Effect of Thiazolidinediones (Glitazones) groups on Glycemic control and Lipid profile: A Meta-analysis of Randomized Control Trials

Dr. Bharti. N. Karelia*, Dr. Jatin .G. Buch**

*Assistant Professor, **Professor and head, Department of Pharmacology, P.D.U. Medical College, Rajkot 360 001

Abstracts: Background & objectives: In patients with type 2 diabetes mellitus, all therapeutic options should be evaluated for their effect on cardiovascular risk factors, in addition to glycemic control. Randomized controlled trials of pioglitazone and rosiglitazone in patients with type 2 diabetes to evaluate their effect on either glycemic control or serum lipid profile *individually* have been reviewed and analyzed but analysis of reports of effect on both these parameters simultaneously are very few and such meta-analysis has not been carried out earlier. This article presents meta-analysis of randomized controlled trials of pioglitazone and rosiglitazone in patients with type 2 diabetes to evaluate their effect on glycemic control as well as serum lipid profile. Methods: We identified the citations by searching the web site of MD-consult, National Library of Medicine and Google for identifying randomized controlled trails pertinent to the thiazolidinediones of interest (rosiglitazone and pioglitazone) and evaluated then compared effect of these two drugs on glycemic control and serum lipid profile by applying student's t-test.Results: Twelve randomized controlled trials (n=10052) were identified. Both thiazolidinediones produced significant reduction in HbA_{1c} and FPG. Pioglitazone significantly reduced TG and increased HDL-C levels without significant effect on LDL-C and Total CH; while rosiglitazone significantly increased HDL-C, LDL-C, Total CH and slightly increased TG. Comparatively, they did not differ in their effect on glycemic control but regarding lipid profile, pioglitazone significantly reduced TG whereas rosiglitazone slightly increased TG level. Rosiglitazone produced significantly more increase in LDL-C and total CH level as compared to pioglitazone. Interpretation & conclusion: Pioglitazone had significantly more beneficial effects on lipid profile than Rosiglitazones and is clinically superior in patient of Type-2 DM with dyslipidemia. [Karelia B et al NJIRM 2012; 3(1) : 57-62]

Key Words: Diabetes mellitus, Glycemic control, Lipid profile, Thiazolidinediones.

Author for correspondence: Dr. Bharti .N.Karelia, Department of pharmacology, P.D.U Medical College, Rajkot–36 0001.e- mail: nirbharti_karelia@yahoo.co.in

Introduction: Worldwide prevalence of diabetes mellitus (DM) has risen dramatically over the past two decades from an estimated 30 million cases in 1985 to 177 million in 2000. Based on current trends, more than 360 million individuals will have diabetes by the year 2030. The American Heart Association has designated DM as a major risk factor for cardiovascular diseases (CVD). Increase in cardiovascular morbidity and mortality appears to be related to synergism of hyperglycemia with other cardiovascular risk factors [1.] There is a compelling need for anti-diabetic medication that can also address the problem of accelerated CVD through their impact on other cardiovascular risk factors.

Two thiazolidinediones are currently available to treat patients with type-2 DM, rosiglitazone and pioglitazone. Because of their action on plasma lipids and beneficial effects on inflammatory markers, coagulation and endothelial function, they were predicted to reduce macrovascular complications of DM and insulin resistance [2.] They also have variable effect on lipid profile.

Randomized controlled trials of pioglitazone and rosiglitazone in patients with type 2 diabetes to evaluate their effect on either glycemic control or serum lipid profile *individually* have been reviewed and have been analyzed but analysis of reports on effect on both these parameters simultaneously are very few and such meta-analysis has not been carried out earlier. This article presents meta-analysis of randomized controlled trials of pioglitazone and rosiglitazone in patients with type 2 diabetes to evaluate their effect on glycemic control as well as serum lipid profile.

