



Pioglitazone induced weight changes in type 2 diabetic patients

Sayantani Ghosh, Saugat Dey

International Journal of Collaborative Research on Internal Medicine & Public Health
Vol. 3 No. 6 (June 2011)

International Journal of Collaborative Research on Internal Medicine & Public Health (IJCRIMPH)

ISSN 1840-4529 | Journal Type: Open Access | Volume 3 Number 6

Journal details including published articles and guidelines for authors can be found at:

<http://www.iomcworld.com/ijcrimph/>

To cite this Article: Ghosh S, Dey S. Pioglitazone induced weight changes in type 2 diabetic patients. *International Journal of Collaborative Research on Internal Medicine & Public Health*. 2011; 3(6):534-540.

Article URL: <http://iomcworld.com/ijcrimph/ijcrimph-v03-n06-08.htm>

Correspondence concerning this article should be addressed to Dr. Sayantani Ghosh; B S Medical College, India /
Email: ghoshsayantani@rediffmail.com

Paper publication: 30 June 2011

International Journal of Collaborative Research on Internal Medicine & Public Health

Editors-in-Chief:

Asst. Prof. Dr. Jaspreet S. Brar (University of Pittsburgh, USA)
Forouzan Bayat Nejad

Executive Editor: Mostafa Nejati

Deputy Editor: Dr. Mensura Kudumovic (University of Sarajevo, Bosnia & Herzegovina)

Associate Editors:

Dr. Monica Gaidhane
Dr. Suresh Vatsyayann (FreeGP, New Zealand)

Pioglitazone induced weight changes in type 2 diabetic patients

Sayantani Ghosh *, Saugat Dey

B S Medical College, India

* Corresponding author; Email: ghoshsayantani@rediffmail.com

ABSTRACT

Background: Pioglitazone, a member of the thiazolidinedione drug family, with hypoglycemic action, is widely used for the therapy of type 2 diabetic patients.

Aims and Objectives: The effect of pioglitazone on body weight was investigated and the effects of monotherapy and combinations with other hypoglycemic agents were compared.

Methodology: A prospective study on 379 type 2 diabetic cases, who were being given pioglitazone for the first time, as either monotherapy or in combination with other oral hypoglycemic agents or insulin. Parameters were analyzed by Kruskal-Wallis test, considering $p < 0.05$ as significant.

Results: Pioglitazone therapy resulted in weight gain, especially in females, although triglyceride and lipoprotein levels were not adversely affected. Concomitant use of pioglitazone along with insulin or any of the sulfonylurea group of drugs accounted for more weight gain; (2.57 ± 1.4 kg) and (2.31 ± 1.2 kg) respectively; than that by pioglitazone alone (2.23 ± 1.3 kg). However pioglitazone combination therapy with metformin and alpha glycosidase inhibitors revealed lower weight gain: (0.31 ± 0.2 kg) and (0.16 ± 0.4 kg) respectively. Higher doses of pioglitazone were associated with more important weight gain.

Limitations of the study:

1. The study is an open-label prospective observational study and not a double blinded randomized controlled trial.
2. Long term changes in weight were not assessed, as the mean follow up period was only 6 months.
3. There were very few patients (only 28) on pioglitazone monotherapy.

Conclusions: Pioglitazone increases body weight, although less than other thiazolidinediones. Hence it should not be indiscriminately used in high doses and when used, it should be supplemented with metformin and alpha glycosidase inhibitors.

Keywords: Pioglitazone, thiazolidinedione, body weight, Type- 2 Diabetes Mellitus, insulin, oral hypoglycemic agents

Conflicts of Interest: None

Introduction

Pioglitazone, a member of the thiazolidinedione drug family, selectively stimulates the peroxisome proliferator-activated receptor gamma (PPAR- γ) and to a lesser extent PPAR- α ^{1, 2}. It was developed after troglitazone was removed from the market because of hepatotoxicity. It modulates transcription of insulin-sensitive genes in muscle, adipose tissue and liver. As a result, pioglitazone reduces insulin resistance in liver and peripheral tissues; decreases withdrawal of glucose from the liver; hence reducing the load of glucose, insulin and glycosylated hemoglobin (HbA_{1C}) in the bloodstream and thereby is widely used for the treatment of Type 2 diabetic patients.

