Hindawi Publishing Corporation
Advances in Endocrinology
Volume 2015, Article ID 782530, 6 pages
http://dx.doi.org/10.1155/2015/782530

Research Article

Effects of Low-Dose Pioglitazone on Serum Levels of Adiponectin, Dehydroepiandrosterone, Amyloid Beta Peptide, and Lipid Profile in Elderly Japanese People with Type 2 Diabetes

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Received 31 August 2015; Revised 4 October 2015; Accepted 7 October 2015

Academic Editor: Curtis Triplitt

This study was performed to see how pioglitazone at low doses could affect blood biomarkers related to atherosclerosis and aging. The effects of an add-on treatment with pioglitazone (15 mg for males and 7.5 mg for females) for 6 months were assessed in 24 outpatients (12 males, 12 females) with type 2 diabetes aged ≥ 70 years. As doses of sulfonylurea were reduced in 10 patients, no significant differences in HbA1c and glucose levels were seen. After the treatment, serum levels of HDL cholesterol, arachidonic acid (predominant in males), and high-molecular-weight adiponectin significantly increased. The level of dehydroepiandrosterone sulfate significantly decreased. No significant changes were seen in those of small dense LDL cholesterol, high-sensitivity C-reactive protein, and amyloid beta peptides 1–40 and 1–42. There was a slight but significant increase in body weight, but apparent adverse effects were not observed. In conclusion, pioglitazone at low doses increased serum adiponectin, HDL cholesterol, and arachidonic acid levels but decreased serum dehydroepiandrosterone level, not associated with glycemia, in elderly Japanese people with type 2 diabetes. An optimal dose of pioglitazone should be sought for to minimize its adverse effects and to fully exert its pleiotropic effects such as antiatherosclerotic and antiaging effects.

1. Introduction

According to the statement of management of hyperglycemia in type 2 diabetes, 2015 [1], pioglitazone, a peroxisome proliferator-activated receptor γ (PPARγ) agonist that improves insulin sensitivity, has high efficacy and an insulin-sparing effect at the expense of weight gain, fluid retention, and increased risk of heart failure as well as bone fractures predominant in females. When used, therefore, low doses are advisable still with caution for its possible adverse effects. An earlier concern that pioglitazone is associated with bladder cancer has largely been allayed by subsequent evidence [2, 3], leaving potentially increased risk of prostate and pancreatic cancers [3]. Taking into account the risk-benefit ratio for the use of pioglitazone in the treatment of type 2 diabetes, several studies have been undertaken to examine the efficacy and safety of low-dose pioglitazone for its optimal use [4–8].

In addition to glycemic control through insulin sensitization, pioglitazone has been demonstrated to have the potency to exert antioxidative and anti-inflammatory effects in experimental studies [9–11] and protective effects in neurodegenerative diseases of animal models [12–14]. The present study was performed to see how pioglitazone at low doses could affect blood biomarkers related to atherosclerosis and aging, such as adiponectin [15, 16], dehydroepiandrosterone sulfate (DHEA-S) [17, 18], amyloid beta peptide [19, 20], and lipid profile including small dense low-density lipoprotein (LDL) cholesterol [21, 22] and polyunsaturated fatty acids [23, 24], in elderly Japanese people with type 2 diabetes.

2. Materials and Methods

2.1. Study Patients. Twenty-four outpatients (12 males, 12 females) with type 2 diabetes aged ≥ 70 years, who gave their

Table 1: Baseline clinical characteristics of 24 elderly patients with type 2 diabetes.

	Male	Female
n	12	12
Age (year)	76.3 ± 3.9	76.5 ± 7.0
Body height (cm)	163.0 ± 6.6	148.0 ± 5.9
Body mass index (kg/m^2)	23.1 ± 2.4	22.9 ± 4.2
Duration of diabetes (year)	14.0 ± 10.1	16.2 ± 12.0
Diabetic retinopathy		
(none/simple/preproliferative)	9/2/1	10/1/1
Albuminuria (norm/micro/macro-)	7/3/2	7/5/0
Diabetic therapy		
(diet/non-SU/SU included)	0/3/9	0/2/10
Morbidities (treated with oral agents)		
Hypertension (*n*)	9	11
Hypercholesterolemia (*n*)	2	3
Hypertriglyceridemia (*n*)	0	2
Hyperuricemia (*n*)	1	1
Antiplatelet therapy (*n*)	5	7

SU: sulfonylurea.

