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Anti-Diabetic Agent: Involvement in Hepatic Fat Metabolism In Pioglitazone-Treated Type 2 Diabetic Patients

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Abstract

Pioglitazone (brand name Actos) is a prescription drug of the thiazolidinedione (TZD) class with hypoglycemic (antihyperglycemic, antidiabetic) action to treat diabetes.

Pioglitazone is one of the antidiuretic agents used in the management of type 2 diabetes mellitus (DM). The effect of pioglitazone on blood glucose, lipid profile, liver enzymes and weight has been shown with conflicting results. In this study we aim to evaluate the effect of pioglitazone on the weight, lipid profile and liver enzymes in patients with DM.

Pioglitazone is used to lower blood glucose levels in the treatment of diabetes mellitus type 2 (T2DM) either alone or in combination with a sulfonylurea, metformin, or insulin.

Keywords

lipid profile, liver enzyme, pioglitazone, type 2 diabetes mellitus.

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by raised glucose levels which is associated with macrovascular and microvascular complications as well as dyslipidaemia, that increase morbidity and mortality. There are various medications introduced to reduce glucose levels and improve DM patients' clinical status. Pioglitazone, a thiazolidinedione derivative, is an insulin-sensitizing agent developed for the treatment of T2DM.Pioglitazone is a peroxisome proliferator activated receptor-gamma (PPAR-γ) agonist which can reduce insulin resistance in liver, muscle and adipose tissue] and improve glucose and lipid metabolism.

Pioglitazone treatment in T2DM results in improving lipid profile including decrease in triglycerides and low-density lipoprotein (LDL), increase in high-density lipoprotein (HDL) and decrease in serum fatty acids as well as improved liver function tests Unlike these findings, other studies were not able to demonstrate any significant improvement in liver function tests or lipid profile Unlike its beneficiary effects, weight gain is one major side effect of this medication.

Previous reports indicate that compared with glibenclamide or metformin, pioglitazone alone or in combination with any of these agents could reduce blood glucose further. However, there are controversies in reported effects of pioglitazone. So, it is important to define the exact role of pioglitazone on diabetes control, lipid profile, liver function and possible weight gain. In this study, we aim to evaluate the effect of pioglitazone in Iranian patients with T2DM.

THIAZOLIDINEDIONES, a new class of insulin-sensitizing agents, have recently been introduced for the treatment of patients with type 2 diabetic mellitus. Early studies showed that troglitazone ameliorates insulin resistance and improves hyperglycemia, hyperinsulinemia, and dyslipidemia in type 2 diabetic patients. Although the precise mechanism of action of the thiazolidinediones remains to be determined,

Their glucose-lowering effect seems to depend on the presence of insulin.It is known that thiazolidinediones activate specific receptors, termed PPARγ (6, 7). PPARγ activation causes preadipocytes to differentiate into mature fat cells and causes the induction of key enzymes involved in lipogenesis . Consistent with these observations, clinical studies have demonstrated that thiazolidinedione therapy in type 2 diabetic patients is associated with weight gain, yet glycemic control improves. The increase in body weight is positively related to the reduction in hemoglobin A_{1c} (HbA_{1c}). These results suggest that the improvement in glucose homeostasis after thiazolidinedione treatment may in some way be related to an alteration in fat metabolism and/or fat topography. With respect to the later, Adams *et al* reported that thiazolidinediones promote the differentiation of preadipocytes into mature fat cells in sc, but not visceral, fat depots in humans. Numerous studies have shown that increased visceral fat is associated with insulin resistance and the development of macrovascular complications (14–16). Several recent studies have demonstrated that the thiazolidinedione, troglitazone, decreases visceral fat content in type 2 diabetic patients (10, 17), but no previous study has examined whether the alterations in abdominal fat distribution after thiazolidinedione treatment are related to the improvement in glycemic control and/or insulin sensitivity.

Aim the Study

In the present study we have evaluated the effect of pioglitazone therapy on glucose tolerance, insulin secretion, and hepatic and peripheral tissue sensitivity to insulin, plasma lipid levels, and abdominal fat distribution in type 2 diabetic individuals. To the best of our knowledge, this represents the first study that has examined the relationship between changes in abdominal fat distribution and glucose homeostasis/insulin sensitivity after thiazolidinedione treatment in type 2 diabetic subjects.