But like several other hypoglycemic agents; pioglitazone therapy also causes weight gain. The mechanisms involved include fat cell proliferation, fluid retention, decreased glycosuria, and increased appetite^{3, 4, 5, 6, 7}. To minimize this weight gain, several studies throughout the world have advocated pioglitazone and metformin combination therapy^{8, 9}. However there has been dearth of studies in India, regarding the extent of these weight changes for different combination therapies commonly prescribed to type 2 diabetics in the country. Hence, the influence of pioglitazone on body weight and body mass index (BMI) of patients was investigated, by comparing its monotherapy and combination therapies with other hypoglycemic agents commonly prescribed; and also by comparing between different pioglitazone doses within each of the regimen.

Methodology

The prospective, observational trial included type 2 diabetes mellitus patients of the

outpatient clinics of the department of General Medicine in Bankura Sammilani Medical College and Hospital, India from January 2009 to December 2009 and from May 2010 to September 2010. The patients received pioglitazone for the first time or had been given pioglitazone for < 2 months. The drug was prescribed either as a monotherapy or in combination with other oral hypoglycemic agents or insulin.

Exclusion criteria were: chronic debilitating disease, pregnant mothers, serum creatinine >1.5 mg/dl, abnormal thyroid stimulating hormone level, history of congestive heart failure or unstable coronary artery disease or weight fluctuations in the last 6 months. Patients on steroids, oral contraceptive pills, hormone replacement or those taking medications/ dietary supplements for the treatment of obesity were also excluded from the study. Patients adopting major lifestyle modifications, viz. major dietary adjustments or smoking and alcohol cessation, in the last 6 months were also excluded from the study.

379 patients were found to be eligible for the study and they were assigned to treatment regimens – A, B, C, D and E. A total of 108 patients were on regimen A that included pioglitazone and subcutaneous human mixture insulin, 117 on B with pioglitazone and sulfonylurea, 87 on C with pioglitazone and metformin, 39 on D with pioglitazone and alpha glucosidase inhibitors; and 28 on E including pioglitazone monotherapy. Pioglitazone dose varied from 7.5- 30 mg/day. The prescribed sulfonylurea drugs were: glipizide 5mg/day, glimepride 1-2 mg/day or glyburide 2.5-5 mg/day. The prescribed alpha glucosidase inhibitors were- voglibose 0.2mg/day or acarbose 25- 50 mg/day. Metformin dosing was 500-1000 mg/day. Insulin dosing also varied according to the individual glycemic levels. All the patients were asked to maintain an identical diet based on their caloric requirements and were counseled for

similar intensity of physical exercise. The study was approved by the ethical board of the institute and all patients provided written informed consent before enrolment.

At screening, a history and physical examination was performed and body weight and height were measured to the nearest 0.1 kg and 1 cm respectively. Laboratory tests included complete blood count, fasting and postprandial serum glucose, lipid profile (total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol), thyroid stimulating hormone, HbA_{1c}, serum creatinine and electrocardiogram. Follow up tests were performed at 3, 4, 6, 8, 9 and 10 months; however hundred percent patients could be followed only till the 3 month follow up; as after that there was a steady rise of defaulters. At follow up the body weight, fasting and postprandial serum glucose levels, HbA_{1c} and lipid profile were reevaluated. The weights of all the patients, at all points of time, were measured in a single weighing machine and their height measured using a particular wall-mounted stadiometer. All laboratory tests were done in the general laboratory of the institution.

Statistical Analysis

All data were analyzed using SAS software, version 9.1. All results are presented as mean \pm S.D. Differences in each parameter among groups and differences between separate pioglitazone dosing within a group were analyzed using Kruskal-Wallis test. A both sided p value of ≤ 0.05 was considered statistically significant.