informed consent to the present study in accordance with the Declaration of Helsinki, were examined at the Outpatient Clinic of Matsumoto Medical Center in an ordinary clinical setting. The effects of an add-on treatment with low-dose pioglitazone (15 mg for males, 7.5 mg for females) for 6 months were assessed. Clinical characteristics of the subjects at the baseline are shown in Table 1. In male patients, one patient had been treated with α-glucosidase inhibitor (GI) alone; two patients had been treated with metformin (500 mg) alone; three patients had been treated with metformin (500 mg) and sulfonylurea (SU: gliclazide, 40, 40, and 80 mg); six patients had been treated with SU alone (gliclazide, 20, 40, and 40 mg; glimepiride, 2, 3, and 4 mg). In female patients, one patient had been treated with α-glucosidase inhibitor (GI) alone; one patient had been treated with α-GI and SU (glimepiride, 3 mg); one patient had been treated with metformin (500 mg) alone; two patients had been treated with metformin (500 mg) and SU (gliclazide, 80 mg; glimepiride, 2 mg); seven patients had been treated with SU alone (gliclazide, 20 and 40 mg; glimepiride, 0.5, 0.5, 1, 2, and 4 mg). While non-SU agents and other medications were not changed, SU doses were proactively decreased in order to avoid hypoglycemia.

2.2. Blood Collection and Measurements. Before and after the 6-month treatment with pioglitazone, casual blood samples were collected and stored in serum at −20°C until being used. In all but two male patients, the blood was drawn after eating their breakfast or lunch, respectively, at the similar time of the day for each patient, before and after the 6-month treatment in the outpatient clinic. In the two male patients, the blood was drawn at the fasting state before and after the treatment.

High-molecular-weight adiponectin [5] was measured by chemiluminescent enzyme immunoassay (CLEIA) (reference range of 4.8 ± 3.1 μg/mL for males aged 46.4 ± 10.1 years and 9.0 ± 5.3 μg/mL for females aged 41.5 ± 9.8 years). Dehydroepiandrosterone sulfate (DHEA-S) was measured by CLEIA (reference range of 45 (5, 253) and 35 (7, 177) μg/dL (median (2.5%, 97.5%)) for males and females aged > 71 years). Amyloid beta peptides 1–40 and 1–42 were measured with Human βAmyloid 1–40 and 1–42 ELISA kits (Wako Pure Chemical Industries, Ltd., Osaka, Japan). Small dense LDL cholesterol was measured by a homogeneous assay [21] with sd LDL-EX (Denka Seiken Co., Ltd., Tokyo, Japan). Insulin was measured by CLEIA; free fatty acids were measured by an enzymatic method and polyunsaturated fatty acids were analyzed by gas chromatography; and high-sensitivity C-reactive protein was measured by a latex-enhanced nephelometric assay. All of these measurements were performed by a referee laboratory (SRL, Inc., Tokyo, Japan). The measurements of HbA1c and plasma glucose by automated analyzers ADAMS HA-8160 and GA-1170 (ARKRAY, Tokyo, Japan) and those of LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride by an automated analyzer (Hitachi, Tokyo, Japan) were performed at the outpatient clinic.

2.3. Statistical Analysis. Results are expressed as mean ± SD. Differences between data before and after the 6-month treatment with pioglitazone were analyzed by two-sided paired t-test, with significance level set at $p < 0.05$.

3. Results

When or after adding pioglitazone (15 mg for males, 7.5 mg for females), doses of SU were decreased in 10 (6 males and 4 females) patients. The doses of gliclazide decreased from 44 ± 22 mg to 20 ± 14 mg per day in 5 (3 males and 2 females) patients, and those of glimepiride decreased from 2.7 ± 1.5 mg to 1.2 ± 0.8 mg per day in 5 (3 males and 2 females) patients. SU doses were not changed in 9 (3 males and 6 females) patients.

Table 2 shows changes in metabolic parameters after the add-on treatment of low-dose pioglitazone for 6 months (15 mg for males, 7.5 mg for females). There was a slight but significant increase in body weight, although apparent edema or adverse effects were not observed. As SU doses were decreased in 6 male patients and in 4 female patients, there were no significant differences in HbA1c levels and in casual glucose levels. The insulin levels (μU/mL) taken at the same time were 17.7 ± 16.0 and 12.1 ± 10.9 ($p = 0.137$) before and after the treatment in male patients, 19.3 ± 14.4 and 19.3 ± 14.4 ($p = 0.058$) in female patients, and 18.5 ± 14.9 and 13.2 ± 9.4 ($p = 0.017$) in total patients.

