SHORT REPORT

Relationship between urinary sodium excretion and pioglitazone-induced edema

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ABSTRACT

To investigate the factors contributing to pioglitazone-induced edema, we analyzed sodium excretion and several clinical parameters before and after administration of pioglitazone. We analyzed these parameters before and after 8 weeks of administration of pioglitazone to female subjects with type 2 diabetes. When we evaluated whether a significant correlation was found between salt excretion and blood pressure, six patients showed such correlation and 20 patients did not. After 8 weeks of pioglitazone administration, five patients had developed edema, and, surprisingly, such correlation was not found in all five subjects. Salt excretion after administration of pioglitazone was significantly lower in subjects who developed edema and those who showed the correlation, and the hematocrit was significantly lower after administration in the subjects who showed the correlation, but not in the edema group. Pioglitazone-induced edema would be caused not only by fluid retention, but also by other factors, such as vascular permeability.
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KEY WORDS: Edema, Pioglitazone

INTRODUCTION

The use of thiazolidinediones (TZD) in the management of type 2 diabetes mellitus has been associated with an increased risk of fluid retention and edema[1]. The epithelial sodium channel (ENaC) is reported to play a role in TZD-induced fluid retention[2]. In order to investigate the factors contributing to TZD-induced edema, we analyzed sodium excretion and several clinical parameters before and after administration of pioglitazone.

METHODS

The present study was approved by the institutional review board and written informed consent was obtained from all patients. This study is registered with the University Hospital Medical Information Network (UMIN) clinical trials registry, number UMIN 000001948. All subjects were female type 2 diabetes patients aged 20–75 years at screening, because edema was observed more frequently in females than in males[3]. Patients with congestive heart failure, severe ketosis and type 1 diabetes were excluded. Other exclusion criteria were pregnancy or the possibility of becoming pregnant. Having a history of congestive heart failure, a severe hepatic or renal dysfunction, a severe infection or injury, and an allergic history of pioglitazone were also exclusion criteria.

We analyzed salt excretion, blood pressure, bodyweight, several clinical parameters and conforming with or without edema before and after 8 weeks of administration of pioglitazone at 15 mg/day, reflecting dosage commonly recommended in Japan[3]. Edema was clinically diagnosed by the presence of pitting after pressure was applied to the bilateral lower extremities. Before administration, they were asked to measure daily salt excretion by using a salt monitoring system to measure salt in overnight urine[4]. Specifically, before going to bed, they voided completely and discarded the urine. Overnight urine was collected in a 1-L urine cup. After awakening, they voided and placed the urine in the urine cup, adding any urine they had voided overnight. Then they set the salt monitor and recorded the display value[4]. Also, they were asked to measure their blood pressure daily for 21 days. We then evaluated whether a significant correlation was found between salt excretion and blood pressure (correlation coefficient >0.4, $P < 0.05$)[4]. We asked the participants not to change their lifestyle, including foods, salt intake and daily physical activity, and all medications, including anti-hypertensive drugs, during the study.

Results are expressed as means ± SD. Differences between two groups were analyzed for statistical significance by Student's *t*-test for unpaired comparisons. Paired analyses within groups were carried out using paired *t*-test or Wilcoxon signed-rank test as appropriate. Individual comparisons among three groups were assessed with the Kruskal–Wallis test.

RESULTS

The data of the 26 patients who satisfactorily completed the follow-up examinations were included in the analysis. Baseline characteristics of all subjects are shown in Table 1. After 8 weeks of pioglitazone administration, five patients (19.2%) had developed edema, whereas 21 patients (80.8%) had not developed edema. There were no differences in baseline characteristics between the two groups before administration of pioglitazone (Table 2). Although salt excretion was similar in

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Table 1 | Baseline characteristics of all subjects

No. subjects	26
Age (years)	61.3 ± 7.2
Bodyweight (kg)	59.3 ± 11.0
Body mass index (kg/m^2)	24.7 ± 3.9
Systolic blood pressure (mmHg)	130.7 ± 15.8
Diastolic blood pressure (mmHg)	77.9 ± 9.1
Plasma glucose (mg/dL)	171.0 ± 55.4
HbA_{1c} (%)	7.3 ± 1.0
Hematocrit (%)	39.7 ± 2.3
Salt excretion (g/day)	10.4 ± 1.7

Values are means ± SD.

