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Comparative effects of pioglitazone and rosiglitazone on plasma levels of soluble receptor for advanced glycation end products in type 2 diabetes mellitus patients

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Abstract

Low levels of soluble receptor for advanced glycation end products (sRAGE) have been associated with the occurrence of vascular complications in patients with type 2 diabetes mellitus. Preliminary evidence has suggested that thiazolidinediones have the ability to modulate circulating levels of this molecule in the hyperglycemic milieu. The aim of this pilot study was to assess the differential effect of 2 different thiazolidinediones—pioglitazone and rosiglitazone—on plasma levels of sRAGE in type 2 diabetes mellitus patients. Sixty type 2 diabetes mellitus subjects were randomly assigned to receive pioglitazone (30 mg/d, n = 19), rosiglitazone (4 mg/d, n = 20), or placebo (medical nutrition therapy, n = 21) for 12 weeks. Changes in plasma glucose, glycosylated hemoglobin, insulin resistance (homeostasis model assessment), total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and sRAGE were evaluated at baseline and after 12 weeks. At 12 weeks, the pioglitazone ($P < .001$) group had a significant increase from baseline in sRAGE values that was not seen in the medical nutrition therapy and rosiglitazone groups. We conclude that, in type 2 diabetes mellitus patients, pioglitazone—but not rosiglitazone—significantly raised sRAGE, which may contribute to its antiatherogenic effects.

1. Introduction

The receptor for advanced glycation end products (RAGE) is a multiligand cell-surface receptor that binds to several distinct proinflammatory molecules and has been implicated in the pathogenesis of diabetes and its cardiovascular complications [1,2].

Besides cell-surface RAGE, a circulating isoform of RAGE, termed *soluble RAGE* (*sRAGE*), circulates in human plasma and has emerged as a reliable biomarker in a number of RAGE-mediated metabolic disorders [3,4]. Total sRAGE in plasma consists of an endogenous splice variant of RAGE lacking the transmembrane domain of the receptor (also known as *endogenous secretory receptor* or *esRAGE*) as well as of proteolytically cleaved isoforms shed into the bloodstream upon digestion of cell-surface RAGE by extracellular metalloproteinases [5]. Soluble RAGE acts as a decoy binding protein for circulating RAGE ligands and may therefore be effective in preventing diabetes-accelerated atherosclerosis [6,7]. In this regard, levels of sRAGE have been reported to be reduced in patients with type 2 diabetes mellitus [8] and to be associated with diabetic atherosclerosis [9]. Intriguingly, there is also evidence to suggest that improvement in metabolic control by oral agents or insulin may result in a significant increase in circulating concentrations of sRAGE [10].

Thiazolidinediones (TZDs) are unique oral agents used in the treatment of diabetes. They work by decreasing insulin resistance at peripheral sites as well as by decreasing hepatic glucose output [11]. Thiazolidinediones primarily target the peroxisome proliferator–activated receptor (PPAR) γ receptor, which is chiefly expressed in the

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adipose tissue but which is also found in the liver, pancreas, muscle, and blood vessels [11]. Thiazolidinediones use has been shown to have favorable effects on blood pressure, lipid levels, and various surrogate biochemical markers of cardiovascular risk [12]. Interestingly, it has been recently suggested that activation of PPAR-γ could be involved in the modulation of RAGE expression in endothelial cells and vascular smooth muscle cells [13,14]. In addition, a previous clinical study has demonstrated that rosiglitazone may increase serum sRAGE levels in type 2 diabetes mellitus patients [15].

Although there is suggestive evidence that TZDs can modulate the RAGE axis in diabetes [13-15], there have been no direct comparisons of the effects of different TZDs on circulating sRAGE concentrations. In this context, the purpose of this study was to evaluate the short-term effects of pioglitazone compared with rosiglitazone and medical nutrition therapy on plasma sRAGE levels in type 2 diabetes mellitus patients.