Results

Among the 379 patients, 233 were male and 146 were female. Baseline data regarding the study subjects are displayed in Table I. Mean weight and BMI gain 3 months after starting of pioglitazone therapy was 1.68 ± 1.3 kg and 0.7 ± 0.3 kg/m² respectively. The average weight gained by females was 0.83 kg more than that by males. The glycemic control achieved in all the 5 regimens, in terms of lowering of fasting- postprandial serum glucose and HbA_{1c}, was significant ($p < 0.01$ for each). Also the regimens had an antiatherogenic effect as triglyceride levels decreased ($p = 0.038$) and high density lipoprotein (HDL) ($p = 0.021$) increased. Low density lipoprotein (LDL) levels remained unchanged. The effects of the different regimens on the various parameters is summarized in Table II.

The differences in weight ($p < 0.001$) and BMI ($p = 0.002$) gain were significant among the different treatment regimens. Patients on regimen A had the highest weight gain of 2.57 ± 1.4 kg and BMI gain of 1.01 ± 0.2 kg/m²; with the weight gain increasing with higher insulin doses ($p < 0.01$). The regimen B correspondents also accounted for a significant gain of 2.31 ± 1.2 kg of weight and 0.98 ± 0.4 kg/m² of BMI; while regimen E witnessed a gain of 2.23 ± 1.3 kg and 0.73 ± 0.6 kg/m². However pioglitazone combination therapy with metformin and alpha glucosidase inhibitors (regimen C and D) revealed lower weight and BMI gain: 0.31 ± 0.2 kg and 0.11 ± 0.09 kg/m²; and 0.16 ± 0.4 kg and 0.06 ± 0.02 kg/m² respectively. In regimen B and regimen D, different drugs of the same class did not show any noticeable variation in terms of glycemic control or weight gain.

Patients on regimen A, B, C and E were subjected to varying doses of pioglitazone: 7.5, 15 and 30 mg/day, while all of the subjects on regimen D received a fixed dose of 15 mg/day. Although the glycemic control was comparable for the different pioglitazone dosing with treatment regimen, increasing doses of pioglitazone were found to be associated with more weight gain ($p < 0.001$). Weight gain due to different pioglitazone doses is included in Table II.

Discussion

In India thiazolidinediones, especially pioglitazone, are frequently used in type 2 diabetic patients, either as monotherapy or as a combination therapy with other hypoglycemic agents. This study also reiterated the fact that they are excellent drugs for glycemic control in insulin resistant patients. An improved glycemic control with significant reductions in fasting and postprandial glucose levels and HbA_{1c} were demonstrated in all five groups. Plasma lipid levels also improved over the course of the follow up. But these drugs were found to be causing substantial weight gain; which may undermine the benefits of improved glycemic control and also reduce drug compliance also known as “psychological insulin resistance”¹⁰.

There have been several theories to explain the weight gain associated with thiazolidinediones: increased appetite⁷, increase in the amount of subcutaneous fat^{5, 6}, fluid retention^{4, 6} etc. Many studies calculated how much of the weight gain is due to body fat and what proportion of it is attributed to body water. A study by Smith et al¹¹ estimated a weight gain of 3.9 kg over 24 weeks in pioglitazone-treated patients, due to an increase in fat mass measured by Dual-energy X-ray absorptiometry. In contrast, Basu et al¹²

found that the 3.1 kg increase in weight on pioglitazone was primarily due to a 2.4 liters increase in total body water measured by deuterated water.

In the present study, pioglitazone monotherapy and its combination therapy with insulin and sulfonylurea group of drugs led to the most important weight gain; whereas pioglitazone combinations with metformin and alpha glucosidase inhibitors resulted in the lowest weight gain. This could be explained by increased lipid accumulation due to insulin and increased release of insulin caused by sulfonylurea drugs; thus addition of pioglitazone to these drugs probably augmented the adipogenicity of each agent. On the contrary, metformin and alpha glucosidase inhibitors are both known to decrease body weight by reduction of caloric intake and loss of adipose tissue¹³; and reduction of insulin levels^{14, 15} respectively. Hence, the combination of either of these drugs with pioglitazone may have a balancing effect on body weight.

The study also revealed that increased doses of pioglitazone were associated with higher weight and BMI gain, although glycemic control and the anti atherogenic effect were similar for all doses (Table II). Previously Majima et al¹⁶ have also demonstrated that a dose of 7.5 mg/day pioglitazone significantly improved glucose and lipid metabolism with less weight gain compared to higher doses, although in that study all the subjects were female.