Table 2 | Baseline characteristics of subjects with or without edema

	With edema	Without edema	*P*-value
No. subjects	5 (19.2%)	21 (80.8%)	
Age (years)	62.6 ± 10.2	61.0 ± 6.6	NS
Bodyweight (kg)	67.0 ± 16.8	57.4 ± 8.8	NS
Body mass index (kg/m^2)	26.7 ± 5.8	24.2 ± 3.3	NS
Systolic blood pressure (mmHg)	132.3 ± 19.0	130.3 ± 15.4	NS
Diastolic blood pressure (mmHg)	75.0 ± 13.9	78.5 ± 7.9	NS
Plasma glucose (mg/dl)	169.6 ± 47.5	171.3 ± 58.2	NS
HbA_{1c} (%)	8.0 ± 1.2	7.2 ± 0.9	0.09
Hematocrit (%)	38.7 ± 1.7	39.9 ± 2.4	NS
Salt excretion (g/day)	11.2 ± 1.8	10.1 ± 1.7	NS

Values are means ± SD. NS, not significant.

the two groups before administration of pioglitazone, it was significantly decreased by administration of pioglitazone in the subjects with edema (−1.16 ± 0.96 g; $P < 0.05$), but it was not changed in the subjects without edema (−0.27 ± 1.05 g). We therefore investigated the relationship between the correlation between salt excretion and blood pressure and the development of edema. Six patients (23%) showed such a correlation and 20 patients (77%) did not. There were no differences between the

Table 3 | Baseline characteristics of subjects with or without the correlation between salt excretion and blood pressure

	With correlation	Without correlation	*P*-value
No. subjects	6 (23.1%)	20 (76.9%)	
Age (years)	60.5 ± 6.7	61.5 ± 7.5	NS
Bodyweight (kg)	54.6 ± 10.0	60.6 ± 11.2	NS
Body mass index (kg/m^2)	23.5 ± 4.4	25.0 ± 3.8	NS
Systolic blood pressure (mmHg)	138.8 ± 14.3	128.2 ± 15.7	NS
Diastolic blood pressure (mmHg)	78.2 ± 10.3	77.8 ± 9.0	NS
Plasma glucose (mg/dL)	182.0 ± 64.3	167.7 ± 53.9	NS
HbA_{1c} (%)	7.5 ± 1.3	7.3 ± 1.0	NS
Hematocrit (%)	39.3 ± 2.3	39.8 ± 2.4	NS
Salt excretion (g/day)	10.6 ± 1.8	10.3 ± 1.7	NS

Values are means ± SD. NS, not significant.

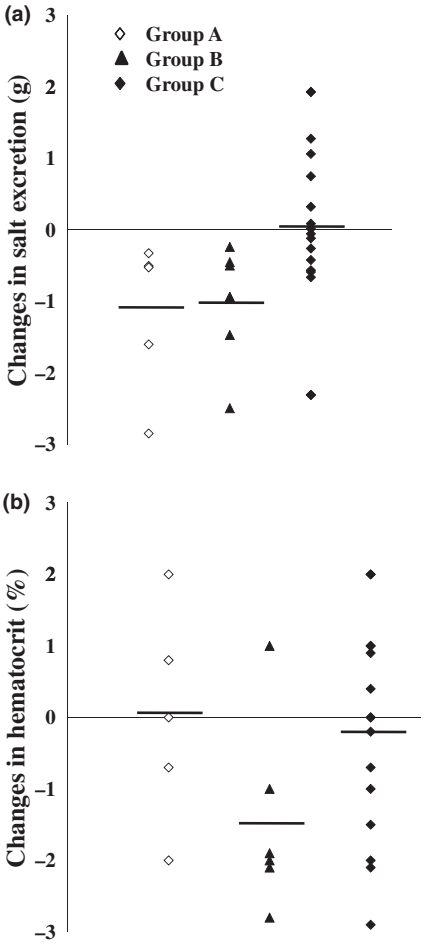

Figure 1 | Changes in (a) salt excretion and (b) hematocrit after administration of pioglitazone to three groups for 8 weeks: a group that had no correlation between salt excretion and blood pressure but had edema (group A: open diamonds), a group that had correlation but did not have edema (group B: filled triangles), and a group that had neither correlation nor edema (group C: filled diamonds). Bars indicate the mean of each group.

characteristics of the two groups, including salt excretion, before administration of pioglitazone (Table 3). As previously stated, five patients (19.2%) had developed edema, and, surprisingly and interestingly, all five subjects did not show a correlation between salt excretion and blood pressure, although the proportion was not statistically significant. We therefore divided the subjects into three groups based on the presence of a correlation between salt excretion and blood pressure and the development of edema; a group that had no correlation but had edema (group A), a group that had correlation but did not have edema (group B), and a group that had neither correlation nor edema (group C). The correlation coefficient between salt excretion and blood pressure was significantly higher in group B than in group A and C ($P < 0.01$). As shown in Figure 1, salt excretion after administration of pioglitazone was significantly lower than before pioglitazone administration in group A and group B

Table 4 | Changes in blood pressure after administration of pioglitazone to three groups for 8 weeks

	Pre-administration	Post-administration	*P*-value
Systolic blood pressure (mmHg)			
Group A	132.3 ± 19.0	133.7 ± 22.8	NS
Group B	138.9 ± 14.2	134.3 ± 13.9	NS
Group C	126.8 ± 14.9	123.4 ± 13.9	NS
Diastolic blood pressure (mmHg)			
Group A	75.1 ± 13.9	75.1 ± 12.0	NS
Group B	78.2 ± 10.3	75.7 ± 11.2	NS
Group C	78.7 ± 7.1	74.2 ± 7.5	<0.05

A group that had no correlation between salt excretion and blood pressure, but had edema (Group A); a group that had a correlation, but did not have edema (Group B); and a group that had neither a correlation nor edema (Group C). Values are means ± SD. NS, not significant.