While HDL cholesterol level increased significantly, LDL and small dense LDL cholesterol levels did not change significantly. It is of note that arachidonic acid level significantly increased predominantly in male patients. When two male patients whose blood samples were taken in the fasting state were excluded, the levels of plasma glucose (mg/dL), LDL cholesterol (mg/dL), small dense LDL cholesterol (mg/dL), HDL cholesterol (mg/dL), triglyceride (mg/dL), and free fatty acid (μEq/L) before and after the treatment were 200 ± 72 and 153 ± 54 ($p = 0.113$), 103 ± 23 and 105 ± 24 ($p = 0.533$),

Table 2: Metabolic parameters before and after the add-on treatment of low-dose pioglitazone for 6 months (15 mg for males, 7.5 mg for females).

	Male ($n = 12$)			Female ($n = 12$)			Total ($n = 24$)		
	Before	After	p value	Before	After	p value	Before	After	p value
Body weight (kg)	61.4 ± 7.2	62.1 ± 7.2	0.099	50.0 ± 8.0	50.8 ± 7.9	0.062	55.7 ± 9.5	56.4 ± 9.3	0.010*
HbA1c (%)	7.3 ± 0.6	7.0 ± 0.5	0.105	6.8 ± 0.7	6.9 ± 1.1	0.142	7.0 ± 0.7	6.9 ± 0.8	0.474
Casual plasma glucose (mg/dL)	189 ± 70	151 ± 50	0.124	169 ± 47	169 ± 52	0.958	179 ± 60	160 ± 51	0.199
Casual serum levels of									
LDL cholesterol (mg/dL)	105 ± 27	110 ± 29	0.214	109 ± 20	115 ± 20	0.379	107 ± 23	113 ± 25	0.148
Small dense LDL-C (mg/dL)	23.8 ± 12.6	25.5 ± 13.4	0.201	24.2 ± 7.8	24.2 ± 10.2	0.993	24.0 ± 10.3	24.8 ± 11.7	0.645
HDL cholesterol (mg/dL)	45.3 ± 6.7	48.3 ± 7.1	0.132	50.5 ± 11.0	53.8 ± 12.2	0.035*	48.0 ± 9.3	51.0 ± 10.1	0.009**
Triglyceride (mg/dL)	118 ± 7	125 ± 58	0.717	136 ± 38	117 ± 28	0.154	127 ± 50	121 ± 45	0.584
Free fatty acid (μEq/L)	260 ± 225	223 ± 165	0.497	283 ± 219	258 ± 175	0.589	272 ± 218	240 ± 167	0.370
Arachidonic acid (μg/mL)	111 ± 30	123 ± 28	0.021*	129 ± 47	143 ± 35	0.108	120 ± 39	133 ± 33	0.007**
Eicosapentaenoic acid (μg/mL)	44.4 ± 19.3	54.0 ± 24.4	0.015*	49.9 ± 27.8	44.0 ± 20.9	0.280	47.2 ± 23.6	49.0 ± 22.8	0.610
Docosahexaenoic acid (μg/mL)	106 ± 30	119 ± 35	0.082	111 ± 20	117 ± 19	0.730	113 ± 30	118 ± 28	0.300

LDL-C: low-density lipoprotein cholesterol; HDL: high-density lipoprotein; * $p < 0.05$, ** $p < 0.01$ by two-sided paired t-test.
Doses of sulfonylurea were reduced in 6 male patients and in 4 female patients.

Table 3: Serum levels of adiponectin, dehydroepiandrosterone, C-reactive protein, and amyloid beta before and after 6-month add-on treatment of low-dose pioglitazone (15 mg for males, 7.5 mg for females).

	Male ($n = 12$)			Female ($n = 12$)			Total ($n = 24$)		
	Before	After	p value	Before	After	p value	Before	After	p value
High-molecular-weight adiponectin (μg/mL)	4.7 ± 3.2	12.3 ± 6.9	<0.001**	6.3 ± 3.0	12.3 ± 4.6	<0.001**	5.5 ± 3.2	12.3 ± 5.7	<0.001**
Dehydroepiandrosterone sulphate (μg/dL)	95.8 ± 52.0	89.8 ± 48.4	0.265	72.1 ± 40.5	62.5 ± 33.1	0.061	84.0 ± 47.2	76.2 ± 42.9	0.030*
High-sensitivity C-reactive protein (μg/L)	934 ± 1022	833 ± 1298	0.840	877 ± 1141	520 ± 290	0.248	905 ± 1060	676 ± 934	0.424
Amyloid beta peptide 1–40 (pmol/L)	49.8 ± 10.9	49.2 ± 8.9	0.789	42.5 ± 15.4	50.0 ± 11.4	0.062	46.1 ± 13.6	49.6 ± 10.0	0.132
Amyloid beta peptide 1–42 (pmol/L)	2.8 ± 0.8	2.6 ± 0.8	0.656	2.9 ± 1.6	3.3 ± 1.4	0.272	2.9 ± 1.2	2.9 ± 1.1	0.713

* $p < 0.05$, ** $p < 0.01$ by two-sided paired t-test.
Doses of sulfonylurea were reduced in 6 male patients and in 4 female patients.

