

ORIGINAL ARTICLE

Effect of Low (7.5 mg/day), Standard (15 mg/day) and High (30 mg/day) Dose Pioglitazone Therapy on Glycemic Control and Weight Gain in Recently-Diagnosed Type 2 Diabetes Patients

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Abstract

Objective: To study the effect of different daily doses of pioglitazone on glycemic control and weight gain in newly-diagnosed type 2 diabetes mellitus (DM) patients.

Research Design and Methods: Chart reviews were performed of recently-diagnosed (<24 months) type 2 DM patients receiving oral therapy including pioglitazone. Patients were excluded if they had heart disease, liver dysfunction or renal insufficiency; or were being treated with insulin or the incretin drugs. Patients had received 7.5 mg/day (Group A), 15 mg/day (Group B) or 30 mg/day (Group C) of pioglitazone. Characteristics including demographics, weight, body mass index and glycated hemoglobin (HbA1c) were recorded at baseline and at six months.

Results: At the end of six months, there was significant weight gain in all groups from baseline ($P < 0.01$). Weight gain was greatest in Group C (2.72 kg; $SD = 2.97$), intermediate in Group B (1.62 kg; $SD = 2.91$) and least in Group A (0.88 kg; $SD = 2.77$). The difference was statistically significant between Groups A and C; and Groups B and C; but not between Groups A and B. There was no difference between HbA1c lowering in the three groups ($P > 0.05$). Dose correlated with weight gain ($r = 0.254$; $P < 0.001$) but not with HbA1c reduction ($r = 0.012$; $P = 0.85$). There was no correlation between HbA1c reduction and BMI increase ($r = -0.024$; $P = 0.72$).

Conclusions: The glycemic effect of pioglitazone is preserved even at lower doses, while the propensity to cause weight gain increases with dose. We suggest that low-dose pioglitazone (7.5 mg/day) should be the preferred dose at which to initiate therapy in recently-diagnosed patients. Pioglitazone is an extremely useful agent in the treatment of type 2 diabetes mellitus (DM) through its actions on alleviating insulin resistance.

Editorial Viewpoint

- This is a retrospective dose finding study of pioglitazone on glycemic control and weight gain in type 2 diabetes mellitus.
- Low dose of pioglitazone achieves good glycemic control; however at higher dosage there is a propensity for weight gain.

2 diabetes mellitus. Beyond these effects on glucose metabolism, pioglitazone has shown positive effects on lipid metabolism, blood pressure, and endothelial function, adiponectin, and C-reactive protein levels. These make pioglitazone treatment effective beyond glucose control.¹

Pioglitazone generally has been viewed as a safer option for patients who warrant treatment with a thiazolidinedione-class drug and has been used widely as part of combination regimens in India. While pioglitazone is reputed to have cardioprotective actions, one

Introduction

Pioglitazone was first approved over 15 years ago, as an adjunct to exercise and diet to improve glycemic control in adults with type

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Table 1: Baseline characteristics of patients

	Group A	Group B	Group C	P value
No. of pts.	77	80	80	
Male %	41/77 (52.6%)	45/80 (56.3%)	48/80 (60%)	0.70
Age (years)	58.23 (10.96)	56.64 (10.56)	53.79 (8.45)	0.02
DM diagnosis (mths)	6.65 (4.17)	5.99 (5.64)	6.25 (5.69)	0.74
Height (cm)	163.79 (6.6)	162.15 (9.12)	163.75 (8.46)	0.35
Weight (kg)	74.03 (15.27)	69.68 (12.41)	69.11 (12.84)	0.05
BMI (kg/m ²)	27.63 (5.51)	26.62 (4.91)	25.87 (4.84)	0.10
HbA1c (%)	7.44 (0.57)	7.60 (0.40)	7.77 (0.75)	0.003

Legend: Groups A, B and C refer to patients who received 7.5, 15 and 30 mg/day pioglitazone, respectively. P value refers to the difference between groups. DM, diabetes mellitus; BMI, body mass index; Continuous variables are expressed as mean (standard deviation).

of the reasons for restricting its use has been weight gain.²

Over the years, a large number of studies have shown that despite increases in weight, pioglitazone as add-on therapy to either metformin or sulphonylurea treatments have shown sustained improvements in serum levels of triglycerides (TGs) and HDL-C and favourable effects on LDL-C particle size. Indeed, in comparison with rosiglitazone, pioglitazone has different and potentially favourable effects on plasma lipids.³

This study was undertaken to study the effect of different daily doses of pioglitazone on glycemic control and weight gain in newly-diagnosed type 2 diabetes mellitus (DM) patients.

Research Design and Methods

Study Design

A retrospective chart review was performed on patients enrolled at two endocrinology clinics in Mumbai – Joshi Clinic and KJ Somaiya Medical College. Patients included for the study were: (i) being treated with oral anti-diabetic drugs including pioglitazone, (ii) between the age of 30-80 years and (iii) time since diagnosis of diabetes <24 months. Exclusion criteria were: (i) any cardiac abnormalities, including history of symptomatic angina, cardiac insufficiency or history of myocardial infarction or abnormal electrocardiographic findings, (ii) any renal dysfunction,

including diagnosed renal failure or serum creatinine levels >1.5 mg/dl in males or >1.4 mg/dl in females, (iii) any hepatic dysfunction, including elevation of hepatic transaminases more than 2 times the upper limit of normal, or patients consuming >24 g of alcohol per day, and (iv) patients receiving incretin or insulin therapy. A written informed consent was taken from the participants of the study.

