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Long-term effects of pioglitazone versus gliclazide on hepatic and humoral coagulation factors in patients with type 2 diabetes

GABRIELE PERRIELLO, SIMONE PAMPANELLI, PAOLO BRUNETTI, CINZIA DI PIETRO, SEGUNDO MARIZ, ON BEHALF OF THE ITALIAN PIOGLITAZONE STUDY GROUP

Abstract

This study compared the long-term effects of pioglitazone and gliclazide on the production of coagulation factors in patients with type 2 diabetes. Patients (n=283) with glycosylated haemoglobin > 7.5% were randomised to receive either pioglitazone (30–45 mg/day) or gliclazide (80–320 mg/day) for one year. Coagulation factors were measured at baseline and at six and 12 months. While both pioglitazone and gliclazide induced a comparable improvement in glycaemic control, only pioglitazone improved insulin sensitivity. Pioglitazone significantly ($p \leq 0.001$) decreased circulating levels of von Willebrand factor (-9.7%, -9.4%) and plasminogen activator inhibitor-1 (-16.8 ng/ml, -12.3 ng/ml), and increased levels of antithrombin-III (+1.3 mg/dL, +1.5 mg/dL) after six and 12 months, respectively. The beneficial effects of pioglitazone on glycaemic control, lipid homeostasis, and coagulation and thrombosis, may improve vascular outcomes in patients with type 2 diabetes.

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Key words: cardiovascular disease, coagulation, diabetes, gliclazide, pioglitazone, thrombosis.

Introduction

Type 2 diabetes is characterised by insulin resistance and a

cluster of homeostatic abnormalities, which contribute to an increased risk for cardiovascular disease and the associated morbidity and mortality.^{1,2} Several mechanisms that maintain vascular integrity are known to be impaired in patients with diabetes, including platelet function,³ endothelial function,⁴ fibrinolysis and coagulation;⁵ all of these contribute to a pro-thrombotic state and an increased risk of vascular disease.^{6,7} Increases in procoagulation factors have been associated with increased thrombus formation, a key part of the atherosclerotic process.^{8–11} Although recent work suggests that hyperglycaemia itself can stimulate coagulation in healthy adults and that hyperinsulinaemia can impair fibrinolysis,¹² it is unknown whether these alterations are glucose-dependent or linked to insulin resistance, and what their relative contributions to macrovascular disease might be in patients with type 2 diabetes.

There is increasing interest in therapies aimed at improving the coagulation factor profile of patients with type 2 diabetes. Insulin sensitisation through thiazolidinedione (TZD) therapy appears to be one promising strategy for modifying multiple cardiovascular risk factors associated with type 2 diabetes.¹³ A number of oral hypoglycaemic agents, including several TZDs, appear to modulate the levels of some key coagulation factors.^{14–17} Recent studies suggest that these changes are not related to improvements in glycaemic control,^{18,19} although whether the effects are drug-related or, more likely, driven by insulin resistance remains unclear.

This study was designed to compare the effects of the TZD pioglitazone and the sulphonylurea gliclazide on hyperglycaemia in patients with type 2 diabetes. These data have been presented elsewhere and showed comparable improvements in glycaemic control between the treatment groups.²⁰ The inclusion of two agents that induce a similar level of glycaemic control, but via different mechanisms of action (an insulin secretagogue [gliclazide] versus an insulin sensitiser [pioglitazone]), provided an ideal opportunity to examine the effects on key coagulation factors and determine whether any changes were dependent on glucose and/or insulin resistance. We measured changes in key coagulation factors produced by the liver (plasminogen activator inhibitor-1 [PAI-1] and antithrombin III [AT-III]) and by the vascular endothelium (von Willebrand factor [vWf]) in both treatment groups after one year of therapy.

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Patients and methods

The experimental design and patient population are summarised below and have been reported previously in full.²⁰

Study design

This was a one-year, double-blind, randomised, parallel-group study designed to compare the long-term efficacy and safety of pioglitazone and gliclazide in patients with type 2 diabetes. It was conducted at 33 centres across Italy.

