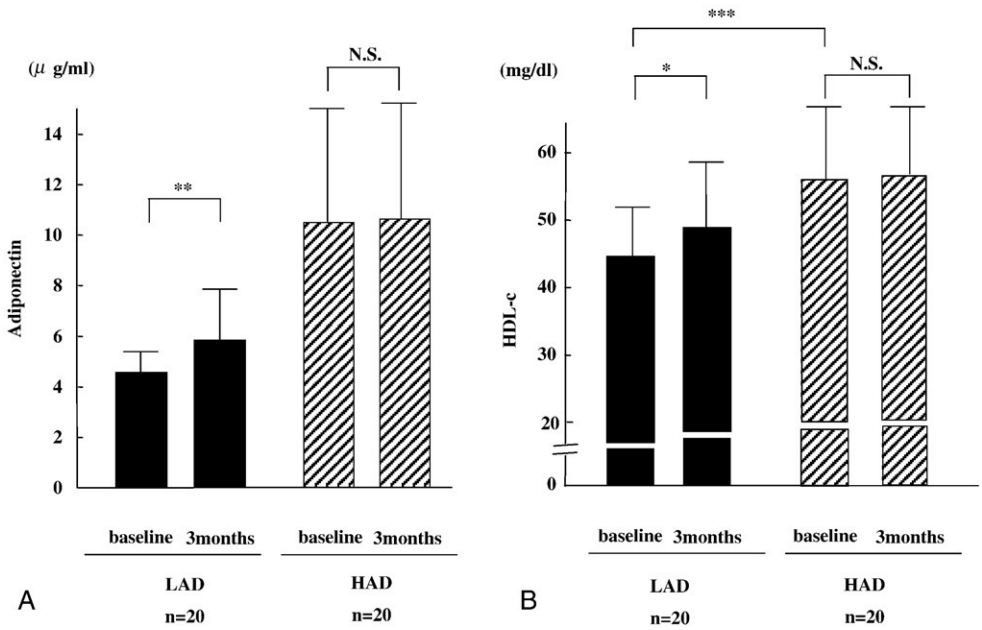

Fig. 1. Changes of plasma adiponectin level (A) and HDL-c level (B) after glimepiride treatment in each group of the LAD group or the HAD group. Black bars, LAD group; oblique line bar, HAD group. ***P < .001, **P < .01, and *P < .05.

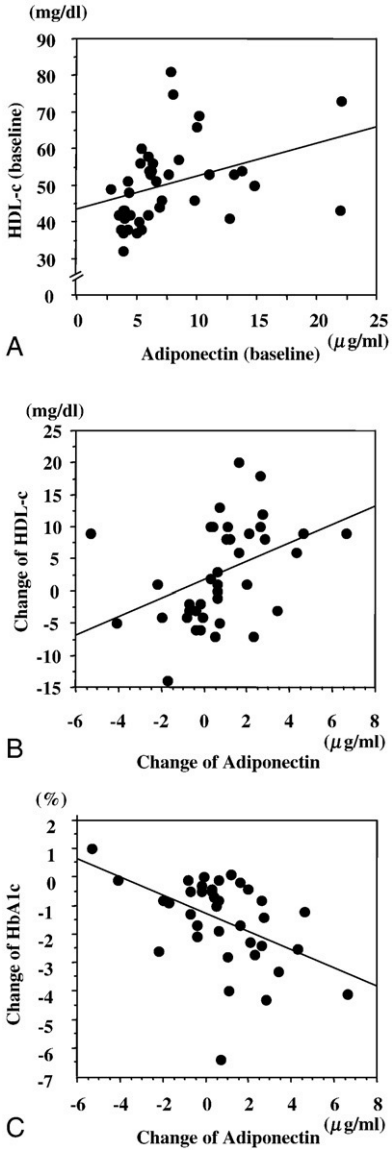

Fig. 2. The association of plasma adiponectin and its change after glimepiride treatment with HDL-c (A), or change of HDL-c (B) and HbA_{1c} (C) after treatment in all subjects. Plasma adiponectin level positively correlated with HDL-c level (A) ($r = 0.365$, $P = .021$), and changes of plasma adiponectin level positively correlated with change of HDL-c (B) ($r = 0.411$, $P = .008$) and inversely with that of HbA_{1c} (C) ($r = -0.473$, $P = .002$).

(Fig. 2C), although there were no significant associations of plasma adiponectin level with HbA_{1c} before treatment ($r = -0.268$, $P = .095$). We found no significant associations of plasma adiponectin level with TG, nor fasting plasma glucose level before treatment (TG: $r = 0.191$, $P = .238$; FPG: $r = 0.157$, $P = .333$) and its change of each after treatment (Δ adiponectin vs ΔTG: $r = 0.155$, $P = .340$; Δ adiponectin vs ΔFPG: $r = 0.177$, $P = .276$). To explore the impact of the change of adiponectin level on the change of HDL-c, the multiple regression analysis was performed, in which change of HDL-c after glimepiride treatment was set as a dependent variable and change of adiponectin level and other clinical parameters possibly affecting HDL-c level were set as independent variables as shown in Table 3. Only change of plasma adiponectin level was a significant independent factor for change in HDL-c level after adjustment for other factors in the all-subjects group ($\beta = .574$, $P = .009$, $R^2 = 0.524$, $P = .036$) (Table 3).