Material and Methods: We identified the citations by searching the web site of MD-consult, National Library of Medicine and Google for identifying randomized controlled trails pertinent to the

thiazolidinediones of interest (rosiglitazone and pioglitazone). Reference lists of all relevant articles were also checked. To be included, the citation had to meet the following criteria: (1) Randomized controlled trial (blind or open), (2) Enrolled at least 30 adults with type-2 DM, (3) Evaluated the effect of rosiglitazone (4 to 8 mg) or pioglitazone (30 or 45 mg) in monotherapy or in combination with other antidiabetic medication, (4) Evaluated the effect of drug on HbA_{1C}, fasting plasma glucose and serum lipid profile, (5) Had a minimum treatment duration of 12 weeks, (6) Was published in English and available as online free full article.

We evaluated and compared effects of pioglitazone and rosiglitazone on glycemic control and serum lipid profile by applying paired and unpaired t- test. We calculated the weighted mean difference (WMD) and 95% confidence interval (CI) for all variables. P-value was calculated by using online software Statistics Calculators (version 2.0) [3.]

Result: Twelve randomized controlled trials (n=10052) met the inclusion criteria [4-14.] The design of each trial included in this analysis is presented in Table-1.

Table:1 Summary of trials included in this meta-analysis

No.	Source	Design	Duration of treatment	Groups
Pioglitazone				
1.	Spanheimer R et al, [4] 2009 (n=5238)	RDBP	24 wk	Placebo P 45mg/d
2.	Goldberg R B et al, [5] 2005 (n=802)	Randomized controlled trail	24 wk	P 45mg/d R 8mg/d
3.	Aronoff S et al, [6] 2000 (n=408)	RDBP	26 wk	Placebo P 7.5mg/d P 15mg/d P 30mg/d P 45mg/d
4.	Kipnes M S et al, [7] 2001 (n=560)	RDBP	23 wk	Placebo+ SU P :15mg/d+SU P :30mg/d+SU
5.	Hanefeld M et al, [8] 2004 (n=639)	Randomized double blind parallel group study	52 wk	P 45mg/d+SU M+SU
6.	Pfutzner A et al, [9] 2005 (192)	ROL	26 wk	P 45mg/d Glimepiride
7.	Nishio K et al, [10] 2006 (n=54)	Randomized controlled trail	24 wk	Control P 45mg/d
Rosiglitazone				
1.	Goldberg R B et al, [5] 2005 (n=802)	Randomized controlled trail	24 wk	P 45mg/d R 8mg/d
2.	Raskin P et al, [11] 2001 (n=319)	RDBP	26 wk	Placebo R 4mg/d R 8mg/d
3.	Lebovitz H E et al, [12] 2001 (n=533)	RDBP	26 wk	Placebo R 4mg/d R 8mg/d
4.	Phillips L S et al, [13] 2001 (n=959)	RDBP	26 wk	Placebo R 4mg/d R 8mg/d
5.	Fonsecs V et al, [14] 2000 (n=348)	RDBP	26 wk	Placebo+ MR 4mg/d+ MR 8mg/d+M

*Abbreviations: RDBP, randomized double blind placebo controlled; P, pioglitazone; SU, sulfonyl urea; M, metformin; ROL, randomized open label; R, rosiglitazone.

The effects of thiazolidinediones on glycemic control, as measured by glycosylated haemoglobin (HbA_{1C}) and fasting plasma glucose (FPG) and serum lipid profile are presented in **Table-2**.

Pioglitazone significantly reduced HbA_{1C} level by 0.99% (95% CI, -1.38 to -0.80) and FPG concentration by 38.56 mg/dl (95% CI, -51.20 to -29.10). Rosiglitazone also significantly reduced HbA_{1C} level by 0.57% (95% CI, -0.96 to -0.28) and FPG concentration by 45.53 mg/dl (95%, -53.18 to -38.88).

