Journal of Diabetes Science and Technology
Volume 2, Issue 2, March 2008

ORIGINAL ARTICLES

Pioglitazone Improves Metabolic Markers in Patients with Type 2 Diabetes Independently from Physical Activities: Results from the IRIS III Study

Thomas Schöndorf, Ph.D.,[1,2] Andreas Pfützner, Ph.D., M.D.,[1,3] Georg Lübben, M.D.,[4] Efstrathios Karagiannis, M.D.,[4] Werner Roth, Dipl-Math,[1] and Thomas Forst, Ph.D., M.D.[1]

Abstract

Aim:
Pioglitazone is an established peroxisome proliferator-activated receptor γ agonist for the treatment of insulin resistance in patients with type 2 diabetes mellitus. This analysis of the observational IRIS III study was performed to evaluate the effects of pioglitazone treatment in relation to the degree of physical exercise activities in a large patient population under daily life conditions.

Methods:
A total of 1298 patients out of 2092 enrolled into the IRIS III study who had provided information about their exercise level could be included in the final analysis (622 female, 676 male; age: 63.1 ± 10.4 years, diabetes duration: 6.6 ± 5.0 years, mean ± SD). All patients were glitazone naïve prior to study entry. They received pioglitazone in addition to their previous oral antidiabetic treatment. The patients were stratified according to their physical activity level (never, sometimes, and regularly). Data were evaluated at baseline and after 20 ± 2 weeks of treatment. Observation parameters were fasting blood glucose, lipids, and blood pressure. Hemoglobin A1c (HbA1c) was determined in a central laboratory, and insulin sensitivity was assessed by the IRIS II score.

Results:
Glycemic control, blood pressure, and the lipid profile improved independently from the degree of physical activity (e.g., no exercise vs frequent exercise: ΔHbA1c: −0.89 ± 1.2% vs −0.72 ± 1.1%, not significant). A positive impact of exercise on insulin resistance could be observed at baseline, which, however, was further decreased by pioglitazone treatment [IRIS II score (baseline/end point): no exercise vs frequent exercise: 74.0 ± 15.9/62.5 ± 20.2 vs 66.7 ± 19.0/58.0 ± 21.8, $p < 0.001$/not significant].

continued →

Author Affiliations: [1]Institute for Clinical Research and Development, Mainz, Germany; [2]University of Cologne Medical Center, Cologne, Germany; [3]University of Applied Sciences, Rheinbach, Germany; and [4]Takeda Pharma, Aachen, Germany

Abbreviations: (BMI) body mass index, (HbA1c) hemoglobin A1c, (HDL) high-density lipoproteins, (LDL) low-density lipoproteins, (PPARγ) peroxisome proliferator-activated receptor γ, (TZD) thiazolidinediones

Keywords: diabetes, exercise, glitazones, metabolism

Corresponding Author: Dr. Thomas Schöndorf, Associate Professor, ikfe GmbH, Ernst-Ludwig-Straße 6-8, D-55116 Mainz, Germany; email address *thomass@ikfe.de*

Abstract cont.

Conclusions:
These observational results, obtained from a nonselected patient population under daily routine conditions, confirm that the benefits of pioglitazone treatment on glycemic control, lipid metabolism, and blood pressure are independent from physical activity. Exercise has a positive influence on insulin sensitivity, but pioglitazone shows additional favorable effects and is, therefore, recommended for use independently from the activity level of the patients.

J Diabetes Sci Technol 2008;2(1):244-249

Introduction

It is well established that a sedentary lifestyle, in concert with a long-term imbalance of energy uptake and expenditure, is a major cause for the alarming high incidence of type 2 diabetes mellitus in western countries. Consistently, the suggested initial antidiabetic therapy consists of a change in diet together with an augmentation of the patient´s physical activities. Physical exercise increases the need for fat and carbohydrates and improves glycemic control and dyslipidemia in diabetes patients.[1,2] Individualized training programs for type 2 diabetes patients were established to meet this therapeutic option.[3]