($P < 0.05$), but not group C, and the hematocrit was significantly lower after administration in group B ($P < 0.05$), but not in group A or group C (Figure 1). Although systolic blood pressure was not changed by administration of pioglitazone in these three groups, diastolic blood pressure was significantly decreased by administration of pioglitazone in group C, but not in group A or group B (Table 4). There were no differences in bodyweight gain (group A, 0.6 ± 1.7 kg; group B, 0.7 ± 0.6 kg; group C, 0.6 ± 0.7 kg) and the changes in HbA_{1c} level (group A, −0.8 ± 0.8%; group B, −0.1 ± 0.2%; group C, −0.3 ± 0.3%) among the three groups, and there was no association of the changes in salt excretion with the changes in bodyweight after the treatment with pioglitazone (correlation coefficient = 0.15).

DISCUSSION

From the results of the present study, we could speculate the hypothesis on the mechanisms of pioglitazone-induced edema and the correlation between salt excretion and blood pressure (Figure 2). Administration of pioglitazone to the subjects who developed pioglitazone-induced edema (group A) caused fluid retention because of sodium reabsorption, and increased fluid in the intravascular space would be mobilized into the extravascular space because of a vascular mechanism as discussed in more detail later, and edema was observed as a result. In contrast, administration of pioglitazone caused fluid retention in the subjects that had a correlation between salt excretion and blood pressure (group B), but the increased fluid was retained in the intravascular space, explaining why they did not develop edema. In subjects who had neither correlation nor edema (group C), as administration of pioglitazone did not cause fluid retention, the hematocrit did not decrease.

The mechanism responsible for the difference in vascular permeability has not been well characterized, but might involve a number of factors, such as vascular endothelial growth factor (VEGF) and protein kinase C[5,6]. Since Emoto *et al.*[7] reported that plasma VEGF concentration was significantly higher in type 2 diabetic patients treated with troglitazone with edema

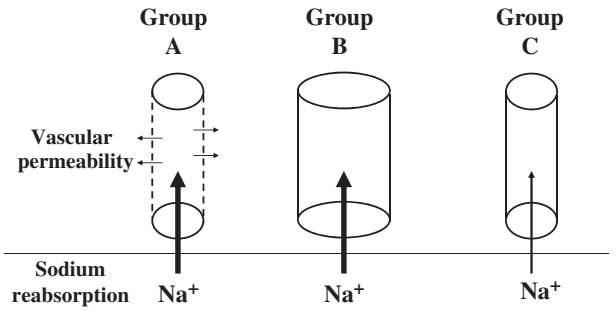

Figure 2 | Hypothesis on mechanisms of pioglitazone-induced edema. Administration of pioglitazone to the subjects who developed pioglitazone-induced edema (group A) caused fluid retention because of sodium reabsorption and increased fluid in the intravascular space would be mobilized to extravascular space because of vascular hyperpermeability. In contrast, administration of pioglitazone caused fluid retention in the subjects that had a correlation between salt excretion and blood pressure (group B); however, increased fluid would be retained in the intravascular space. Administration of pioglitazone to the subjects that had neither correlation nor edema (group C) did not cause fluid retention.

than in those without edema, it is suggested that VEGF might affect the vascular permeability of the patients who developed pioglitazone-induced edema, although it is still unclear whether plasma VEGF concentration is directly associated with vascular permeability. Thus, more study is required to identify the factors responsible for vascular permeability.

TZD decreases blood pressure in diabetic subjects[8,9]. In subjects in groups A and B, blood pressure was not changed after administration, whereas diastolic blood pressure was significantly reduced in subjects in group C. In the former, it is suggested that sodium reabsorption might cancel out pioglitazone-induced peripheral vasodilatation. Also, there were no differences in bodyweight gain among the three groups. Although there has been some controversy regarding the etiology of weight gain[10], we assume that fluid retention is so mild that it is not reflected as bodyweight gain. From another point of view, because the amount of urinary sodium excretion reflects the amount of sodium intake in the steady state, there was no correlation of the changes in salt excretion with the changes in bodyweight after the treatment of pioglitazone.

In conclusion, pioglitazone-induced edema would be caused not only by fluid retention, but also by other factors, such as vascular permeability. Because administration of pioglitazone caused fluid retention in the subjects who developed pioglitazone-induced edema, assessment of salt excretion and treatment by inhibiting sodium reabsorption might be useful in preventing the adverse effects of pioglitazone.

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