Patients and treatments

Patients (aged 35–70 years) with type 2 diabetes who were currently managed by diet alone or with a maximum of one glucose-lowering agent, who had glycosylated haemoglobin (HbA_{1C}) > 7.5% and with no history of major cardiovascular events (myocardial infarction or stroke) within the 12 months before enrolment, were eligible for inclusion in this study. Patients were randomised to receive either pioglitazone 30–45 mg/day or gliclazide 80–320 mg/day for up to one year. Stepwise upward titration every four weeks to the maximum tolerated dose was permitted, based on the results of patient-monitored blood glucose levels and fasting blood glucose levels and at the investigator's discretion.

All patients provided their written informed consent prior to any study treatment. The study was approved by the local ethical committee at each study centre and was conducted in accordance with the guidelines laid down in the Declaration of Helsinki and according to the Good Clinical Practice Guidelines of the International Conference on Harmonisation.

Efficacy variables

The primary efficacy end point for this study was improvement of HbA_{1C} levels, expressed as the percentage of patients who reached an HbA_{1C} < 7.5% at the end of treatment. Insulin sensitivity was assessed by monitoring circulating insulin levels and using the homeostasis model assessment (HOMA) of insulin resistance. Secondary efficacy end points included changes in PAI-1, AT-III, vWf and platelets, and are the focus of this paper. The secondary parameters were measured at baseline and after six and 12 months of treatment. Nephelometry was used to measure AT-III, whereas vWf and PAI-1 were measured by enzyme immunoassay.

Safety and tolerability

Safety and tolerability of the two treatments were assessed via physical examination, standard laboratory assessments including liver function tests (alanine transaminase [ALT], aspartate aminotransferase [AST], γ -glutamyl transferase [γ -GT]) and monitoring of adverse events throughout the study.

Statistical analyses

An analysis of variance (ANOVA) with repeated measures and multiple comparisons within and between groups was applied to both the primary and secondary end points.

Results

A total of 283 patients were eligible for inclusion in this study. Of

Table 1. Baseline demographic and metabolic characteristics of the intention-to-treat population

Characteristic	Pioglitazone	Gliclazide
n	140	135
Age ^a (years)	58±8	59±7
Gender (male/female)	94/46	88/47
Weight ^a (kg)	81.1±12	78.8±10.7
Body mass index ^a (kg/m ²)	29.2±3.1	28.8±2.8
Fasting glucose ^a (mM)	10.9±2.1	10.4±2.1
HbA _{1C} ^a (%)	8.83±0.91	8.67±0.94
Coagulation parameters ^a		
PAI-1 (ng/ml)	54.1±38.7	46.6±37.4
vWf (%)	135.3±45.1	134.9±39.1
AT-III (mg/dL)	25.3±4.0	25.8±4.1
Platelets (10 ⁹ /L)	222.5±52.3	219.4±47.2

Key: ^a = mean ± standard deviation; HbA_{1C} = glycosylated haemoglobin; PAI-1 = plasminogen activator inhibitor-1; vWf = von Willebrand factor; AT-III = antithrombin-III

these, eight patients were excluded for violation of inclusion criteria or withdrawal of their consent after randomisation but before receiving any study treatment. The remaining 275 were included in the intention-to-treat (ITT) population and were randomised to receive either pioglitazone (n=140) or gliclazide (n=135) therapy for up to one year. There were no significant differences between the treatment groups in baseline characteristics (table 1) or in the number of patients reporting concomitant diseases or taking medications. The most common managed concomitant disease in both treatment groups was hypertension.

Glycaemic control

As reported previously,²⁰ glycaemic control improved in both treatment groups during the study; a similar proportion of patients in each treatment group achieved an HbA_{1C} level < 7.5% (pioglitazone 39.6%, gliclazide 38.7%).

Insulin resistance

As reported previously,²⁰ pioglitazone treatment was associated with a significant decrease in the level of circulating insulin (p=0.002) and an improvement in insulin sensitivity (p=0.002); such improvements were not observed during gliclazide therapy.