In response to a failure of lifestyle changes to combat diabetes progression, administration of glitazones, also referred to as thiazolidinediones (TZD), is an additional therapeutic option. Glitazones improve hyperglycemia through activation of the nuclear peroxisome proliferator-activated receptor γ (PPARγ). Pioglitazone, a member of the TZD family, also ameliorates the lipid metabolism as assessed by a decrease in low-density lipoproteins and an increase in high-density lipoproteins.[4,5]

As far as both exercise and TZD medication improving the metabolic conditions of a type 2 diabetes patient, data are contradictory: In an animal model, a combination effect of troglitazone treatment and voluntary running was not detected.[6] However, Reusch *et al.*[7] assumed that the pleiotropic effects of TZDs may act beneficially on exercise capacity and that TZDs may improve the metabolic control synergistically with physical exercise. Furthermore, rosiglitazone improves exercise capacity but the underlying mechanisms remain to be elucidated.[8]

Only insufficient data are available in regard to a combination of glitazone therapy and physical exercise under daily routine conditions. This observational trial analysis aims to fill this gap. We collected socio-demographic and metabolic data from type 2 diabetes patients starting pioglitazone therapy and analyzed it in respect to their physical exercise activities at baseline and after 20 weeks of pioglitazone medication.

Observational Trial Design and Methods

Study Design

The IRIS III study was designed as a multicenter observational drug-monitoring trial with an entire trial duration of 12 months and an individual observational period of about 20 weeks following the regulations of Good Clinical Practice. The open-label prospective observational study was approved by the Independent Ethical Review Board of Freiburg, Germany. The design did allow conduct under daily routine conditions. Main inclusion criteria were glitazone-naïve patients with type 2 diabetes mellitus and a hemoglobin A1c (HbA1c) value between 6.6 and 9.9%. Main exclusion criteria were all the contraindications as defined in the instructions for the use of pioglitazone. The patients received pioglitazone in addition to their current antidiabetic therapy. Patients receiving insulin therapy were excluded. Pioglitazone was given to the patients orally before breakfast in the morning (fasting period >8 hours).

The following observation parameters were collected at baseline and after 20 weeks of treatment: fasting blood glucose, lipid profile [triglyceride, high-density lipoproteins (HDL), low-density lipoproteins (LDL)], weight, body mass index (BMI), and blood pressure. Physical activity was assessed during anamnesis and was classified individually as "never," "sometimes," or "regularly." Additionally, the measurement of HbA1c was

performed in a central laboratory at baseline and at endpoint. HbA1c was measured colorimetrically with an automatic glycohemoglobin analyzer (Adams™ A1c) according to the manufacturer's instructions (HA-8160 kit, Menarini Diagnostics, Neuss, Germany).

Data Analysis

For the final analysis, patients were stratified into three categories according to their physical activity. As appropriate, baseline values were adjusted to eliminate significant differences. Statistical analysis was performed using standard descriptive statistics and appropriate parametrical and nonparametrical tests. Calculations were made with the SPSS statistical package (version 9.0, SPSS Inc., Chicago, IL). The means of the variables were compared using a two-sided Student´s *t* test and Mann–Whitney´s *U* test. Results with *p* values less than 0.05 were considered statistically significant. The Spearman´s rank test was used to calculate the correlation coefficients. Because this study was designed as an observational trial, all *p* values are to be interpreted in an exploratory sense.

Results

This observational trial included 2092 patients. The study population consisted of 988 female and 1104 male patients. On average (± SD), the patients were 63 ± 10 years old, had been suffering from diabetes for 6.1 ± 5.0 years, and had an initial BMI of 30.5 ± 5.4 kg/m^2. Information about physical exercise activities was available from 1313 patients. From 15 patients of this group, no further laboratory or clinical data were reported. Thus, 1298 patients with complete data sets were included in the final analysis. The entire analysis group consisted of 622 women and 676 men (in mean, height: 169.1 ± 8.7 cm, age: 63.1 ± 10.3 years, diabetes duration: 6.6 ± 5.0 years), and the physical activity subgroups did not differ considerably at baseline (never, height: 168.5 ± 8.7 cm, age: 62.8 ± 11.5 years, diabetes duration: 6.8 ± 4.7 years; sometimes, height: 169.3 ± 8.6 cm, age: 63.0 ± 9.9 years, diabetes duration: 6.3 ± 4.7 years; regularly, height: 169.6 ± 9.1 cm, age: 63.6 ± 10.0 years, diabetes duration: 7.5 ± 6.1 years).