Regarding serum lipid profile, pioglitazone significantly reduced serum triglyceride (TG) level by 26.92 mg/dl (95% CI, -52.78 to -25.56) and increased HDL-C level by 7.36 mg/dl (95% CI, 5.13 to 7.78) whereas rosiglitazone increased TG level by

7.04 mg/dl (95% CI, -1.67 to 10.43) and significantly increased HDL-C level by 4.24 mg/dl (95% CI, 3.53 to 6.39). Pioglitazone increased LDL-C level by 7.54 mg/dl (95% CI, 1.10 to 9.74) and Total CH level by 6.09 mg/dl (95% CI, 1.71 to10.09), whereas rosiglitazone significantly increased LDL-C level by 20.52 mg/dl (95% CI, 17.24 to 22.78) and Total CH level by 28.84 mg/dl (95% CI, 27.94 to 30.44). Rosiglitazone significantly reduced free fatty acids (FFA) level by 0.03 g/L (95% CI, -0.04 to -0.02).

Table:2 Effects of thiazolidinediones on glycemic control and serum lipid level

Drug	No. of study	Variable	WMD (95% CI)	p-value
Pioglitazone	6	HbA_{1C}	-0.99 (-1.38 to -0.80)	0.000746 **
	6	FPG	-38.56 (-51.20 to -29.10)	0.000848 **
	6	TG	-26.92 (-52.78 to -25.56)	0.002431 **
	6	HDL-C	7.36 (5.13 to 7.78)	0.000202 **
	6	LDL-C	7.54 (1.10 to 9.74)	0.057229
	5	Total-CH	6.09 (1.71 to 10.09)	0.050850
Rosiglitazone	5	HbA_{1C}	-0.57 (-0.96 to -0.28)	0.023376 *
	4	FPG	-45.53 (-53.18 to -38.88)	0.001075 **
	4	TG	7.04 (-1.67 to 10.43)	0.250089
	5	HDL-C	4.24 (3.53 to 6.39)	0.002470 **
	5	LDL-C	20.52 (17.24 to 22.78)	0.000145 **
	5	Total-CH	28.84 (27.94 to 30.44)	0.000145 **
	4	FFA	-0.03 (-0.04 to -0.02)	0.023376

*p<0.05, **p<0.01, †Abbreviations: WMD, weighted mean difference; CI, confidence interval; $HbA_{1C,}$ glycosylated haemoglobin; FPG, fasting plasma glucose; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CH, cholesterol; FFA, free fatty acid, †unit for TG, HDL-C, LDL-C, Total CH, FPG is (mg/dl), FFA is (g/L) and for HbA_{1C} is (%). † Millimoles per liter converted to milligrams per deciliter: value/conversion factor, where conversion factor = 0.01129 for TG, 0.02586 for HDL-C, LDL-C and Total CH, 0.0354 for FFA and 0.0555 for FPG.

Comparisons of the effects of pioglitazone with rosiglitazone are presented in **Table-3.** Pioglitazone and rosiglitazone did not differ in their effect on glycemic control. Regarding serum lipid profile, pioglitazone significantly reduced whereas rosiglitazone slightly increased TG level. Rosiglitazone significantly increased LDL-C and total CH level as compared to pioglitazone.

Table:3 Comparisons of the effects of pioglitazone with rosiglitazone

Variable	Pioglitazone Mean of difference (n)	Rosiglitazone Mean of difference (n)	SD of unpaired 't' test	p-value
HbA_{1C}	-1.09 (6)	-0.62 (5)	0.38	0.068364
FPG	-40.15 (6)	-46.03 (4)	11.80	0.463428
TG	-39.17 (6)	4.38 (4)	13.97	0.001305**
HDL-C	6.44 (6)	4.96 (5)	1.64	0.170411
LDL-C	5.42 (6)	20.01 (5)	4.54	0.000507**
Total-CH	5.9 (5)	29.19 (5)	3.53	0.000006**

* p<0.05, **p<0.01, †n= no. of study, †Abbreviations: WMD, weighted mean difference; CI, confidence interval; $HbA_{1C,}$ glycosylated haemoglobin; FPG, fasting plasma glucose; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CH, cholesterol; FFA, free fatty acid, †unit for TG, HDL-C, LDL-C, Total CH, FPG is (mg/dl), FFA is (g/L) and for HbA_{1C} is (%). † Millimoles per liter converted to milligrams per deciliter: value/conversion factor, where conversion factor = 0.01129 for TG, 0.02586 for HDL-C,

LDL-C and Total CH, 0.0354 for FFA and 0.0555 for FPG.