Materials and Methods

In this single-arm clinical trial, 110 patients aged 35–75 years with uncontrolled diabetes mellitus and no previous history of taking thiazolidinediones, who were on maximum dose of metformin (1.5–2 g) and glibenclamide (15–20 mg) for at least 1 month, having HbA1c 7.5–11% and fasting blood sugar (FBS) ⩾140 mg/dl were enrolled. Patients with significant renal, cardiac, liver, lung, or neurological disease, anaemia, systemic glucocorticoid therapy patients receiving β-blockers, prior use of or known allergy to any type of available thiazolidinediones, patients currently pregnant, breastfeeding, smokers, and subjects who abused alcohol or drugs and those with a body mass index (BMI) greater than 40 kg/m^2 were excluded from this study. Subjects were also excluded if they had been treated with insulin or had started treatment with a statin or any fibric acid derivative within 2 months of the beginning of the study. All patients underwent a complete laboratory survey including FBS, lipid profile including cholesterol, triglyceride, low-density lipoprotein (LDL) and high-density lipoprotein (HDL), alkaline phosphatase (ALK-P), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and the weight of patients were assessed at the time of laboratory survey. Then the pioglitazone at a dose of 30 mg was added to the treatment protocol of all patients and they were followed up for 3 months. All above-mentioned laboratory investigations and weight assessing were repeated after 3 months and the obtained data before and after therapeutic intervention were studied.

Results

Abdominal fat distribution

Visceral and sc fat area were measured by MRI, using previously described imaging procedures (18). Briefly, images were acquired on a 1.9 T Elscint Prestige MRI system using a T1-weighted spin echo pulse sequence with a TR of 500 msec and a TE of less than 20 msec. A sagittal localizing image was used to center transverse sections on the line through the space between L4 and L5. Ten 5.0-mm thick sections were acquired with a gap of 1.0 mm to prevent signal cross-over from adjacent sections. The field of view ranged from 30–50 cm, depending on body size. Phase encoding was in the antero-posterior direction to minimize the effects of motion-induced phase artifacts that might otherwise be distributed laterally through a large portion of the abdomen. The field of view was adjusted for body size to ensure 2-mm pixel spacing. Signal averaging (four signals averaged) were used to reduce the effects of motion-related artifacts. Additionally, respiratory gating was used to combat motion-induced artifacts and to reduce the blurring of fat boundaries in the anterior region of the abdomen. Images were processed using Alice software (Perceptive Systems, Inc., Boulder, CO) to determine abdominal sc and visceral fat areas. The sc fat area was analyzed by selecting the outer and inner margins of sc adipose tissue as region of interests from the cross-sectional images, and counting the number of pixels between the outer and inner margins of sc adipose tissue. The visceral (intraabdominal) fat area was determined using histograms specific to the visceral regions. The histograms were summed over a range of pixel values designated as fat by fitting two normal analysis distribution curves to them.

n this study, 110 patients with type 2 DM including 70 (63.6%) females and 40 (36.4%) males with a mean age of 54.26 ± 8.96 years were studied.

Table 1.

Demographic and anthropometric findings between groups.

Variable	Before intervention	After intervention	*p* value
FBS (mg/dl)	221.01±46.61	146.24±46.61	<0.001
HbA1C (%)	8.51±1.54	7.29±0.90	<0.001
Cholesterol (mg/dl)	156.93±27.16	155.55±29.26	0.61
Triglyceride (mg/dl)	165.15±72.35	145.83±67.19	<0.001
LDL (mg/dl)	80.38±23.19	82.28±23.35	0.42
HDL (mg/dl)	43.60±10.19	44.39±9.77	0.34
AST (IU/ml)	21.49±8.65	21.45±8.16	0.95
ALT (IU/ml)	26.74±13.19	23.66±12.29	<0.005
ALK-P (IU/L)	190.41±63.29	173.62±57.05	<0.001
Weight (kg)	76.78±11.40	77.60±11.79	0.000

Table 1 shows the laboratory findings before and after the intervention. As the table shows FBS, HbA1c, TG, ALT, ALK-P were significantly decreased and patients' weight was increased following intervention. However, no significant differences were observed in the level of cholesterol, HDL, LDL and AST before and after the intervention. Mean percentage of increase in weight was 1.07 ± 0.29%.