4. Discussion

Glimepiride has been reported to enhance intrinsic PPARγ activity [1] and increase adiponectin [17] in experimental studies. However, it is still unclear whether glimepiride increases plasma adiponectin level in type 2 diabetes mellitus. Tsunekawa et al [15] showed that 8-week glimepiride treatment (1-6 mg/d) increased plasma adiponectin level from 6.61 ± 3.06 to 10.2 ± 7.14 μg/mL (54%) and improved insulin sensitivity index assessed by euglycemic hyperinsulinemic clamp in 17 elderly diabetic subjects without obesity (BMI, 21.2 ± 2.2 [SD]). Their findings suggested an insulin-sensitizing effect of glimepiride via an increase of plasma adiponectin level. Nagasaka et al [16,23] reported that 3-month glimepiride treatment at 1 to 3 mg/d increased plasma adiponectin from 11.1 ± 1.3 to 14.2 ± 1.4 (SE) μg/mL (29%) with decreases of fasting insulin and HOMA-R index in 28 diabetic subjects. No changes of BMI during glimepiride treatment were found in their study. Therefore, they suggested the possibility that glimepiride may increase adiponectin level by improving hyperinsulinemia and/or glycemic control. However, Pfutzer et al [18] recently reported that glimepiride (1-6 mg/d for 6 months) did not significantly increase plasma adiponectin level in 84 diabetic subjects (from 6.5 ± 3.4 to 6.0 ± 2.6 μg/mL). The BMI of their subjects, 31.8 ± 4.3 kg/m^2, was greater than that of our subjects. The inconsistency of our findings from those of the study by Pfutzer et al may be explained by the

Table 3
Standard coefficients of clinical parameters possibly affecting the change of HDL-c (ΔHDL) during glimepiride treatment on multiple regression analysis

	β	P
Age	−.135	.468
Sex (M/F)	.157	.390
Duration	−.072	.676
HDL-c (baseline)	−.202	.276
ΔBMI	−.090	.572
ΔTG	−.303	.121
ΔHbA_{1c}	.343	.115
ΔHOMA-IR	.014	.943
Δadiponectin	.574	.009
R^2	.524	.036

The change in HDL-c after glimepiride treatment was set as a dependent variable and other clinical parameters in Table 3 were set as independent variables on the multiple linear regression analyses. Male sex was entered as 1; female, 0. Δ indicates the change after glimepiride treatment in each independent variable; β, standard coefficients; R^2, coefficients of the determination of the model.

differences in the degree of obesity, doses and period of glimepiride treatment, and ethnicity. Furthermore, in these previous studies [15,16,18,23], significant changes of HDL-c level were not found after glimepiride treatment.

In the present study, we showed that glimepiride significantly increased plasma adiponectin levels in subjects with type 2 diabetes mellitus, especially in those with low plasma adiponectin levels before treatment (LAD group). As shown in Fig. 1, glimepiride increased adiponectin level by 31 % in the LAD group. This finding is unique as compared with those of previous studies as stated above. The mean value of adiponectin level in our LAD group was 4.5 μg/mL, which is likely to be relatively lower than those of the subjects in the previous studies. The mechanisms of this unique finding are not clarified from the present study. However, our findings suggest the possibility that the immature state of adipose tissue with low adiponectin secretion activity may be more sensitive to the PPARγ agonist action of glimepiride than its mature state. Glimepiride may no longer exert PPARγ agonist action on adipose tissue when adipose tissue is highly mature. Pischon et al [6] demonstrated that hypoadiponectinemia can be used as a predictor of coronary artery disease, and Kumada et al [5] showed that subjects with less than 4 μg/mL in plasma adiponectin level had significantly higher odds ratio for coronary artery disease even after adjusting for other known risk factors. Therefore, the subjects in our LAD group seem to have greater risk of coronary artery disease.

Serum HDL-c level is mainly determined by lipoprotein lipase [24] and hepatic lipase activities [24-26]. Von Eynatten et al [9,10] revealed that plasma adiponectin independently contributed to postheparin lipoprotein lipase activity positively and hepatic lipase activity inversely in both diabetic and nondiabetic patients. A significant positive correlation between HDL-c and adiponectin level was also found in diabetic patients [11]. In our regression analysis, an increase in plasma adiponectin levels was the strongest factor affecting HDL-c levels that were increased during glimepiride treatment, independently of changes in other metabolic parameters. Our findings strongly suggest that adiponectin could increase HDL-c levels directly via increased lipoprotein lipase and decreased hepatic lipase activity, although we did not evaluate these enzymes.

There are a few limitations in our study. First, our study lacks a placebo control group who did not receive glimepiride treatment. Therefore, we cannot definitely deny the possibility of placebo effect of the study on plasma adiponectin level. Second, the treatment in our subjects was initiated from minimum dose of glimepiride, 1 mg/d, to avoid hypoglycemia because all subjects were naive for sulfonylurea treatment. Treatment of glimepiride with higher doses and/or longer period may result in different effects on adiponectin level.

In conclusion, glimepiride improved plasma adiponectin level, especially in the subjects with low plasma adiponectin level before treatment, and may directly contribute to improving HDL-c levels. Further studies are needed to clarify the clinical effects of glimepiride on adiponectin and HDL-c metabolism.

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