Changes in coagulation factors

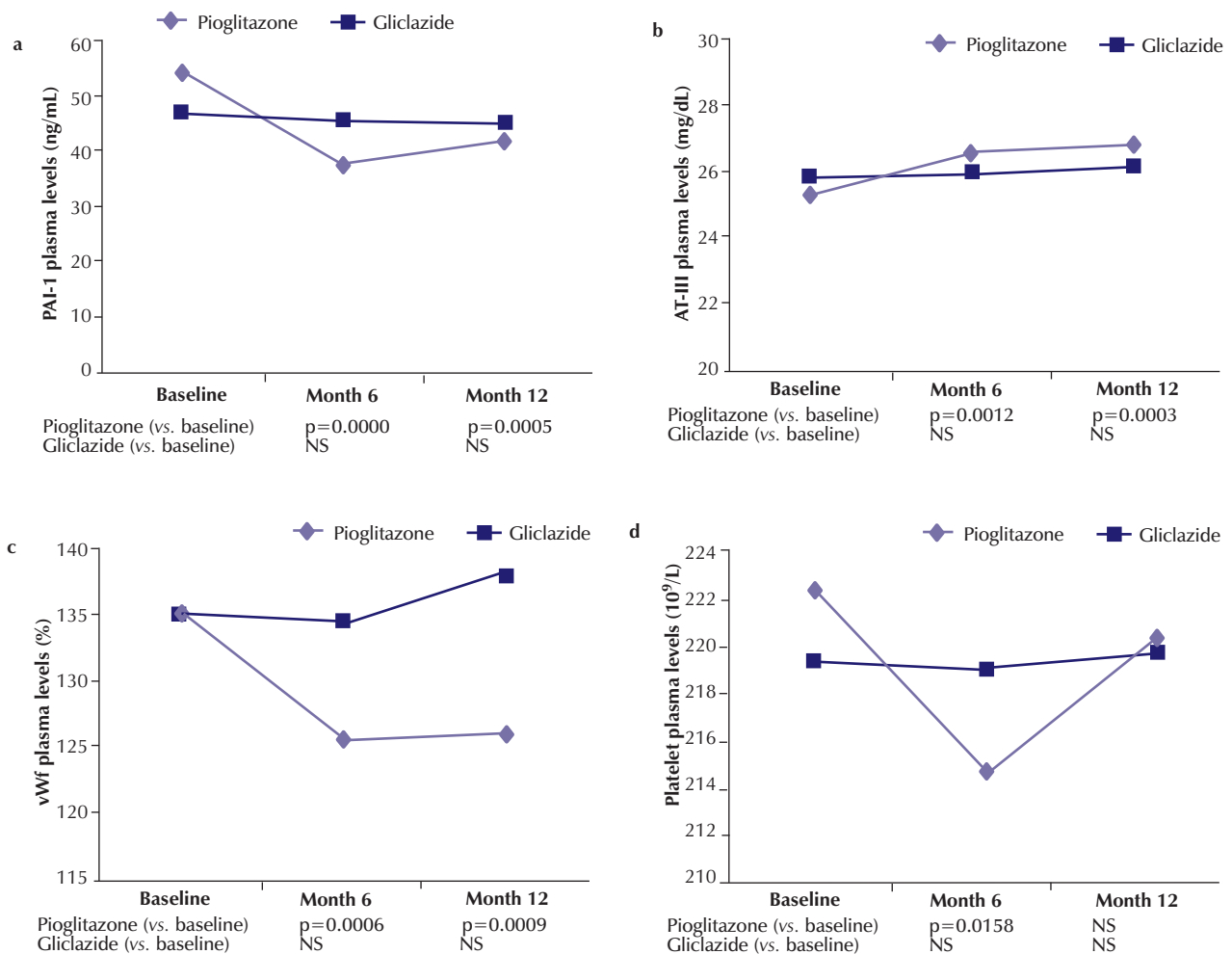
PAI-1

PAI-1 levels decreased significantly (p<0.001) at both the six- and 12-month visits compared with baseline levels in the pioglitazone group (-16.8, -12.3 ng/ml, respectively) but not the gliclazide group (-1.1, -1.5 ng/ml, respectively) (figure 1a). This gave a significant between-treatment difference (p=0.0058).