A total of 237 patient records matched the above criteria, of which 77 received 7.5 mg/day of pioglitazone (Group A), 80 received 15 mg/day of pioglitazone (Group B) and 80 received 30 mg/day of pioglitazone (Group C). All patients had been given standard dietary advice depending on individual caloric requirements by a registered dietitian. All patients were also prescribed a regular exercise regimen in the form of brisk walking for 40 minutes daily or 200 minutes per week.

Ethics Statement

This study was approved by the Ethics Committee of KJ Somaiya Medical College.

Parameters Studied

Patients' age, sex, time since diagnosis of diabetes, weight, height and body-mass index (BMI) and glycated hemoglobin (HbA1c) were noted at the time of initiation of pioglitazone therapy. The values for each of these parameters at a 6-month interval were also recorded for analysis.

Table 2: Data at 6-month follow-up

Parameter	Group A	Group B	Group C	P value
Weight (kg)	74.98 ± 15.94	71.47 ± 12.55	71.56 ± 13.53	0.218
Weight change	+0.88 ± 2.77	+1.62 ± 2.91	+2.72 ± 2.97	<0.001
BMI (kg/m ²)	27.96 ± 5.63	27.60 ± 5.60	27.10 ± 5.18	0.429
BMI change	+0.33 ± 1.01	+0.62 ± 1.10	+1.03 ± 1.14	<0.001
HbA1c (%)	6.2 ± 0.39	6.3 ± 0.46	6.5 ± 0.38	<0.001
% reduction	1.24 ± 0.65	1.18 ± 0.59	1.25 ± 0.84	0.813

Legend: Groups A, B and C refer to patients who received 7.5, 15 and 30 mg/day pioglitazone, respectively. P value refers to the difference between groups. Data is presented as mean ± standard deviation. BMI, body mass index; HbA1c, glycated hemoglobin. Continuous variables are expressed as mean (standard deviation).

Statistical Analysis

All data parameters were fed into Microsoft Excel 2003 (Microsoft Inc., Seattle, WA, USA) and data were analyzed using SPSS 16.0.1 for Windows (SPSS Inc., Chicago, IL, USA). The paired t-test was used for measuring change in weight and glycemic parameters from baseline within the groups. A one-way analysis of variance (ANOVA) was used to compare means between dosage groups and Tukey's HSD test was used for post-hoc analysis wherever applicable. Partial correlation was used for adjusted correlation analyses. A P value of <0.05 was used to define statistical significance. All continuous variables are expressed as mean (standard deviation).

Results

The baseline characteristics of patients are enlisted in Table 1. The differences in age (A vs B: P=0.580; A vs C: P=0.016; B vs C: P=0.173) and baseline HbA1c (A vs B: P=0.198; A vs C: P=0.002; B vs C: P=0.173) were significant between the groups. There was a borderline significant difference in baseline weight, though there was no corresponding difference in the baseline BMI. All patients were Asian Indians and our study group did not include patients from any other racial or ethnic background.

Characteristics of patients at the end of six months are shown in Table 2. At the end of six months, a significant increase in weight (A: P=0.007; B: P<0.001; C: P<0.001)

and BMI (A: $P=0.006$; B: $P<0.001$; C: $P<0.001$) was observed in all groups. However, the magnitude of weight gain was the most in Group C, intermediate in Group B and least in Group A (A vs B: $P=0.243$; A vs C: $P<0.001$; B vs C: $P=0.044$). The difference between groups in magnitude of weight gain was highly significant ($P<0.001$). Similarly, the increase in BMI was also significant between groups (A vs B: $P=0.217$; A vs C: $P<0.001$; B vs C: $P=0.048$).

Dose correlated significantly with weight gain ($r=0.254$; $P<0.001$) and increase in BMI ($r=0.255$; $P<0.001$). However, given the differences in age, baseline weights and HbA1c between groups, an adjusted correlation was carried out. There was a significant correlation between dose and weight gain after controlling for initial weight, initial BMI and age ($r=0.240$; $P<0.001$). There was a similar correlation between dose and increase in BMI after controlling for the same variables ($r=0.242$; $P<0.001$). HbA1c reduced significantly from baseline in all three dosage groups ($P<0.001$ for all groups). There was no correlation between dose and HbA1c reduction ($r=0.012$; $P=0.85$). There was no correlation between HbA1c reduction and increase in BMI ($r=-0.024$; $P=0.72$).