2. Subjects and methods

2.1. Patients

A total of 60 newly diagnosed (duration <6 months) type 2 diabetes mellitus (according to the American Diabetes Association criteria) patients were recruited in the present study. All subjects described here were of Turkish descent and were naive to prior antidiabetic therapy. Patients were excluded if they were taking medications affecting sRAGE metabolism, such as statins [16,17], angiotensin-converting enzyme inhibitors [18], and angiotensin type 1 receptor antagonists [19], and had acute complications in need of insulin therapy, a history of *impaired hepatic function* (defined as plasma aminotransferase and/or γ-glutamyltransferase level higher than the upper limit of normal for age and sex), *impaired renal function* (defined as serum creatinine level higher than the upper limit of normal for age and sex), and severe anemia. Patients with serious cardiovascular disease (eg, New York Heart Association class I-IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions were not included in this study. Women who were pregnant or breastfeeding were similarly excluded.

Patients were randomly assigned to receive pioglitazone (30 mg/d, n = 19), rosiglitazone (4 mg/d, n = 20), or placebo (medical nutrition therapy, n = 21) for 12 weeks. Medical nutrition therapy was based on American Diabetes Association recommendations and contained 50% of calories from carbohydrates, 30% from fat (6% saturated), and 20% from proteins, with a maximum cholesterol content of 300 mg/d and 35 g/d of fiber.

The study protocol was approved by our Institutional Review Boards and was conducted in accordance with the tenets of the Declaration of Helsinki. Informed consent in writing was obtained from each participant.

2.2. Study design

Before starting the study, all patients underwent an initial screening assessment that included a medical history, physical examination, calculation of body mass index (BMI), assessment of glycemic control (hemoglobin A_{1c} [HbA_{1c}], fasting plasma glucose [FPG] and insulin levels, and homeostasis model assessment of insulin resistance [HOMA-IR] index). Body mass index was calculated as weight in kilograms divided by the square of height in meters. The estimate of insulin resistance was calculated using the HOMA-IR index, with the following formula: insulin resistance = fasting plasma insulin (in microunits per milliliter) × FPG (in millimoles per liter)/22.5 (normal if <2.5, presence of insulin resistance if ≥2.5). All measurements were repeated after 12 weeks of TZD therapy.

2.3. Biochemical analysis

Venous blood samples were drawn in all patients between 8:00 and 9:00 AM. We used plasma obtained by addition of Na_2-EDTA (1 mg/mL), which was centrifuged at 3000*g* for 15 minutes at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at −80°C for less than 3 months. The HbA_{1c} level was measured using high-performance liquid chromatography (DIAMAT; Bio-Rad Laboratories, Hercules, CA), with intra- and interassay coefficients of variation (CsV) of less than 2%. Plasma glucose was assayed using a glucose-oxidase method (GOD/PAP; Roche Diagnostics, Mannheim, Germany) with intra- and interassay CsV less than 2%. Plasma insulin was assayed with Phadiaseph Insulin Radioimmunoassay (Pharmacia, Uppsala, Sweden) using a second antibody to separate the free and antibody-bound 125 I-insulin (intra- and interassay CsV of 4.6% and 7.3%, respectively). Plasma total sRAGE levels were determined using a commercially available enzyme-linked immunosorbent assay kit (Quantikine; R&D Systems, Minneapolis, MN) according to the manufacturer's protocol. Measurements were performed in duplicate, and the results were averaged. All samples were processed blindly to the clinical status of the participants. The intra- and interassay CsV were less than 6% and less than 8%, respectively.

2.4. Statistical analysis

StatMate 2.0 (GraphPad, San Diego, CA) was used for determining the power of the study. The power calculation was based on previous results from a study on the effect of rosiglitazone on serum sRAGE in patients with type 2 diabetes mellitus [15]. In this study, rosiglitazone induced an increase of serum sRAGE levels from a mean of 708 to 824 pg/mL (mean increase, 116 pg/mL). To detect a difference in increase of 100 pg/mL with a 2-sided significance level of .05 and a power of 80%, 17 patients had to be included in each group.