There are several limitations to the current study. First, the study was an open-label prospective observational study; but not a double-blind, randomized, controlled trial. Second, long term changes in weight were not assessed, as the mean follow up period was only 6 months. Third, there were very few patients on group D (39) and E (28) compared to group A, B or C. Even though it was the

first study of its kind in India to study the influence of pioglitazone on the body weight and BMI on both its monotherapy as well as its combination therapy with other hypoglycemic agents, in all possible dosing commonly prescribed.

Pioglitazone increases body weight and BMI and, therefore, it should not be indiscriminately used in high doses. Pioglitazone therapies supplemented with metformin and alpha glycosidase inhibitors have less impact on the body weight. Comprehensive lifestyle-weight-management programmes are also helpful on weight reduction associated with pioglitazone¹⁷. Hence, to avoid excess weight gain, there should be a comprehensive approach towards type 2 diabetics treated with pioglitazone, including extensive lifestyle changes, dose regulated pharmacologic interventions and a proper health education.

References

1. Gillies PS, Dunn CJ. Pioglitazone. *Drugs* 2000; 60 (2): 333–43.
2. Smith U. Pioglitazone: mechanism of action. *Int J Clin Pract Suppl* 2001; (121): 13–8.
3. Fonseca V. Effect of thiazolidinediones on body weight in patients with diabetes mellitus. *Am J Med* 2003; 115(Sup 8A):42S–48S.
4. Staels B. Fluid retention mediated by renal PPAR γ . *Cell Metabolism* 2005; 2: 77–78.
5. Miyazaki Y, Mahankali A, Matsuda M et al. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. *J Clin Endocrinol Metab* 2002; 87:2784–2791.
6. Basu A, Jenson MD, McCann F et al. Effects of pioglitazone versus glipizide on body fat distribution, body water content, and hemodynamics in type 2 diabetes. *Diabetes Care* 2006; 29:510–514.
7. Shimizu H, Tsuchiya T, Sato N, Shimomura Y, Kobayashi I, Mori M. Troglitazone decreases plasma leptin concentration but increases hunger in NIDDM patients. *Diabetes Care* 1998; 21:1470–4.
8. Schernthaner G, Matthews D, Charbonnel B, Hanefeld M, Brunetti P. Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double blind, randomized trial. *J Clin Endocrinol Metab* 2004; 89: 6068–6076.
9. Kawai T, Funae O, Shimada A et al. Effects of pretreatment with low-dose metformin on metabolic parameters and weight gain by pioglitazone in Japanese patients with type 2 diabetes. *Intern Med* 2008; 47:1181–1188.
10. Carver C. Insulin treatment and the problem of weight gain in type 2 diabetes mellitus. *Diabetes Educ* 2006; 32(6): 910–7.
11. Kawai T, Takei I, Oguma Y, et al. Effects of troglitazone on fat distribution in the treatment of male type 2 diabetes. *Metabolism* 1999; 48: 1102–1107.
12. Smith SR, De Jonge L, Volaufova J, Li Y, Xie H, Bray GA. Effect of pioglitazone on body composition and energy expenditure: a randomized controlled trial. *Metabolism* 2005; 54:24–32.
13. Basu A, Jenson MD, McCann F et al. Effects of pioglitazone versus glipizide on body fat distribution, body water content, and hemodynamics in type 2 diabetes. *Diabetes Care* 2006; 29:510–514.

14. Sels J, Huijberts M, Wolffenbuttel B. Miglitol, a new alpha-glucosidase inhibitor. *Expert Opin Pharmacother* 1999; 1:149–56.
15. Clissold S, Edwards C. Acarbose: A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. *Drugs* 1988; 35:214–43.
16. Majima T, Komatsu Y, Doi K, et al. Safety and efficacy of low-dose pioglitazone (7.5 mg/day) vs. standard-dose pioglitazone (15 mg/day) in Japanese women with type 2 diabetes mellitus. *Endocr J* 2006; 53: 325–330.
17. Kushner R F, Sujak M. Prevention of weight gain in adult patients with type 2 diabetes treated with pioglitazone. *Obesity* 2009; 17 (5): 1017–1022.