21.7 ± 6.2 and 23.6 ± 8.0 ($p = 0.268$), 47.4 ± 5.5 and 50.2 ± 5.6 ($p = 0.190$), 120 ± 63 and 126 ± 61 ($p = 0.792$), and 211 ± 188 and 224 ± 177 ($p = 0.445$), respectively, in male patients ($n = 10$). Similarly, the arachidonic or eicosapentaenoic acid levels (μg/mL) before and after the treatment were 115 ± 27 and 125 ± 22 ($p = 0.053$) or 43.4 ± 20.9 and 50.6 ± 24.7 ($p = 0.066$) in male patients ($n = 10$) and 123 ± 39 and 135±31 ($p = 0.016$) or 47.0 ± 24.6 and 47.0±22.4 ($p = 0.998$) in total patients ($n = 22$).

Table 3 shows changes in serum levels of high-molecular-weight adiponectin, DHEA-S, high-sensitivity C-reactive protein, and amyloid beta peptides after the 6-month treatment with low-dose pioglitazone. The adiponectin level obviously increased in all patients. The DHEA-S level decreased significantly in total patients, and no significant differences were seen in the C-reactive protein and amyloid beta peptides 1–40 and 1–42, although there was a tendency that the amyloid beta peptide 1–40 increased in female patients.

4. Discussion

Since clinical studies have suggested that pioglitazone has a stronger effect in females than in males [25], 15 mg for males and 7.5 mg for females were employed as a low dose of pioglitazone in the present study. Although such low-dose pioglitazone has been demonstrated to improve glycemic control especially in patients naive to antidiabetic therapy or newly diagnosed with type 2 diabetes [4, 26], HbA1c and blood glucose levels were not significantly improved probably due to dose reduction of SU in the present study. Without glycemic improvement, it is of interest that significant changes after the add-on treatment with low-dose pioglitazone were seen in serum levels of HDL cholesterol, arachidonic acid, adiponectin, and DHEA-S. In addition, apparent adverse effects were not seen.

With cell culture and animal studies, it has been demonstrated that pioglitazone exerts its effect as an insulin sensitizer by both adiponectin-dependent and -independent pathways [27]. Pioglitazone, a PPARγ agonist, can upregulate adiponectin, which has a protective effect on atherosclerosis, by generating small adipocytes that abundantly express and secrete adiponectin and/or directly activating *adiponectin* gene transcription. At a relatively low dose, pioglitazone can ameliorate insulin sensitivity by an adiponectin-dependent pathway increasing adenosine 5′-monophosphate-activated protein kinase activation and decreasing gluconeogenesis in the liver, without an adiponectin-independent pathway increasing muscle glucose uptake or decreasing adipocyte size, serum FFA levels, and expression of tumor necrosis factor-α in adipose tissues. Such adiponectin-dependent effects of pioglitazone may have been seen in the present study where all the patients showed an obvious increase in high-molecular-weight adiponectin level following the low-dose pioglitazone treatment. The decrease in serum insulin levels without changes in the corresponding blood glucose levels suggested improvement of insulin sensitivity. It is presumed that an increase in HDL cholesterol level was mediated through activating the PPARα pathway by adiponectin and pioglitazone [27–29]. The present study did not demonstrate a decrease in small dense LDL cholesterol as shown in the well-designed study using 45 mg pioglitazone [30], where HDL cholesterol level was not changed.

The increase in arachidonic acid level predominant in male patients as shown in the present study is interesting but not readily understandable. Since insulin stimulates Δ^5 desaturase to produce arachidonic acid and eicosapentaenoic acid, insulin resistance is thought to lead to low plasma and tissue concentrations of them [31]. Although arachidonic acid is typically thought of in a negative context because of the precursor of proinflammatory eicosanoids, it actually has physiological importance in the brain [32]. Interestingly, serum level of amyloid beta peptide 1–40 tended to increase in female patients, which may suggest that a low-dose pioglitazone could enhance clearing amyloid beta peptides from the brain [33, 34]. With regard to the decrease in DHEA-S level, its production may be inhibited by pioglitazone [35], but the association of its level with diabetes, atherosclerosis, and aging seems to be unclear [36, 37].

In conclusion, pioglitazone at low doses increased serum adiponectin, HDL cholesterol, and arachidonic acid levels but decreased serum dehydroepiandrosterone level, not associated with glycemia, in elderly Japanese people with type 2 diabetes. An optimal dose of pioglitazone should be sought for to minimize its adverse effects and to fully exert its pleiotropic effects such as antiatherosclerotic and antiaging effects [38–40].

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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