AT-III

A significant (p≤0.001) increase from baseline was observed

Figure 1. Mean change in plasma levels for PAI-1 (a), AT-III (b), vWf (c) and platelets (d), among adult patients with type 2 diabetes treated with either pioglitazone (30–45 mg/day) or gliclazide (80–320 mg/day) for up to one year



Key: PAI-1 = plasminogen activator inhibitor-1; AT = antithrombin; vWf = von Willebrand factor

in the levels of AT-III at both the six- and 12-month assessments in the pioglitazone group (+1.3, +1.5 mg/dL, respectively) but not the gliclazide group (+0.1, +0.3 mg/dL, respectively) (figure 1b). The difference between treatment groups was statistically significant ($p=0.0494$).

vWf

A similar pattern was observed for vWf as for PAI-1 in that a significant ($p<0.001$) decrease from baseline was noted at both six- and 12-month assessments among patients treated with pioglitazone (-9.7, -9.4%, respectively) but not among patients treated with gliclazide (-0.3, +3.4%, respectively) (figure 1c). The between-group difference also reached statistical significance ($p=0.0040$).

Platelets

There was a significant ($p=0.0158$) reduction in platelet numbers after six months' treatment with pioglitazone ($-7.8 \times 10^9/L$), which returned to baseline values after 12 months of treatment. No change in platelet levels was

observed in the gliclazide group at either the six- or 12-month assessment (figure 1d).

Safety and tolerability

Both agents were generally well tolerated over the course of the study.²⁰ A significant decrease from baseline in levels of ALT, AST and γ -GT was noted at six and 12 months for pioglitazone only.

Discussion

We have shown a significant improvement in the levels of coagulation markers PAI-1, AT-III and vWf among patients with type 2 diabetes during therapy with the TZD pioglitazone, but not during treatment with the insulin secretagogue gliclazide. Comparable improvements in terms of glycaemic control between these two agents in this study have previously been reported.²⁰ Therefore, the differential effect between pioglitazone and gliclazide on coagulation factors, reported here, appears to be independent of glycaemic control.

Key coagulation factors such as PAI-1, AT-III and vWf are altered in patients with type 2 diabetes, and these changes are associated with an increased risk of thrombosis and higher levels of atherosclerosis.⁸⁻¹⁰ Coagulation factors are produced primarily in the liver and at the vascular endothelium; PAI-1 is produced by the liver, adipose tissue and endothelial cells whereas AT-III is produced exclusively in the liver.^{21,22} vWf is produced and secreted by the endothelium.²³

Modest improvements in a number of coagulation factor profiles have previously been reported in patients with type 2 diabetes receiving other insulin-sensitising agents, including the biguanide metformin. Metformin therapy has been associated with significant reductions in PAI-1 levels in studies among patients with type 2 diabetes.²⁴⁻²⁶ Metformin has also been shown to reduce vWf levels significantly in obese, non-diabetic patients²⁷ and in those with impaired glucose tolerance.²⁸ Rosiglitazone has been shown to improve a number of circulating procoagulation markers when given as monotherapy.¹⁵ Furthermore, rosiglitazone and pioglitazone have been shown to reduce PAI-1 levels when administered in combination with glimepiride.¹⁷ Both rosiglitazone and pioglitazone have been shown to inhibit tumour necrosis factor- α -mediated induction of PAI-1 expression *in vitro* in vascular endothelial cells.²⁹ Pioglitazone monotherapy has also been shown to reduce C-reactive protein (CRP) and intimal media thickness in patients with type 2 diabetes after six months.³⁰ Pioglitazone is thought to reduce levels of CRP primarily through a reduction in interleukin-6.³¹ Changes in CRP may also influence vWf levels by modulating its expression at the vascular level.³² Both hepatic and humoral changes in coagulation factors are likely to be mediated through the same mechanisms, perhaps insulin resistance.