The Kolmogorov-Smirnov test was used to check for normal distribution. Baseline characteristics are given as mean ± standard deviation or counts, as appropriate.

Table 1
Baseline characteristics of patients enrolled in the study (N = 60)

	Baseline
Age (y)	56.4 ± 7.9
Sex (male/female)	25/35
BMI (kg/m^2)	29.5 ± 4.1
FPG (mg/dL)	143.4 ± 18.8
HbA_{1c} (%)	7.4 ± 1.3
TC (mg/dL)	208.6 ± 43.1
HDL-C (mg/dL)	50.0 ± 9.9
LDL-C (mg/dL)	118.4 ± 33.4
TG (mg/dL)	205.5 ± 89.3
HOMA-IR	4.2 ± 2.9
sRAGE (pg/mL)	1079 ± 368

TC indicates total cholesterol.

Correlations were tested using Pearson correlation coefficient. χ^2 testing was used for categorical data. Unpaired *t* test analysis was performed to compare the general characteristics between the 3 study groups (controls, patients treated with pioglitazone, and patients treated with rosiglitazone) at baseline. One-sample paired *t* tests were performed for within-group comparisons between baseline and posttreatment values. Linear mixed models were used to detect potential interactions, which might influence the relation between treatment and change in the study variables (including age and sex). Data analysis was performed using the Statistical Package for Social Sciences software, version 17.0 (SPSS, Chicago, IL). A 2-tailed $P < .05$ was considered statistically significant.

3. Results

The general characteristics of the study participants are shown in Table 1. A total of 60 patients (25 men and 35 women; mean age, 56.4 ± 7.9 years) were enrolled in the study. The characteristics of the patient population at the initial period of the study were similar in the 3 treatment groups with regard to age (P = .86) and sex (P = .11). Baseline BMI, glycemic control values, lipid variables, and sRAGE did not differ significantly across the 3 study groups.

3.1. Body mass index

There was a significant reduction in the mean BMI value of the subjects in the medical nutrition therapy group. No mean BMI change was observed after 12 weeks in either TZD group (Table 2).

3.2. Glycemic control

There was no significant decrease in FPG after 12 weeks (P = not significant) in the medical nutrition therapy group, whereas both TZDs reduced plasma glucose values (both P values < .001). A significant reduction of HbA_{1c} was observed after 12 weeks both in the pioglitazone and rosiglitazone groups ($P < .001$ and $P = .003$, respectively), whereas no HbA_{1c} change was obtained in the medical nutrition therapy group after 12 weeks compared with baseline values. A significant improvement in HOMA-IR index was obtained at 3 months in both TZD groups but not in the medical nutrition therapy group (Table 2).

3.3. Lipid variables

No significant changes in total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were observed in the 3 study groups at the 12-week assessment when compared with the baseline. A significant decrease in triglyceride (TG) (P = .011) was observed with pioglitazone treatment after 12 weeks compared with the baseline values (Table 2).

3.4. Measurements of plasma sRAGE

At 12 weeks, the pioglitazone ($P < .001$) group had a significant increase from baseline in sRAGE values that was not seen in the medical nutrition therapy and rosiglitazone groups (Fig. 1). No sex interaction was present on the effect of pioglitazone and rosiglitazone on plasma sRAGE level. Of note, the correlation between changes in sRAGE and TG

Table 2
Baseline characteristics and parameter changes at 12 weeks in the 3 study groups