Table 1 displays changes of the observation parameters after 20 weeks of pioglitazone treatment in comparison to baseline values. Amelioration of all values known to indicate the metabolic syndrome could be observed, including (1) a significant improvement of hyperglycemia as assessed by lowering fasting blood glucose and HbA1c and (2) a significant improvement of the lipid profile as assessed by decreased triglycerides and LDL cholesterol and increased HDL cholesterol values. Additionally, the blood pressure was reduced significantly.

We further stratified the entire study cohort to compare the results of pioglitazone treatment on laboratory markers according to the subject´s physical activity. Baseline values for fasting blood glucose, HDL, weight, BMI, and diastolic blood pressure were adjusted to eliminate the significant differences prior to any analyses.

Table 1.
Summary of Data of the Entire Study Group [a]

	Baseline	After 20 weeks of pioglitazone therapy	Significance (*p* value baseline vs end point)
Fasting blood glucose (m*M*)	9.13 ± 2.58	7.81 ± 2.32	< 0.001
HbA1c (%)	7.76 ± 1.29	6.99 ± 1.17	< 0.001
Total cholesterol (m*M*)	5.67 ± 1.06	5.51 ± 0.98	< 0.001
LDL (m*M*)	3.48 ± 0.92	3.36 ± 0.84	< 0.001
Triglycerides (m*M*)	2.41 ± 1.44	2.11 ± 1.06	< 0.001
HDL (m*M*)	1.27 ± 0.34	1.37 ± 0.40	< 0.001
Insulin sensitivity (IRIS II score)	70.3 ± 17.9	59.5 ± 21.3	< 0.001
Weight (kg)	87.3 ± 16.9	86.9 ± 16.8	0.002
Systolic blood pressure (mm Hg)	140.3 ± 15.6	136.5 ± 14.0	< 0.001
Diastolic blood pressure (mm Hg)	83.0 ± 8.2	81.2 ± 7.3	< 0.001

[a] Significant improvement by pioglitazone treatment was shown for all observed parameters. Insulin sensitivity was assessed using the IRIS II score (values exceeding 70 are considered insulin resistant).

The improvement in each parameter is given in **Table 2**. The effects of pioglitazone treatment on glycemic control and on the lipid profile were independent of the physical activity of the patients, whereas the positive effects on insulin sensitivity were related to exercise and were additionally supported by pioglitazone treatment.

Discussion

This study investigated the impact of pioglitazone treatment on metabolic markers in type 2 diabetes patients under daily routine conditions. Comparative data of glycemic control, lipid profile, and clinical measures were obtained before and after 20 weeks of pioglitazone administration. This study confirmed the well-known potency of pioglitazone to improve the metabolic situation with respect to glycemic control hypertension and the overall lipid profile.[9–14]

Data were further stratified according to the patient´s physical activity into the following three activity categories: "never," "sometimes," and "regularly." Analysis of the results in relation to physical exercise revealed the different effects of physical activity and pioglitazone treatment. As expected, both blood glucose and hypertension are influenced beneficially by exercise. It is well established that regular physical activity yields reduced fasting glucose levels[15–17] and decreased systolic blood pressure.[1,17–20] This study confirmed these results and emphasized the fundamental role of physical exercise in the treatment of diabetes. However, it is noteworthy that pioglitazone treatment has a synergistic effect to exercise and can improve glucose levels and blood pressure to a greater extent than physical activity alone. The impact of oral antidiabetic treatment in concert with exercise on both lowering blood glucose[21] and improving cardioprotective markers[22] has also been shown for rosiglitazone treatment. These data are in line with an interventional study showing that rosiglitazone amplifies some benefits of lifestyle intervention, including physical activity in poorly controlled type 2 diabetes patients.[23]

