Effects of Pioglitazone Versus Glipizide on Body Fat Distribution, Body Water Content, and Hemodynamics in Type 2 Diabetes

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OBJECTIVE — Pioglitazone, a peroxisome proliferator–activated receptor agonist and glipizide, an insulin secretagogue, are commonly used to treat type 2 diabetes. Our study was designed to examine the effects of pioglitazone versus glipizide on body water, body composition, and hemodynamic parameters in the presence of comparable glycemic control between groups.

RESEARCH DESIGN AND METHODS — We studied 19 diabetic subjects randomly assigned to either 45 mg pioglitazone ($n = 8$) or 10 mg (median dose) glipizide ($n = 11$) for 12 weeks. Body water content was measured with deuterated water, body composition by dual-energy X-ray absorptiometry and computed tomography, and cardiac output and systemic vascular resistance by acetylene rebreathing technique both before and after therapy.

RESULTS — Pioglitazone increased ($P < 0.001$ from baseline) total body water (+2.4 ± 0.5 l) accounting for 75% of the total weight gain (+3.1 ± 2.0 kg) but did not alter vascular endothelial growth factor concentrations. Total abdominal (−32.2 ± 19 cm^2) and visceral fat area (−16.1 ± 8 cm^2) tended to decrease with pioglitazone but increased ($P < 0.02$ for differences between groups) with glipizide (+38.4 ± 17 cm^2 abdominal; +19.1 ± 9 cm^2 visceral). Pioglitazone tended to reduce ($P = 0.05$) diastolic (−8.4 ± 4 mmHg) and mean (−9.5 ± 5 mmHg; $P = 0.08$) blood pressure and reduced ($P < 0.001$) systemic vascular resistance (2,785 ± 336 vs. 2,227 ± 136 dynes/s per m^2), while there were no differences in these parameters with glipizide. Neither therapy altered circulating catecholamine concentrations.

CONCLUSIONS — When pioglitazone and glipizide are given in doses sufficient to achieve equivalent glycemic control in people with type 2 diabetes, pioglitazone increases total body water, thereby accounting for the majority of weight gain, tended to decrease visceral and abdominal fat content and blood pressure, and reduces systemic vascular resistance.

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Thiazolidinediones are widely used to treat type 2 diabetes. These agents work through activation of the nuclear receptor peroxisome proliferator–activated receptor γ (PPAR)γ, which is a ligand-dependent transcription factor expressed predominantly in adipose tissue (1). Treatment with a thiazolidinedione results in an increase in insulin action in adipose tissue, muscle (2), and perhaps liver (3). However, in addition to improved glycemic control, these agents cause weight gain, edema, and redistribution of body fat in individuals with type 2 diabetes (4–6). Scarce animal and human data have suggested that renal sodium retention could be a causal factor for the development of fluid retention (7,8). Vascular endothelial growth factor (VEGF) also has been implicated as a causal factor in thiazolidinedione-induced edema (9). Furthermore, although there have been several reports (10–12) of favorable effects of thiazolidinediones on endothelial function and blood pressure, information on global effects of these agents on systemic vascular resistance, cardiac output, and cardiac index have been scant. Also, the effects of these agents on body water content in humans are unknown.

The present experiments were undertaken to address these questions. Body composition, total body water, blood pressure, systemic vascular resistance, cardiac index, plasma VEGF, and catecholamine concentrations were measured in people with type 2 diabetes before and after 3 months of treatment with the PPARγ agonist pioglitazone. To avoid the confounding effects of differences in glycemic control, results were compared with those observed when a comparable level of glycemic control was achieved with the sulfonylurea glipizide.

RESEARCH DESIGN AND METHODS

— After approval from the Mayo Clinic Institutional Review Board, 21 participants (7 women and 14 men) with type 2 diabetes between the ages of 30 and 75 years were enrolled (7 were previously treated with dietary and lifestyle changes alone, 7 with metformin alone, 2 with sulfonylureas alone, and the remaining 5 with a combination of metformin and sulfonylurea agents). Table 1 provides the demographic characteristics of the subjects at baseline.