In conclusion, the study shows that pioglitazone has multiple beneficial effects on hepatic and endothelial coagulation factors that are not mediated by improvements in glycaemic control, although a related effect on insulin resistance cannot be ruled out. Pioglitazone, but not gliclazide, was associated with an improvement in three key coagulation factors among patients with type 2 diabetes. The data reported here suggest an additional pathway through which pioglitazone may reduce the risk of cardiovascular events in patients with type 2 diabetes, namely amelioration of a prothrombotic state characterised by abnormal levels of circulating coagulation factors.

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Conflicts of interest statement

GP as received consulting fees for lectures and for participating in scientific boards from Novo Nordisk, GlaxoSmithKline and Takeda Italy. SP has received fees from participating in research by Takeda Italy, Aventis and Eli Lilly. PB has received honoraria for lectures given in meetings organised by Eli Lilly, Novo Nordisk and Takeda Italy. CdiP is the Medical Director of Takeda Italy.

References

1. Schnell O, Standl E. Impaired glucose tolerance, diabetes, and cardiovascular disease. *Endocr Pract* 2006;**12**(suppl 1):16-19.
2. Thorand B, Baumert J, Chambless L *et al*. Elevated markers of endothelial dysfunction predict type 2 diabetes mellitus in middle-aged men and women from the general population. *Arterioscler Thromb Vasc Biol* 2006;**26**:398-405.
3. Colwell JA, Nesto RW. The platelet in diabetes. Focus on prevention of ischemic events. *Diabetes Care* 2003;**26**:2181-8.
4. Candido R, Zanetti M. Current perspective. Diabetic vascular disease: from endothelial dysfunction to atherosclerosis. *Ital Heart J* 2005;**6**:703-20.
5. Schneider DJ. Abnormalities of coagulation, platelet function, and fibrinolysis associated with syndromes of insulin resistance. *Coron Artery Dis* 2005;**16**:473-6.
6. Jokl R, Colwell JA. Arterial thrombosis and atherosclerosis in diabetes. *Diabetes Metab Rev* 1997;**5**:1-15.
7. Jokl R, Colwell JA. Clotting disorders in diabetes. In: Alberti KGMM, Zimmet P, Defronzo R, Koen H, ed. *International Textbook of Diabetes Mellitus*. 2nd edition. Chichester: Wiley, 1997:1543-57.
8. Blann AD. Plasma von Willebrand factor, thrombosis, and the endothelium: the first 30 years. *Thromb Haemost* 2006;**95**:49-55.
9. Juhan-Vague I, Alessi MC, Mavri A *et al*. Plasminogen activator inhibitor-1, inflammation, obesity, insulin resistance, and vascular risk. *J Thromb Haemost* 2003;**1**:1575-9.
10. Vaughan DE. PAI-1 and atherothrombosis. *J Thromb Haemost* 2005;**3**:1879-83.
11. Vaidyula VR, Rao AK, Mozzoli M *et al*. Effects of hyperglycaemia and hyperinsulinemia on circulating tissue factor procoagulant activity and platelet CD40 ligand. *Diabetes* 2006;**55**:202-08.
12. Stegenga ME, van der Crabben SN, Levi M *et al*. Hyperglycemia stimulated coagulation, whereas hyperinsulinemia impairs fibrinolysis in healthy humans. *Diabetes* 2006;**55**:1807-12.
13. Verges B. Clinical interest of PPARs ligands. Particular benefit in type 2 diabetes and metabolic syndrome. *Diabetes Metab* 2004;**30**:7-12.
14. Grant PJ. Beneficial effects of metformin on haemostasis and vascular function in man. *Diabetes Metab* 2003;**29**:S44-52.
15. Chu JW, Abbasi F, Lamendola C *et al*. Effect of rosiglitazone on circulating vascular and inflammatory markers in insulin-resistant subjects. *Diabetes Vasc Dis Res* 2005;**2**:37-41.
16. Kruszynska YT, Yu JG, Olefsky JM *et al*. Effects of troglitazone on blood concentrations of plasminogen activator inhibitor 1 in patients with type 2 diabetes and in lean and obese normal subjects. *Diabetes* 2000;**49**:633-9.
17. Derosa G, Cicero AF, Gaddi A *et al*. A comparison of the effects of pioglitazone and rosiglitazone combined with glimepiride on prothrombotic state in type 2 diabetic patients with the metabolic syndrome. *Diabetes Res Clin Pract* 2005;**69**:5-13.
18. De Jager J, Kooy A, Leher P *et al*. Effects of short-term treatment with metformin on markers of endothelial function and inflammatory activity in type 2 diabetes mellitus: a randomized, placebo-controlled trial. *J Intern Med* 2005;**257**:100-09.
19. Fonseca V, Theuma P, Mudaliar S *et al*. Diabetes treatments have differential effects on non-traditional cardiovascular risk factors. *J Diabetes Complications* 2006;**20**:14-20.
20. Perriello G, Pampanelli S, Di Pietro C *et al*. Comparison of glycaemic