Discussion: Metabolic syndrome (also known as Syndrome X) is the term used for a group of interrelated risk factors that increase the risk of Coronary Artery Disease (CAD), stroke and type -2 diabetes. These factors include dyslipidemia (elevated TG, LDL-C and low HDL-C), raised blood pressure, dysglycemia and obesity [15.] Patients with any of these are also at a higher risk of developing the other component of the syndrome, especially type-2 diabetes [16.] The incidence of this syndrome is quite high and is increasing with sedentary life style. As a result, now metabolic syndrome is regarded not just as a clinical problem but has assumed proportions of a major public health problem [15.]

Because hyperglycemia and hyperlipidemia are additive to cardiovascular risk, it is important that lipid abnormality should be detected early and treated aggressively as a part of comprehensive diabetes care. Most common pattern of dyslipidemia is hypertriglyceridemia and decreased HDL-C. Diabetic dyslipidemia is more frequent among individuals with type-2 DM [1.]

Thiazolidinediones are a new group of antidiabetic drugs indicated in type-2 DM. They are called insulin sensitizers and act as selective agonist for the nuclear peroxisome proliferator activated receptor γ (PPARγ) which is thought to be the mechanism behind increased tissue sensitivity to insulin in type-2 DM. Thiazolidendiones cause an average reduction in HbA_{1C} of 0.5-1.4% [2.] According to this meta-analysis, reduction in HbA_{1C} and FPG were statistically significant for both the drugs. We also found these effects to be comparable. However, their effect on lipid profile shows important differences. Pioglitazone lowers TG and increases HDL-C level without change in LDL-C level because it's action on PPARα [17.] In a head to head study among dyslipidemic patients, pioglitazone decrease TG by 20%, modestely increase in HDL particle number and size and improvement in both LDL particle number and size [18.]

In the present meta-analysis involving seven studies and 7893 patients on pioglitazone and five studies with 2961 patients on rosiglitazone, we found that pioglitazone significantly reduced TG and increased HDL-C level without significant effect on LDL-C and Total CH. As against this, the effect of rosiglitazone on lipid profile was inconsistent. There was slight increase (~5%) in TG with increase in HDL-C and LDL-C also. Unlike pioglitazone, rosiglitazone does not interact with PPARα [2, 17.] which explains the reason behind this difference [18.]

For a clinician, apart from the changes in lipid profile, actual benefit in terms of effects on cardiovascular (CV) morbidity and mortality are of greater importance. Although pioglitazaone changes lipid profile favourably, it is yet to be established whether it is sufficient to lower the risk of CVD. Long-term effects of pioglitazone and rosiglitazone on cardiovascular morbidity and mortality are being evaluated in several large randomized controlled trials: ADOPT (A Diabetes Outcome Progression Trial), RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes), and PROACTIVE (Prospective Pioglitazone Clinical Trial in Macrovascular Events) [19.] Now conclusion of one such trial is available, which suggests that pioglitazone treatment resulted in significant risk reduction in major adverse cardiovascular events (MACE) [20.] Rosiglitazone was associated with an increase of heart failure but the data were insufficient to determine whether the drug was associated with an increase risk of myocardial infarction (MI) [21.] Among the patients with type 2 diabetes, use of rosiglitazone is associated with significantly higher odds of congestive heart failure, myocardial infarction, and death relative to pioglitazone in real world settings [22.] Recent evidence suggests that rosiglitazone, but not pioglitazone increases the risk of cardiovascular events (MI, stroke).While degree of the risk remains controversial, an expert panel reviewing this question for the FDA recommended caution in the use of rosiglitazone [2.] Apart from beneficial effect on lipid profile, pioglitazone also reduces MACE in DM.