None of the diabetic subjects had been on thiazolidinediones. The participants were in good health and did not have any complications apart from mild background retinopathy. None of the participants engaged in regular vigorous physical activity. Apart from oral hypoglycemic agents and stable thyroid hormone therapy, none of the participants were on any other medications at the time of screening. No participants had a history of edema, cardiac, hepatic, or renal problems at the time of enrollment. At the time of screening, body composition (in-

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Abbreviations: PPAR, peroxisome proliferator–activated receptor; VEGF, vascular endothelial growth factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline demographic characteristics of diabetic subjects*

	Pioglitazone	Glipizide
Age (years)	56 ± 2	58 ± 4
Weight (kg)	92 ± 7	87 ± 5
BMI (kg/m^2)	32 ± 2	31 ± 2
Fat-free mass (kg)	56 ± 4	51 ± 3
Total abdominal fat (cm^2)	500 ± 80	412 ± 47
Visceral fat (cm^2)	217 ± 48	180 ± 32
% Body fat	39 ± 6	36 ± 4
A1C (%)	6.9 ± 0.3	6.5 ± 0.3
Fasting plasma glucose (mmol/l)	8.4 ± 0.7	8.0 ± 0.8

Data are means ± SE.

cluding fat-free mass and total fat mass) was measured using dual-energy X-ray absorptiometry (DPX-IQ scanner, SmartScan Version 4.6C; Lunar, Madison, WI). A single-cut computed tomography scan of the abdomen was also performed at the L_2–L_3 level to estimate visceral fat and abdominal subcutaneous fat contents as previously described (13,14). Total body water was measured using deuterated (D_2) water technique as previously described (15). Before measurement, each subject was placed on a controlled sodium (3 g salt/day) diet for 72 h to ensure avoidance of acute changes in total body water content. Subjects ingested 1 ml 99.7% pure ^2H_2O (Cambridge Isotopes, Andover, MA) diluted in 10 ml distilled water. Baseline and 3- and 4-h urine samples were collected for measurement of ^2H_2O enrichment using isotope ratio mass spectrometry. During this time period, the patient was not allowed to consume food or fluids.

After the screening visit, all oral hypoglycemic agents were discontinued for 3 weeks before the study. All participants were instructed to follow a weight-maintaining diet containing 55% carbohydrate, 30% fat, and 15% protein for at least 3 days before the study. The participants were admitted at 1700 on the evening before the study day, and a standard 10 cal/kg meal (55% carbohydrate, 30% fat, and 15% protein) was consumed at 1800. The subjects remained nil per mouth except water till the morning of the study.

On the morning of the study, resting blood pressure with the participant lying relaxed in bed was measured on three occasions 5 min apart. Baseline blood samples were drawn for catecholamine and VEGF concentrations an hour after line placements. Subsequently, a mixed-meal test was performed (starting at 0800) as part of another study to measure carbohydrate and fat metabolism. A light lunch was served at 1400, and subjects were then fed a standard meal at 1800 and kept NPO except water overnight.

On the following morning, cardiac output and systemic vascular resistance were measured using the acetylene uptake method as previously described (16). Briefly, subjects breathed a gas mixture containing 0.7% acetylene, 9.0% helium, 20.9% O_2, and balance N_2 for seven to ten breaths. During the wash-in phase, breath-by-breath acetylene and helium uptakes were measured. Since uptake of acetylene is proportional to pulmonary blood flow, it also is proportional to cardiac output. An automatic three-way sliding-valve (Hans Rudolph, Kansas City, MO) on the inspiratory side allowed measurement of cardiac output without interruption of the subject's normal breathing pattern. Systemic vascular resistance was estimated by: $[^{(MBP\ -\ 10)}/_{CI}] \times 80$, where MBP is the mean blood pressure and CI the cardiac index.