Table 2.
Improvement of Observational Parameters from Baseline to 20 Weeks of Pioglitazone Treatment According to Physical Activity [a]

	Parameter baseline value adjustment according to subgroup "no physical activity"	Improvements after 20 weeks of pioglitazone treatment			Correlation coefficient	Significance (p value, never vs sometimes)	Significance (p value, never vs regularly)
		No physical activity	Sometimes physical activity	Regular physical activity			
Fasting blood glucose (m*M*)	Yes	-1.6 ± 2.7	-1.3 ± 2.6	-0.9 ± 2.8	0.077	0.130	0.269
HbA1c (%)	Yes	-0.89 ± 1.21	-0.72 ± 1.21	-0.72 ± 1.14	0.05	0.954	0.231
Total cholesterol (m*M*)	Yes	-0.14 ± 0.86	-0.20 ± 0.96	-0.06 ± 0.92	0.015	0.484	0.600
LDL (m*M*)	No	-0.11 ± 0.79	-0.14 ± 0.80	-0.04 ± 0.82	0.016	0.943	0.440
Triglycerides (m*M*)	No	-0.35 ± 1.24	-0.28 ± 0.95	-0.31 ± 1.18	0.016	0.205	0.959
HDL (m*M*)	Yes	+0.07 ± 0.29	+0.11 ± 0.31	+0.11 ± 0.29	0.04	0.992	0.630
Insulin sensitivity (IRIS II score)	Yes	-11.5 ± 18.1	-11.2 ± 19.6	-8.7 ± 18.3	0.04	**0.023**	**0.038**
Weight (kg)	Yes	-0.84 ± 3.6	-0.35 ± 4.6	+0.28 ± 3.45	0.08	0.202	0.248
Systolic blood pressure (mm Hg)	No	-5.9 ± 15.0	-3.0 ± 12.3	-1.3 ± 13.3	0.103	0.178	0.421
Diastolic blood pressure (mm Hg)	Yes	0.0 ± 8.6	-0.3 ± 7.1	-0.7 ± 8.3	0.086	0.405	0.656

[a] Data are given as mean values ± standard of deviation. Significant changes are indicated by a p value in bold numbers. All data are to be interpreted as reductions, except HDL, which increased after the observational period, and the weight gain in the "regular physical activity" group.

Glitazones, like pioglitazone, effectively improve the insulin sensitivity of patients with metabolic syndrome.[24] This clinical effect is based on its PPARγ-activating properties.[4] Additionally, moderate exercise also increases insulin sensitivity.[25] However, troglitazone failed to increase insulin sensitivity in concert with physical activities.[6] In this study, the recently published IRIS II score[26] was used to define insulin sensitivity. The score uses an algorithm that takes metabolic markers into account for a high specific insulin resistance assessment. The effect of pioglitazone treatment on the reduction of insulin resistance occurred in each subgroup. Physical activity alone significantly increased insulin sensitivity according to the IRIS II score in our study. Although additional pioglitazone treatment supported this effect in all three subgroups, the most impressive beneficial effect could be observed in patients not performing exercise. Results from our observational trial are in line with a study showing the beneficial effects of a combination of physical activity and pioglitazone treatment under controlled clinical trial conditions.[27]

One metabolic difference between the effects of the two commercially available glitazones, pioglitazone and rosiglitazone, is the improvement in the patient´s lipidemic profile.[28] Pioglitazone reduces triglycerides and LDL cholesterol and increases HDL cholesterol to a significantly greater extent than rosiglitazone. Some studies revealed an improvement of the lipid profile in response to regular exercise.[17,29,30] Furthermore, exercise is considered to hamper LDL oxidation.[31] In contrast to other studies, this trial analyzed a nonselected patient cohort under clinical routine conditions. In all three exercise subgroups, a comparable effect on the lipid profile could be reported. Therefore, the observed improvement can be traced back to the effects of the pioglitazone treatment alone.