FBS, fasting blood sugar; HbA1C, haemoglobin A1C; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ALK-P, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

	16-wk treatment		*P* value
	Before	After	
Basal (−30 to 0 min)			
Plasma glucose (mg/dl)	155 ± 10	127 ± 10	0.004
Plasma insulin (μU/ml)	15 ± 2	10 ± 1	0.013
Endogenous glucose production (mg/kg FFMmiddot;min)	2.83 ± 0.17	2.66 ± 0.07	
Hepatic insulin resistance (mg/kg FFMmiddot;min × μU/ml)[1]	41 ± 7	25 ± 3	0.011
1st insulin clamp step (60–90 min)			
Endogenous glucose production (mg/kg FFMmiddot;min)	1.07 ± 0.14	0.63 ± 0.16	0.025
Total body glucose disposal (mg/kg FFMmiddot;min)	3.57 ± 0.41	4.29 ± 0.39	0.091
Total body glucose clearance (ml/kg FFMmiddot;min)	3.51 ± 0.47	4.38 ± 0.44	0.042
2nd insulin clamp step (150–180 min)			
Endogenous glucose production (mg/kg FFMmiddot;min)	0.44 ± 0.14	0.34 ± 0.09	
Total body glucose disposal (mg/kg FFMmiddot;min)	7.80 ± 0.91	10.30 ± 1.00	0.001
Total body glucose clearance (ml/kg FFMmiddot;min)	8.65 ± 0.99	11.31 ± 1.11	0.004

Table 2.

Hepatic and whole body glucose metabolism during the two-step insulin clamp (insulin infusion rates: 40 and 160 mU/m^2 · min) performed before and after 16 wk of pioglitazone treatment Product of EGP and fasting plasma insulin concentration in the postabsorptive state.

Statistical analysis

Statistics were performed with StatView for Windows, version 5.0 (SAS Institute, Inc., Cary, NC). Values before and after treatment were compared using paired *t* test. Linear regression analysis was used to examine the relationships between hepatic/peripheral insulin sensitivity and abdominal/sc fat area before and after pioglitazone treatment. All data are presented as the mean ±se. *P* value less than 0.05 was considered statistically significant.

Discussion

The beneficial effects of the thiazolidinediones on glucose metabolism are believed to be mediated by their binding to the nuclear receptor PPARγ (6). PPARγ receptors are most abundant in adipocytes and are present in low concentrations in muscle (24). PPARγ activation results in stimulation of adipogenesis (6, 8, 9, 25) and gene transcription of key enzymes involved in lipogenesis (6, 8). There is significant variability in the adipose tissue distribution of PPARγ.

Conclusion

It is concluded that pioglitazone is a good antidiabetic agent in patients with T2DM who do not respond properly to maximum dose of glibenclamide and metformin. This agent has no negative impact on lipid profile and liver function tests but carries a trivial risk of weight gain which would limit its utility.