After completion of the baseline studies, subjects were randomly assigned to receive either 45 mg pioglitazone once daily ($n = 10$) or 5 mg glipizide once daily ($n = 11$) for 12 weeks, following which the baseline studies were repeated. During therapies, subjects were asked to maintain a diary of self-monitored blood glucose twice daily. The dose of glipizide was titrated to a max of 20 mg daily in an effort to reduce fasting and presupper self-monitored glucose values to <8 mmol/l. The median dose of glipizide at the end of the study was 10 mg once daily. Two of the subjects (both male) on pioglitazone dropped out of the study since they left the area for employment reasons and could not return for completion of the protocol. Hence, they were excluded from analyses. These two subjects did not differ from the rest of the group at baseline. During this 12-week period, the subjects were reviewed every 4 weeks for pill count, vital signs, review of records of self-monitoring of blood glucose, and any new signs and symptoms. At each outpatient visit, the study medications were provided for the next 4 weeks. Pill counts performed at each outpatient visit indicated that two subjects on glipizide and one on pioglitazone missed their medications for a total of 3 days each during the 12-week period of the study.

Statistical analysis

All results are expressed as means ± SE. Between-group comparisons were performed by nonpaired Student's *t* test, while within-group comparisons were done by paired *t* tests. All *t* tests were two tailed. $P < 0.05$ was considered statistically significant.

RESULTS

Fasting plasma glucose and HbA_{1c} concentrations

There were no differences in fasting glucose or HbA_{1c} (A1C) concentrations either before or following 12 weeks of treatment with pioglitazone or glipizide, respectively (Table 2). While both parameters tended to increase in both groups, these changes were not significant, enabling assessment of the effects of these agents on body composition and vascular function to be evaluated independent of significant changes in glycemic control.

Body weight, lean body mass, and body fat distribution

The increment in total body weight during the 12 weeks of study tended to be greater ($P = 0.09$) following treatment with pioglitazone compared with glipizide (Table 2). The increment in total body fat did not differ ($P = 0.2$) following treatment with either pioglitazone or glipizide. Total abdominal fat and visceral fat tended ($P = 0.06$) to decrease on pioglitazone and increased ($P < 0.05$) on glipizide, resulting in a greater ($P < 0.02$) increment in both following treatment with glipizide compared with pioglitazone. Leg fat content remained unchanged following treatment with either pioglitazone or glipizide (data not tabulated).

Body water and plasma VEGF concentrations

Total body water increased ($P < 0.001$) during treatment with pioglitazone but did not change ($P = 0.9$) during treatment with glipizide (Table 2). The ratio of total body water to fat-free mass increased ($P < 0.01$) with pioglitazone, while there were no changes with glipizide, implying that pioglitazone but not glipizide increased the proportion of total body water content that is contained within the extracellular space. Of note, two of the eight subjects on pioglitazone developed new-onset pitting leg edema that subsided within a few weeks after completion of the study. However, the magnitude of the in-

Table 2—*Outcome variables before and after pioglitazone or glipizide therapies for 12 weeks*