Based on the guidelines provided by the American Diabetic Association (ADA) and American Heart Association, the order of priorities in the treatment of hyperlipidemia are to (1) lower LDL-C (2) increase HDL-C (3) lower TG [1.] Considering this, when we compare the effects of both thiazolidinediones, we realized that pioglitazone significantly decreases TG in comparison to rosiglitazone. Rosiglitazone significantly increases LDL-C and Total CH as compared to pioglitazone. Regarding HDL-C, HbA_{1C} and FPG, there was no significant difference

between the two. Results of our analysis suggest that since pioglitazone affects lipid profile in a more favorable way than rosiglitazone it is also likely to be clinically superior in patients of type-2 DM with dyslipidemia. Clinical trials involving effect of thiazolidinediones on lipid profile or MACE are available separately, but studies including both the variables simultaneously are very few. Meta-analysis of such clinical studies in which both variables are studied simultaneously would be more meaningful and conclusive.

Conclusion: Pioglitazone had significantly more beneficial effects on lipid profile than Rosiglitazones and is clinically superior in patient of Type-2 DM with dyslipidemia.

References:

1. Power AC. Diabetes mellitus. In: Kasper DL, Braunwald E, Fauci AS, et al editors. Harrison's principles of internal medicine volume-2. 16th ed. USA: McGraw Hill; 2005. p. 2152-2180.
2. Power AC, D'alessio D. Endocrine pancreas and pharmacotherapy of diabetes mellitus and hypoglycemia. In: Bruntun LL, Chabner BA, Knollrrann BC editors. Goodman & Gillman's the pharmacological basis of therapeutics. 12th ed. McGraw Hill; 2011. P. 1237-1273.
3. Statistics calculaters (version 2.0) [online]. Available from: http://www.danielsoper.com/statcalc/c9/co8.aj px. Accessed 2011, March 15.
4. Spanheims R, Betteridge DJ, Tan MH, et al. long term lipid effects of pioglitazone by baseline antihyperglycemia medication therapy and statin use from the PROacive experience (PROactive 14). The American journal of cardiology [serial online] 2009 july: 104(2). Available from: http://www.mdconsult.com/das/article/body/237643931-4/jorg. Accessed 2011, February 22.
5. Goldberg RB, Kendall DM, Deeg MA. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patient with type 2 diabetes and dyslipidemia. Diabetes care [serial online] 2005:28(No.7): 1547-1554. Available from: http://care.diabetesjournals.org/content/28/7/1547.full. Accessed 2011, February 22.
6. Aronoff S, Rosenblath S, Braithwaite S, et al. pioglitazone hydrochloride monotherapy omproves glycemic control in the treatment of patients with type 2 diabetes. Diabetes care [serial online] 2000:23:1605-1611. Available from: http://care.diabetesjournals.org/content/23/11/1605.full. Accessed 2011, February 22.
7. Kipnes MS, Krosnick A, Rendell MS, et al. pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized placebo-controlled study. The American journal of medicine [serial online] 2001 July: 111(1). Available from: http://www.mdconsult.com/das/article/body/237779776-4/jorg. Accessed 2011, February 22.
8. Hanefeld M, Brunetti P, Schernthaner GH, et al. One year glycemic control with a sulfonylurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes. Diabetes care [serial online] 2004 January: 27(1):141-147. Available from: http://care.diabetesjournals.org/content/27/1/141.short. Accessed 2011, February 22.
9. Pfutzner A, Marx n, Lubben G, et al. improvement of cardiovascular risk markers by pioglitazone is independent from glucemic control. J Am Coll [serial online] 2005:45:1925-1931. Available from: http://content.onlinejace.org/cgggi/content/short/45/12/1925. Accessed 2011, February 22.
10. Nishio K, Sakorai M, Kusuyama T, et al. a randomized comparison of pioglitazone to inhibit restenosis after coronary stenting in patients with type-2 diabetes. Diabetes care [serial online] 2006 January: 29(1): 101-106. Available from: http://care.diabetesjournals.org/content/29/1/101.full. Accessed 2011, February 22.
11. Raskin P, Rendell M, Riddle MC, et al. a randomized trail of rosiglitazone therapy in patients with inadequately controlled insulin treated type-2 diabetes. Diabetes care [serial online] 2001 July: 24(7): 1226-1232. Available from: http://care.diabetesjournals.org/content/24/7/1226.full. Accessed 2011, February 22.
12. Lebovitz HE, Dole JF, Patwardhan R, et al. rosiglitazone monotherapy is effective in