References

1. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356:2457–71.
2. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005;366:1279–89.
3. Wilcox R, Bousser MG, Betteridge DJ, et al. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04) Stroke. 2007;38:865–73.
4. Mannucci E, Monami M, Lamanna C, Gensini GF, Marchionni N. Pioglitazone and cardiovascular risk. A comprehensive meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2008;10:1221–38.
5. Mazzone T, Meyer PM, Feinstein SB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. Jama. 2006;296:2572–81.
6. Nissen SE, Nicholls SJ, Wolski K, et al. Comparison of pioglitazone vs. glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. Jama. 2008;299:1561–73.
7. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. Jama. 2007;298:1180–8.
8. Tzoulaki I, Molokhia M, Curcin V, et al. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. Bmj. 2009;339:b4731.
9. Spanheimer R, Betteridge DJ, Tan MH, Ferrannini E, Charbonnel B. Long-term lipid effects of pioglitazone by baseline anti-hyperglycemia medication therapy and statin use from the PROactive experience (PROactive 14) Am J Cardiol. 2009;104:234–9.
10. Bajaj M, Baig R, Suraamornkul S, et al. Effects of pioglitazone on intramyocellular fat metabolism in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 95:
11. Pershadsingh HA. Peroxisome proliferator-activated receptor-gamma: therapeutic target for diseases beyond diabetes: quo vadis? Expert Opin Investig Drugs. 2004;13:215–28.
12. Rosmarakis ES, Falagas ME. Effect of thiazolidinedione therapy on restenosis after coronary stent implantation: a meta-analysis of randomized controlled trials. Am Heart J. 2007;154:144–50.
13. Giaginis C, Tsantili-Kakoulidou A, Theocharis S. Peroxisome Proliferator-Activated Receptor-gamma Ligands: Potential Pharmacological Agents for Targeting the Angiogenesis Signaling Cascade in Cancer. PPAR Res. 2008:431763.
14. Desouza CV, Gerety M, Hamel FG. Long-term effects of a PPAR-gamma agonist, pioglitazone, on neointimal hyperplasia and endothelial regrowth in insulin resistant rats. Vascul Pharmacol. 2007;46:188–94.
15. Aljada A, O'Connor L, Fu YY, Mousa SA. PPAR gamma ligands, rosiglitazone and pioglitazone, inhibit bFGF- and VEGF-mediated angiogenesis. Angiogenesis. 2008;11:361–7.
16. Takagi T, Okura H, Kobayashi Y, et al. A prospective, multicenter, randomized trial to assess efficacy of pioglitazone on in-stent neointimal suppression in type 2 diabetes: POPPS (Prevention of In-Stent Neointimal Proliferation by Pioglitazone Study) JACC Cardiovasc Interv. 2009;2:524–31.
17. Pfutzner A, Schondorf T, Hanefeld M, Forst T. High-Sensitivity C-Reactive Protein Predicts Cardiovascular Risk in Diabetic and Nondiabetic Patients: Effects of Insulin-Sensitizing Treatment with Pioglitazone. J Diabetes Sci Technol. 4:706–16.
18. Permana PA, Zhang W, Wabitsch M, Fischer-Posovszky P, Duckworth WC, Reaven PD. Pioglitazone reduces inflammatory responses of human adipocytes to factors secreted by monocytes/macrophages. Am J Physiol Endocrinol Metab. 2009;296:E1076–84.
19. Hu YY, Ye SD, Zhao LL, Zheng M, Chen Y. Hydrochloride pioglitazone decreases urinary TGF-beta1 excretion in type 2 diabetics. Eur J Clin Invest
20. Glatz T, Stock I, Nguyen-Ngoc M, et al. Peroxisome-proliferator-activated receptors gamma and peroxisome-proliferator-activated receptors beta/delta and the regulation of interleukin 1 receptor antagonist expression by pioglitazone in ischaemic brain. J Hypertens
21. Huang PH, Sata M, Nishimatsu H, Sumi M, Hirata Y, Nagai R. Pioglitazone ameliorates endothelial dysfunction and restores ischemia-induced angiogenesis in diabetic mice. Biomed Pharmacother. 2008;62:46–52.
22. Gensch C, Clever YP, Werner C, Hanhoun M, Bohm M, Laufs U. The PPAR-gamma agonist pioglitazone increases neoangiogenesis and prevents apoptosis of endothelial progenitor cells. Atherosclerosis. 2007;192:67–74.
23. Vlckova V, Cornelius V, Kasliwal R, Wilton L, Shakir SA. Hypoglycaemia with oral antidiabetic drugs: results from prescription-event monitoring cohorts of rosiglitazone, pioglitazone, nateglinide and repaglinide. Drug Saf. 2009;32:409–18.
24. Jain R, Osei K, Kupfer S, Perez AT, Zhang J. Long-term safety of pioglitazone versus glyburide in patients with recently diagnosed type 2 diabetes mellitus. Pharmacotherapy. 2006;26:1388–95.
25. Meneghini LF, Traylor L, Schwartz S. Improved Glycemic Control with Insulin Glargine vs. Pioglitazone as ADD-ON Therapy to Sulfonylurea or Metformin in Patients with Uncontrolled Type 2 Diabetes. Endocr Pract. 2010 Mar;29:1–6. [Epub ahead of print].
26. Charbonnel B, Defronzo R, Davidson J, et al. Pioglitazone Use in Combination with Insulin in the Prospective Pioglitazone Clinical Trial in Macrovascular Events Study (PROactive19) J Clin Endocrinol Metab. 2010 May;95(5):2163–71.
27. Basu A, Jensen MD, McCann F, Mukhopadhyay D, Joyner MJ, Rizza RA. Effects of pioglitazone versus glipizide on body fat distribution, body water content, and hemodynamics in type 2 diabetes. Diabetes Care. 2006;29:510–4