	Pioglitazone			Glipizide		
	Before	After	Δ	Before	After	Δ
Fasting plasma glucose (mmol/l)	8.4 ± 0.7	8.8 ± 0.9	+0.4	8.0 ± 0.8	8.4 ± 0.7	+0.4
A1C (%)	6.9 ± 0.3	7.5 ± 0.8	+0.6	6.5 ± 0.3	6.9 ± 0.8	+0.4
Weight (kg)	92.1 ± 7	95.2 ± 9	+3.1	87.4 ± 5	87.9 ± 5	+0.5
Body fat (kg)	38.3 ± 5	39.2 ± 6	+0.9	30.5 ± 4	30.3 ± 4	−0.2
Total abdominal fat (cm^2)	500 ± 80	468 ± 67	−32	412 ± 47	450 ± 58	+38*†
Visceral fat (cm^2)	217 ± 48	201 ± 43	−16	180 ± 32	199 ± 31	+19*†
Body water (l)	47.6 ± 3.6	50 ± 3.3	+2.4*	42.9 ± 3	43.4 ± 4	+0.5
Body water/fat-free mass	0.84 ± 0.02	0.88 ± 0.02	+0.04*	0.83 ± 0.06	0.82 ± 0.06	−0.01
VEGF (pmol/l)	6.2 ± 1.3	7.0 ± 1.4	+0.8	3.9 ± 0.8	3.0 ± 0.7	−0.9
Diastolic blood pressure (mmHg)	84.2 ± 4	75.8 ± 4	−8.4	75.8 ± 3	75.5 ± 3	−0.3
Mean blood pressure (mmHg)	102 ± 5	92.5 ± 5	−9.5	92.7 ± 4	92 ± 4	−0.7
Systemic vascular resistance (dynes/s per m^2)	2,785 ± 336	2,227 ± 136	−561*	2,556 ± 205	2,446 ± 223	−110
Cardian output (l/min)	6.2 ± 0.4	6.7 ± 0.4	+0.5	5.3 ± 0.4	5.6 ± 0.4	+0.3
Cardiac index (l per m^2/min)	2.8 ± 0.2	3.0 ± 0.2	+0.2	2.7 ± 0.2	2.9 ± 0.2	+0.2

Data are means ± SE. *Denotes $P < 0.05$ from baseline. †Denotes $P < 0.05$ for difference between therapies.

crease in total body water in these two subjects did not differ in the other six subjects who did not develop edema. The increase in total body water in the six subjects who did not develop edema (+2.7 ± 0.6 l) did not differ from the entire pioglitazone-treated cohort (+2.4 ± 0.5 l).

Previous studies have suggested that an increase in VEGF may contribute to thiazolidinedione-induced fluid retention and edema (9). Plasma VEGF concentrations did not change following treatment with pioglitazone and decreased ($P = 0.08$) slightly but nonsignificantly with glipizide. Of interest, there was no correlation between changes in plasma VEGF concentrations and body water content either in the entire cohort ($r = 0.16$; $P = 0.5$) or in the glipizide ($r = 0.01$; $P = 0.98$) treatment group. However, there appeared to be trend ($r = 0.6$; $P = 0.1$) between changes in plasma VEGF concentrations and total body water in the pioglitazone treatment group.

Effect on hemodynamic parameters

Treatment with pioglitazone tended to decrease diastolic blood pressure ($P = 0.05$) and mean blood pressure ($P = 0.08$), while there were no changes with glipizide on diastolic or mean blood pressure. The decrement in diastolic blood pressure tended to be lower ($P = 0.05$) with pioglitazone than glipizide treatment. Systolic blood pressure did not differ with either therapy.

Pioglitazone resulted in ($P < 0.001$) reduction of systemic vascular resistance, whereas there was no change following treatment with glipizide. Cardiac output and cardiac index did not change following treatment with pioglitazone or with glipizide.

Plasma norepinephrine (0.84 ± 0.1 vs. 0.9 ± 0.1 pmol/ml), epinephrine (0.07 ± 0.02 vs. 0.07 ± 0.01 pmol/ml), or dopamine (0.3 ± 0.15 vs. 0.07 ± 0.01 pmol/ml) concentrations did not change during treatment with pioglitazone. Likewise, plasma norepinephrine (1.0 ± 0.1 vs. 1.05 ± 0.1 pmol/ml), epinephrine (0.1 ± 0.03 vs. 0.07 ± 0.01 pmol/ml), or dopamine (0.16 ± 0.05 vs. 0.25 ± 0.07 pmol/ml) concentrations also did not change during treatment with glipizide.