	Control (n = 21)			Pioglitazone (n = 19)			Rosiglitazone (n = 20)		
	Baseline	12 wk	*P*	Baseline	12 wk	*P*	Baseline	12 wk	*P*
BMI (kg/m^2)	29.6 ± 4.1	28.8 ± 4.3	.001	29.3 ± 3.0	29.4 ± 3.1	NS	29.6 ± 4.8	29.5 ± 5.3	NS
FPG (mg/dL)	138.9 ± 22.6	130.5 ± 21.7	NS	146.2 ± 26.3	113 ± 15.2	<.001	146.8 ± 19.1	108 ± 10.3	<.001
HbA_{1c} (%)	7.3 ± 0.9	7.2 ± 0.7	NS	7.6 ± 1.5	6.5 ± 0.6	<.001	7.3 ± 1.3	6.2 ± 0.5	.003
TC (mg/dL)	196.3 ± 31.5	195.6 ± 25.2	NS	221.1 ± 37.1	210.4 ± 34.8	NS	209.3 ± 55.5	205.7 ± 49.5	NS
HDL-C (mg/dL)	50.6 ± 12.2	50.5 ± 12.6	NS	49.9 ± 5.9	51.1 ± 9.7	NS	49.4 ± 10.1	48.3 ± 11.2	NS
LDL-C (mg/dL)	116.7 ± 30.1	119 ± 23.7	NS	120.8 ± 29.4	126.9 ± 34.1	NS	119.1 ± 40.4	121.3 ± 36.5	NS
TG (mg/dL)	204.3 ± 74.7	181.1 ± 60.3	NS	206.4 ± 94.1	161.9 ± 73.4	.011	203.4 ± 117.9	180.7 ± 107.4	NS
HOMA-IR	4.1 ± 1.7	3.7 ± 1.4	NS	4.2 ± 2.1	2.5 ± 1.6	.002	4.3 ± 2.1	2.1 ± 1.1	.004
sRAGE (pg/mL)	1073 ± 324	1058 ± 271	NS	1069 ± 302	1200 ± 271	<.001	1099 ± 350	1156 ± 287	NS

NS indicates not significant.

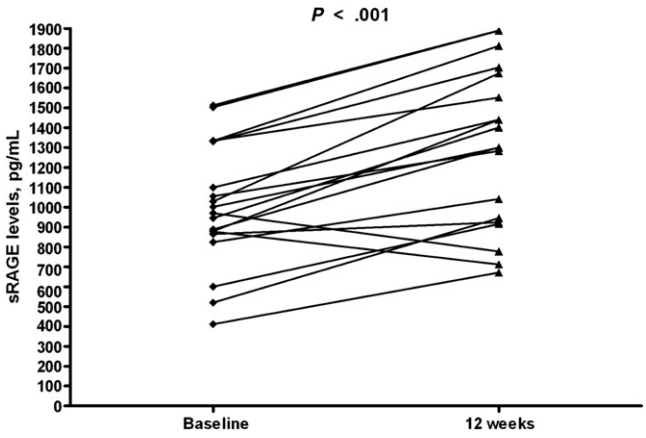

Fig. 1. Changes in plasma sRAGE associated with pioglitazone treatment.

was significant in patients receiving pioglitazone (n = 19, $r = -0.476$, $P < .05$).

4. Discussion

Growing evidence has suggested that TZDs might modulate RAGE expression. In this regard, stimulation of human endothelial cells with rosiglitazone or pioglitazone has been shown to decrease the expression of RAGE on the cell surface in vitro [13]. Another study has shown that pretreatment of rat aortic smooth muscle cells with rosiglitazone significantly down-regulated cell-surface RAGE expression [14]. Recently, Tan and coworkers [15] have demonstrated that rosiglitazone increased circulating levels of sRAGE in type 2 diabetes mellitus patients, an effect that was not seen in patients who received sulfonylurea.

To the best of our knowledge, no direct comparison of the effect of pioglitazone and rosiglitazone on plasma sRAGE has been carried out in patients with type 2 diabetes mellitus. The central question addressed in this pilot study was whether pioglitazone and rosiglitazone could display different metabolic effects on plasma sRAGE in this patient group. The novel finding of our study is that sRAGE was significantly increased by pioglitazone, whereas no significant change was seen with rosiglitazone treatment.