Data of this observational trial show a considerable degree of variations, resulting in the observed lack of correlation between physical activity given in an ordinal scale and metabolic improvements by glitazone treatment. The heterogeneity of baseline and outcome data reflects the situation in clinical routine practice. To confirm the observations reported here, current trials are investigating the concerted benefits of pioglitazone and exercise in more detail. In summary, this study confirmed earlier results of metabolic improvements by a pioglitazone therapy under daily routine conditions and demonstrated that pioglitazone treatment has clinical benefits that are independent of the physical activities of the patient.

Funding:

This study was financed by an unrestricted grant of Takeda Pharma GmbH, Aachen, Germany.

Disclosures:

Andreas Pfützner and Thomas Forst have received speaker fees and research support from Takeda Pharma; Georg Lübben and Efstrathios Karagiannis are employees of Takeda Pharma.

References:

1. Carroll S, Dudfield M. What is the relationship between exercise and metabolic abnormalities? A review of the metabolic syndrome. Sports Med. 2004;34(6):371-418.
2. Ainslie PN, Reilly T, Maclaren DP, Campbell IT. Changes in plasma lipids and lipoproteins following 10-days of prolonged walking: influence of age and relationship to physical activity. Ergonomics. 2005;48(11-14):1352-64.
3. Eriksson JG. Exercise and the treatment of type 2 diabetes mellitus. An update. Sports Med.1999;27(6):381-91.
4. Campbell IW. The clinical significance of PPAR gamma agonism. Curr Mol Med. 2005;5(3):349-63.
5. Giannini S, Serio M, Galli A. Pleiotropic effects of thiazolidinediones: taking a look beyond antidiabetic therapy. J Endocrinol Invest. 2004;27(10):982-91.
6. Kitakoshi K, Oshida Y, Nakai N, Han YQ, Sato Y. Effects of troglitazone and voluntary running on insulin resistance induced high fat diet in rat. Horm Metab Res. 2001;33(6):365-9.
7. Reusch JE, Regensteiner JG, Watson PA. Novel actions of thiazolidinediones on vascular function and exercise capacity. Am J Med. 2003;115 Suppl 8A:69S-74S.
8. Regensteiner JG, Bauer TA, Reusch JE. Rosiglitazone improves exercise capacity in individuals with type 2 diabetes. Diabetes Care. 2005;28(12):2877-83.
9. Martens FM, Visseren FL, Lemay J, de Koning EJ, Rabelink TJ. Metabolic and additional vascular effects of thiazolidinediones. Drugs. 2002;62(10):1463-80.
10. Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. Diabetes Care. 2000;23(11):1605-11.
11. Scherbaum WA, Göke B; German Pioglitazone Study Group. Metabolic efficacy and safety of once-daily pioglitazone monotherapy in patients with type 2 diabetes: a double-blind, placebo-controlled study. Horm Metab Res. 2002;34(10):589-95.
12. Herz M, Johns D, Reviriego J, Grossman LD, Godin C, Duran S, Hawkins F, Lochnan H, Escobar-Jiménez F, Hardin PA, Konkoy CS, Tan MH. A randomized, double-blind, placebo-controlled, clinical trial of the effects of pioglitazone on glycemic control and dyslipidemia in oral antihyperglycemic medication-naive patients with type 2 diabetes mellitus. Clin Ther. 2003;25(4):1074-95.
13. Rosenblatt S, Miskin B, Glazer NB, Prince MJ, Robertson KE; Pioglitazone 026 Study Group. The impact of pioglitazone on glycemic control and atherogenic dyslipidemia in patients with type 2 diabetes mellitus. Coron Artery Dis. 2001;12(5):413-23.
14. Göke B; German Pioglitazone Study Group. Improved glycemic control and lipid profile in a randomized study of pioglitazone compared with acarbose in patients with type 2 diabetes mellitus. Treat Endocrinol. 2002;1(5):329-36.

15. Chipkin SR, Klugh SA, Chasan-Taber L. Exercise and diabetes. Cardiol Clin. 2001;19(3):489-505.

16. Castaneda C, Diabetes control with physical activity and exercise. Nutr Clin Care. 2003;6(2):89-96.

17. Di Loreto C, Fanelli C, Lucidi P, Murdolo G, De Cicco A, Parlanti N, Ranchelli A, Fatone C, Taglioni C, Santeusanio F, De Feo P. Make your diabetic patients walk: long-term impact of different amounts of physical activity on type 2 diabetes. Diabetes Care. 2005;28(6):1295-302.