CONCLUSIONS

— Most (4–6,17), but not all, studies have shown that treatment with the PPARγ agonists pioglitazone or rosiglitazone causes an increase in body weight with the magnitude of the increase generally being inversely correlated with the resultant decrease in A1C concentration (6,18). It therefore has been difficult to disassociate the effects of these agents on body composition and vascular function from those due to weight gain and improved glycemic control. The present experiments circumvented these problems by studying individuals whose antecedent diabetes programs resulted in a degree of glycemic control that was essentially equivalent to that observed during treatment with pioglitazone or glipizide as evident by the lack of change in A1C over the 12 weeks of study. In addition, results obtained during treatment with pioglitazone were compared with those observed during treatment with the active comparator glipizide. The increases in total body weight with either therapy were not statistically significant. This is likely due to the relatively short duration of study. However, it is noteworthy that the ~3-kg increase in weight on pioglitazone was primarily due to the 2.4-l increase in total body water. Thus, the increase in body water accounted for ~75% of the total weight gain. Consistent with previous reports (4–6,19,20), there also was redistribution within body fat compartments with pioglitazone therapy, causing a tendency to decrease in both abdominal and visceral fat, whereas both tended to increase following treatment with glipizide. We presume that variability of measurement and/or offsetting decreases in other unmeasured compartments accounts for the lack of statistically significant changes in total body weight.

PPARγ agonists can cause peripheral edema. The prevalence appears to vary from ~5% during treatment with a PPARγ agonist alone to ~15% when combined with insulin (21–23). The mechanism of edema is currently an area of active investigation. Previous studies (9) have suggested the PPARγ agonist increases plasma VEGF concentrations, which in turn could increase vascular permeability. This proposed relationship was not confirmed in the present studies since plasma VEGF concentrations did not increase following treatment with pioglitazone and did not differ from those

observed during treatment with glipizide. However, although there was no correlation between changes in total body water content and plasma VEGF concentrations in the cohort as a whole, there was a suggestion of a correlation in the pioglitazone treatment cohort.

PPARγ agonists have been reported to decrease urinary sodium excretion and to increase plasma renin activity (8). This is thought to be mediated by an increase in the abundance of aquaporins 2 and 3 within the renal tubules (7). Furthermore, a recent study (24) using selective gene targeting of PPARγ in collecting ducts of mice revealed epithelial sodium channel–mediated renal salt absorption as the principal cause of water retention induced by both pioglitazone and rosiglitazone. The present studies suggest an additional mechanism. Treatment with pioglitazone resulted in a decrease in vascular resistance in the absence of a compensatory increase in cardiac output or plasma catecholamine concentrations. This presumably resulted in a decrease in renal perfusion pressure, which would be anticipated to enhance sodium and fluid retention. A decrease in systemic vascular resistance also could explain why diuretics are relatively ineffective (23) in treating PPARγ agonist–induced peripheral edema, since the increase in body water is a compensatory response to a relative decrease in intravascular volume.

Like any other experiment, our study also has limitations. The sample size is relatively small with a wide age range (42–74 years). Therefore, the trends toward an increase in total body weight or decrease in blood pressures may have become statistically significant if a larger number of patients were studied for a longer period of time. If so, this could have further strengthened our conclusion that pioglitazone has a greater effect on these parameters than does glipizide. A Bonferroni correction was not performed for multiple comparisons. This adds to the limitations of this study. Furthermore, although the distribution of diabetes management strategies of the subjects preenrollment were similar between groups, this could have been a limiting factor as well since only a third in each group were antidiabetes drug naïve at the time of enrollment.

In conclusion, the present data indicate that compared with glipizide, treatment with pioglitazone increases body water and decreases systemic vascular resistance and tended to decrease visceral fat in people with type 2 diabetes. The decrease in systemic vascular resistance occurred in the absence of a change in cardiac index or output. Pioglitazone-induced increase in total body water accounted for ~75% of the total weight gain, indicating that at least over the short term thiazolidinediones increase body weight primarily by increasing fluid retention. The apparently favorable effects of pioglitazone with regards to fat distribution and systemic vascular resistance on long-term micro- and macrovascular complications of diabetes await further study.

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