patients with type-2 diabetes. The journal of clinical endocrinology & metabolism [serial online] 2001: 86(1): 280-288. Available from: http://jcem.endojournals.org/cgi/content/full/jcem;86/1/280. Accessed 2011, February 22.

13. Phillips LS, Gronberger G, Miller E, et al. once and twice-daily dosing with rosiglitazone improves glycemic control in patients with type-2 diabetes. Diabetes care [serial online] 2001 February:24(2): 308-315. Available from: http://care.diabetesjournals.org/content/24/2/308.full. Accessed 2011, February 22.
14. Fonseca V, Rosenstock J, Patwardhan R, et al. effect of metformin and rosiglitazone combination therapy in patients with type-2 diabetes mellitus. JAMA [serial online] 2000 April: 283(13): 1695. Available from: http://jama.ama-assn.org/content/283/13/1695.long. Accesssed 2011, February 22.
15. Albert KG, Eckel RH, Grundy SM, et al. harmonizing the metabolic syndrome. Circulation [serial online] 2009: 120: 1640-1645. Available from: http://circ.ahajournals.org/cgi/content/full/120/16/1640. Accessed 2011, March 19.
16. Grundy SM, Clecman JI, Daniels SR, et al. diagnosis and management of the metabolic syndrome: An American heart association/National heart, lung and blood institute scientific statement. Circulation [serial online] 2005: 112: 2735-2752. Available from: http;//circ.ahajournals.org/cgi/reprint/CIRCULATION AHA .105. 169404v1. Accessed 2011, March 19.
17. Tripathi KP. Essentials of medical pharmacology. 6th ed. New Delhi: Jaypee brothers' medical publishers (p) Ltd; 2008. P. 254-274.
18. Buse JB, polonsky KS, Burant CR. Type 2 diabetes mellitus. In: Kronenberg HM, Melmed S, Polonsky KS, et al editors. Williams's textbook of endocrinology [online] 11th ed.Philadelphia: Saunders Elsevier; 2008. Available from: http://www.mdconsult.com/books/page.do. Accessed 2011, March 20.
19. Chiquette E, Ramirez G, Deofronzo R, et al. A meta-analysis-comparing the effect of thiazolidinediones on cardiovascular risk factor. Archives of Internal Medicine [serial online] 2004 October: 164 (19): 2097-2104. Available from: http://archinte.ama-assn.org/cgi/content/full/164/19/2097. Accessed 2011, February 15.
20. Wilcox R, Kupfer S, Erdmann E, et al. Effects of pioglitazone on major adverse cardiovascular events in high-risk patients with type-2 diabetes: Results from prospective pioglitazone clinical trial in macrovascular event (PROactive 10). American Heart Journal [seria online] 2008 April: 155(4). Available from: http://www.mdconsult.com/das/article/body/237779776-9/jorg. Accessed 2011, March 22.
21. Home PD, Pocock SJ, Nielsen HB, et al. Rosiglitazone evaluated for cardiovascular outcomes-An interim analysis. NEJM [serial online] 2007: 317: 28-38. Available from: http://www.nejm.org/doi/full/10.1056/NEJM00073394/t=abstract. Accessed 2011, March 22.
22. Loke YK. Comparative cardiovascular effects of thiazolidinediones: Systematic review and mata-analysis of observational studies. BMJ [serial online] 2011: 342: d1309. Available from: http://www.bmj.com/content/342/bmj.d1309.full. Accessed 2011, March 21.