- control over 1 year with pioglitazone or gli-clazide in patients with type 2 diabetes. *Diabet Med* 2006;**23**:246-52.
21. Chandler WL, Alessi MC, Aillaud MF *et al.* Formation, inhibition and clearance of plasmin *in vivo*. *Haemostasis* 2000;**30**:204-18.
 22. Spiess B, Chandler WL. Genetic basis of procoagulant and fibrinolytic perioperative adverse events. *Best Practice & Research Clinical Anaesthesiology* 2001;**15**:195-211.
 23. Vischer UM. von Willebrand factor, endothelial dysfunction, and cardiovascular disease. *J Thromb Haemost* 2006;**4**:1186-93.
 24. Cefalu WT, Schneider DJ, Carlson HE *et al.* Effect of combination gli-pazide GITS/metformin on fibrinolytic and metabolic parameters in poorly controlled type 2 diabetic subjects. *Diabetes Care* 2002;**25**:2123-8.
 25. Gin H, Roudaut MF, Vergnot V *et al.* Effect of metformin on fibrinolytic parameters in insulin-treated, type 2 diabetic patients. *Diabetes Metab* 2003;**29**:505-08.
 26. Grant PJ, Stickland MH, Booth NA *et al.* Metformin causes a reduction in basal and post-venous occlusion plasminogen activator inhibitor-1 in type 2 diabetic patients. *Diabet Med* 1991;**8**:361-5.
 27. Charles MA, Morange P, Eschwege E *et al.* Effect of weight change and metformin on fibrinolysis and the von Willebrand factor in obese non-diabetic subjects: the BIGPRO1 Study. Biguanides and the Prevention of the Risk of Obesity. *Diabetes Care* 1998;**21**:1967-72.
 28. Caballero AE, Delgado A, Aguilar-Salinas CA *et al.* The differential effects of metformin on markers of endothelial activation and inflammation in subjects with impaired glucose tolerance: a placebo-controlled randomized clinical trial. *J Clin Endocrinol Metab* 2004;**89**:3943-8.
 29. Liu HB, Hu YS, Medcalf RL *et al.* Thiazolidinediones inhibit TNFalpha induction of PAI-1 independent of PPARgamma activation. *Biochem Biophys Res Commun* 2005;**334**:30-7.
 30. Pflutzner A, Marx N, Lubben G *et al.* Improvement of cardiovascular risk markers by pioglitazone is independent from glycemic control: results from the pioneer study. *J Am Coll Cardiol* 2005;**45**:1925-31.
 31. Yamaguchi M, Nishimura F, Naruishi H *et al.* Thiazolidinedione (pioglitazone) blocks *P. gingivalis* and *F. nucleatum*, but not *E. coli*, lipopolysaccharide (LPS)-induced interleukin-6 (IL-6) production in adipocytes. *J Dent Res* 2005;**84**:240-4.
 32. Blann AD, Lip GY. Effects of C-reactive protein on the release of von Willebrand factor, E-selectin, thrombomodulin and intercellular adhesion molecule-1 from human umbilical vein endothelial cells. *Blood Coagul Fibrinolysis* 2003;**14**:335-40.