Table I: Baseline characteristics of the study subjects.

Characteristics	Males	Females	Ratio	p value
Number	233	146	1.59:1	
Body weight	66.8±4.6 kg	59.61±5.8 kg	1.12:1	0.061
Body Mass Index (BMI)	26.42±0.7 kg/m ²	26.85±0.9 kg/m ²	0.98:1	0.086
Serum glycosylated hemoglobin (HbA _{1c})	9.6±0.8 mg/dl	9.5±0.6 mg/dl	1.01:1	0.41
Serum fasting glucose	143±10.9 mg/dl	147±11.7mg/dl	0.97:1	0.13
Serum postprandial glucose	223±17.8 mg/dl	238±23.1mg/dl	0.94:1	0.11
Serum triglyceride	193±9.3 mg/dl	188±8.9mg/dl	1.03:1	0.68
Serum High Density Lipoprotein (HDL)	38±8.7 mg/dl	43±9.3 mg/dl	0.88:1	0.52
Serum Low Density Lipoprotein (LDL)	178±18.7 mg/dl	176±19.9 mg/dl	1.01:1	0.71
Number of subjects in Group A	68	40	1.7:1	0.
Number of subjects in Group B	65	52	1.25:1	
Number of subjects in Group C	58	29	2:1	
Number of subjects in Group D	25	14	1.79:1	
Number of subjects in Group E	17	11	1.54:1	

Table II: Effects of pioglitazone doses on the observed parameters.

Pioglitazone daily dosing	Group A			Group B			Group C		Group D	Group E		
	7.5 mg/day	15 mg/day	30 mg/day	7.5 mg/day	15 mg/day	30 mg/day	15 mg/day	30 mg/day	15 mg/day	7.5 mg/day	15 mg/day	30 mg/day
Number of patients	12	72	24	6	79	32	38	49	39	5	14	19
Weight gain (in kg)	1.8±1.6	2.5±1.5	3.2±1.4	1.4±1.4	2.2±1.4	2.9±1.2	0.17±0.4	0.4±0.3	0.1±10.2	1.6±1.5	2.03±1.3	2.8±1.4
Fall in serum HbA _{1c} (in mg/dl)	1.16±0.086	1.16±0.094	1.15±1.01	1.08±0.78	1.09±0.88	1.09±0.91	1.14±0.99	1.15±0.83	0.98±0.09	0.84±0.04	0.85±0.07	0.86±0.05
Fall in serum fasting glucose (in mg/dl)	19.4±4.9	20.3±4.1	20.1±3.9	18.1±3.8	18.3±3.5	18.8±4.3	19.3±4.7	19.6±4.1	20.3±4.9	18.6±3.9	17.6±2.9	18.3±3.7
Fall in serum postprandial glucose (in mg/dl)	57.6±9.8	58.6±9.6	57.9±11.1	52.6±7.8	53.7±6.9	54.6±8.3	58.6±9.1	59.9±10.5	60.1±11.3	54.9±9.7	50.8±7.7	51.6±7.8
Fall in serum triglyceride (in mg/dl)	17.4±4.9	17.9±3.9	17.8±5.3	17.4±4.3	16.8±5.1	17.9±5.5	16.3±4.1	16.7±4.6	18.3±5.9	16.2±10.2	19.1±7.6	19.5±8.2
*Rise in serum HDL (in mg/dl)	-1.01±0.44	-0.89±0.53	-0.83±0.23	0.81±0.64	0.89±0.51	1.18±0.67	3.69±0.48	3.79±0.56	3.76±0.63	4.16±0.71	5.39±1.43	5.48±1.79
*Fall in serum LDL (in mg/dl)	-1.6±0.08	-1.16±0.056	1.01±0.54	-1.02±0.071	-1.41±0.053	0.98±0.44	-1.06±0.73	-0.97±0.05	1.18±0.02	1.04±0.03	1.19±0.096	1.23±0.091

NB. * Negative sign in the values indicate fall in serum HDL and rise of serum LDL.