18. Murphy MH, Murtagh EM, Boreham CA, Hare LG, Nevill AM. The effects of a worksite based walking programme on cardiovascular risk in previously sedentary civil servants [NCT00284479]. BMC Public Health. 2006;22;6:136.

19. Baster T, Baster-Brooks C. Exercise and hypertension. Aust Fam Physician. 2005;34(6):419-24.

20. Elley R, Bagrie E, Arroll B. Do snacks of exercise lower blood pressure? A randomised crossover trial. N Z Med J. 2006;119(1235): U1996.

21. Hällsten K, Virtanen KA, Lönnqvist F, Sipilä H, Oksanen A, Viljanen T, Rönnemaa T, Viikari J, Knuuti J, Nuutila P. Rosiglitazone but not metformin enhances insulin- and exercise-stimulated skeletal muscle glucose uptake in patients with newly diagnosed type 2 diabetes. Diabetes. 2002;51(12):3479-85.

22. Kadoglu N, Iliadis F, Angeloppoulou N, Liapis C, Perrea D, Alveizos M. Cardiovascular risk modification after combined intervention of rosiglitazone and exercise in patients with type 2 diabetes mellitus and metabolic syndrome. Diabetologia. 2006;49(Suppl 1):71-2.

23. Reynolds LR, Konz EC, Frederich RC, Anderson JW. Rosiglitazone amplifies the benefits of lifestyle intervention measures in long-standing type 2 diabetes mellitus. Diabetes Obes Metab. 2002;4(4):270-5.

24. Pfützner A, Forst T. Pioglitazone: an antidiabetic drug with the potency to reduce cardiovascular mortality. Expert Opin Pharmacother. 2006;7(4):463-76.

25. Hasbum B, Real JT, Sánchez C, Priego MA, Díaz J, Viguer A, Basanta M, Martínez-Valls J, Marín J, Carmena R, Ascaso JF. Effects of a controlled program of moderate physical exercise on insulin sensitivity in nonobese, nondiabetic subjects. Clin J Sport Med. 2006;16(1):46-50.

26. Forst T, Standl E, Hohberg C, Konrad T, Schulze J, Strotmann HJ, Lübben G, Pahler S, Bachinger A, Langenfeld M, Pfützner A. IRIS II study: the IRIS II score--assessment of a new clinical algorithm for the classification of insulin resistance in patients with type 2 diabetes. Diabet Med. 2004;21(10):1149-53.

27. Shadid S, Stehouwer CD, Jensen MD. Diet/exercise versus pioglitazone: effects of insulin sensitization with decreasing or increasing fat mass on adipokines and inflammatory markers. J Clin Endocrin Metab. 2006;91(9):3418-25.

28. Goldberg RB, Kendall DM, Deeg MA, Buse JB, Zagar AJ, Pinaire JA, Tan MH, Khan MA, Perez AT, Jacober SJ; GLAI Study Investigators. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care. 2005;28(7):1547-54.

29. Lippi G, Schena F, Salvagno GL, Montagnana M, Ballestrieri F, Guidi GC. Comparison of the lipid profile and lipoprotein(a) between sedentary and highly trained subjects. Clin Chem Lab Med. 2006;44(3):322-6.

30. Fritz T, Wändell P, Aberg H, Engfeldt P. Walking for exercise--does three times per week influence risk factors in type 2 diabetes? Diabetes Res Clin Pract. 2006;71(1):21-7.

31. Ziegler S, Schaller G, Mittermayer F, Pleiner J, Mihaly J, Niessner A, Richter B, Steiner-Boeker S, Penak M, Strasser B, Wolzt M. Exercise training improves low-density lipoprotein oxidability in untrained subjects with coronary artery disease. Arch Phys Med Rehabil. 2006 Feb;87(2):265-9.