Discussion

Pioglitazone has been used globally for over two decades. It has proven efficacy as an antidiabetic and is especially valued in the Asian-Indian patients, who have a high level of insulin resistance.⁴ In India, for many patients with diabetes, pioglitazone being an insulin sensitizer, comes as an agent that can delay the need of initiation of insulin therapy for years together.⁵

Our study aimed to assess the effect of different daily doses of pioglitazone on glycemic control and weight gain in newly-

diagnosed type 2 diabetes mellitus (DM) patients. There was a trend towards prescribing a lower dose of pioglitazone to patients who were older or had a greater BMI or had a lower HbA1c, though the differences were not always statistically significant. In other words, the lowest possible dose was used in patients who were closer to target glycemic control and may have been at risk for developing excessive fluid retention or heart failure (probably due to comorbidities or age). Conversely, the highest dose was seen used in patients that were younger, were further away from the glycemic target and had a lower weight/BMI at baseline.

At the end of six months, all patients achieved the HbA1c target of $\leq 7\%$ and there was no significant difference in HbA1c lowering capacity between dosage groups. Weight gain was the least in the low-dose group, though this difference did not reach statistical significance between Groups A and B. This may have been due to an inadequate sample size and larger studies will be needed to verify this difference. However, given that the glycemic goal was achieved in all three groups, we would still consider it prudent to initiate pioglitazone therapy with 7.5 mg/day as this would be the least required dose to achieve the desired effect.

There have been three previous studies examining the relationship between pioglitazone, weight gain and glycemic control that have included a group receiving 7.5 mg/day. The study by Miyazaki *et al.*⁶ compared four dosage groups – 7.5, 15, 30 and 45 mg/day. The size of each study group was small (range 11-13 patients) and the HbA1c in the low-dose group was significantly higher than the 15 and 30 mg/day group. Also, the low-dose group did not show a significant HbA1c reduction compared to baseline, placebo or the other groups.

In the study by Aronoff *et al.*,⁷ once again the same four dosage groups were compared and the size of each group was larger (range 76-85 patients) though close to half of the participants did not complete the study. The 7.5 mg/day group lost 0.6 kg at the end of 26 weeks while the other dose groups (15, 30 and 45 mg/day) all gained weight in the same period. All treatment groups, including the 7.5 mg/day group, had significant HbA1c reduction compared to placebo. However, the study showed a significant inverse correlation between HbA1c reduction and weight gain.

Majima *et al.*⁸ studied the differential effect of varying pioglitazone doses on Japanese women. The size of the groups was moderate (53 and 31 in the 7.5 and 15 mg/day arms, respectively). Their findings closely correlated with the findings from our study, in that there was no significant difference in HbA1c reduction between the 7.5 and 15 mg/day groups, while there was a significantly higher weight gain associated with the higher dose. However, a 30 mg/day arm was not tested in this study. Importantly, this study also showed that the effects on lipid profile normalization were not significantly different between 7.5 and 15 mg/day groups.

Earlier studies have shown that treatment with pioglitazone also alters fat metabolism and/or fat topography. Indeed, studies show that pioglitazone induces decrease in visceral fat, a shift of fat distribution from visceral to subcutaneous adipose depots consequently leading to improvements in both hepatic and peripheral tissue sensitivity to insulin.⁹

Aso *et al.*¹⁰⁷ have shown the beneficial effects of low-dose pioglitazone (7.5 mg/day) on serum high molecular weight (HMW) adiponectin and fluid retention (estimated from hematocrit) in both male and female patients with type

2 diabetes. Pioglitazone therapy at 7.5 mg/day not only significantly improved glycemic control but also resulted in marked increases in serum HMW adiponectin in both male and female Japanese patients with type 2 diabetes.

It is also important to emphasise that pioglitazone (7.5/15/30 mg) added to existing therapy as a combination treatment with other OAD showed no increased risk of bladder-related abnormalities.⁹

In all these previous studies, the duration of DM in patients was not one of the studied parameters and, hence, their results cannot reliably be applied to recently-diagnosed patients. Our results complement the results of Majima *et al*,⁸ which had studied only women. However, one possible limitation of our study is that our patients were exclusively Asian Indians and did not include any other racial or ethnic group.

The results of this study are significant, in the context using the drug on Indian patients. Optimizing the dosage for the agent, without compromising on safety ensures all benefits of pioglitazone for the patient.

In summary, the present study shows that, in recently-diagnosed type 2 DM patients, the glycemic effect of pioglitazone is preserved even at lower doses, while the propensity to cause weight gain increases with dose. Fluid retention and its association with heart failure remain important and dose-limiting adverse effects of this drug.¹¹ Low-dose pioglitazone

therapy (7.5 mg/day) in type 2 DM has been recently gaining popularity.

The current study was performed to investigate differences between different dosages of pioglitazone on weight gain and glycemic control in recently-diagnosed type 2 DM patients. Based on this study, we suggest that low-dose pioglitazone (at 7.5 mg/day) should be the preferred dose at which to initiate therapy in recently-diagnosed patients.

Conclusions

The glycemic effect of pioglitazone is preserved even at lower doses, while the propensity to cause weight gain increases with dose. We suggest that low-dose pioglitazone (7.5 mg/day) should be the preferred dose at which to initiate therapy in recently-diagnosed patients. Pioglitazone is an extremely useful agent in the treatment of type 2 diabetes mellitus (DM) through its actions on alleviating insulin resistance.

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