Although all TZDs are capable to reduce glucose concentrations by improving insulin sensitivity, meta-analyses and prospective trials have suggested the possibility of different cardiovascular outcomes for pioglitazone and rosiglitazone [20-22]. Specifically, pioglitazone has been shown to reduce adverse events in patients with type 2 diabetes mellitus with a prior myocardial infarction [20], whereas the use of rosiglitazone has been associated with adverse or at best neutral effects on cardiovascular outcomes [21,22]. It is therefore of interest to establish whether underlying metabolic or biochemical differences exist between different TZDs, that is, whether distinct biochemical effects can be identified that may explain the clinical observations on the cardiovascular outcomes. Of note, different effects of pioglitazone and rosiglitazone have been identified on plasma lipids, with pioglitazone treatment resulting in a more favorable lipid profile than rosiglitazone treatment [23]. In keeping with these findings, our current study provides evidence that pioglitazone seems to have a better effect on levels of TGs and, for the first time, of circulating sRAGE. Interestingly, we found a significant correlation between changes in sRAGE and TGs in patients receiving pioglitazone. Our report cannot clarify the mechanisms behind the differential modulating effects of pioglitazone and rosiglitazone on plasma sRAGE. One possibility for this metabolic effect may reflect a greater functional PPAR-α cross-reactivity for pioglitazone, as reported previously [24], compared with rosiglitazone. Notably, it is possible that PPAR-α activation could be able to reduce the accumulation of advanced glycation end products, thereby inhibiting the expression of cell-surface RAGE [25].

Tan and coworkers [15] have previously reported a sRAGE-increasing effect of rosiglitazone that was not clearly observed in this study. Several possible explanations might account for these apparent discrepant findings. Firstly, the duration of treatment was shorter in our study, and we cannot exclude that an elevation of sRAGE could have occurred if treatment with rosiglitazone has been continued for more than 12 weeks. Another possibility may be inherent in the different genetic background of our patients (who were of Turkish descent) compared with those of the subjects reported by Tan et al (who were of Chinese ethnicity) [15]. In this context, it is worth noting that sRAGE level could actually display a significant ethnic heterogeneity [26]. We believe in any case that our findings point to a more pronounced sRAGE-increasing effect of pioglitazone compared with rosiglitazone that is conceivably more rapid in its onset.

Some caveats of this study merit consideration. Firstly, the present investigation was designed as an exploratory pilot project; and the primary outcome measure in this study was the level of sRAGE in plasma. Thus, the study was not powered to detect changes in the cardiovascular outcomes as a result of different TZD treatments in type 2 diabetes mellitus patients. Greater numbers and longer treatment duration are required to shed more light on this issue. Secondly, only the total amount of sRAGE was measured in our patients. In this regard, it is known that the total pool of circulating sRAGE consists of esRAGE as well as of proteolytically cleaved isoforms of cell-surface RAGE [3]. Previous studies have shown that esRAGE and sRAGE could have a different predictive power for diabetic complications [27], and further studies measuring esRAGE and not only sRAGE are necessary to confirm whether different TZDs can exert distinct RAGE-modulating effects. Thirdly, in this study, we measured sRAGE in plasma, whereas Tan and coworkers [15] used serum samples. A

recent work has shown that samples for measurement of sRAGE in serum or plasma can be collected without significant difficulties with acceptable analytical performance [28]. In future studies, paired plasma and serum samples should be simultaneously analyzed to clarify whether differences in sRAGE levels exist. Finally, all patients described here were of Turkish ethnicity; and our results may not be generalized to different ethnic groups. Ethnical factors should be taken into account during the study of sRAGE because most studies in white populations found a negative association among sRAGE and inflammatory markers [8,16], whereas Japanese authors consistently reported positive relationships [29,30]. The reasons for this ethnical diversity as well as its implications remain to be established in future studies.

In summary, in this study of patients with type 2 diabetes mellitus, treatment with pioglitazone was associated with a significant improvement in sRAGE levels, although no significant effects were seen in patients treated with rosiglitazone. Further investigations are necessary to clarify the possible long-term differences between pioglitazone and rosiglitazone on plasma sRAGE levels and how this could be related to different cardiovascular outcomes.

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