

INTRODUCTION

The management of T2DM has undergone a paradigm shift after newer insights in its pathogenesis from the classical triumvirate to ominous octet to dirty dozen. Cardio-vascular diseases remain the leading cause of morbidity and mortality in T2DM. It is now prudent to use anti-diabetic drugs with pleotropic effects and additional cardio-vascular risk reduction.

Pioglitazone, a thiazolidinedione, activates the nuclear transcription factor peroxisome proliferator-activated receptor gamma (PPAR-gamma agonist), thus increasing insulin sensitivity. It is cheap with a proven efficacy track record, addressing the core pathology of insulin resistance in both the adipose tissues & skeletal muscles. This is very relevant, especially in the Indian population, as more than 80% of patients with pre-diabetes and T2DM have insulin resistance. Hence, insulin-sensitizing interventions should take priority over interventions that increase insulin secretion because of the potential benefit of cardiovascular risk reduction.¹

Since its approval in India in 2002, it has undergone a roller-coaster ride with being on the verge of extinction [banned on June 18, 2013, by Indian Ministry of Health and Welfare, based on eight case reports of bladder cancer amongst pioglitazone users]² to resurrection (Ban revoked on 31st July 2013, based on recommendation by the Drug Technical Advisory Board).

AFTER METFORMIN IS PIOGLITAZONE THE BEST ADD-ON DRUG IN THE INDIAN CONTEXT ?**Efficacy**

It's efficacy is comparable to the other oral anti-diabetic drugs. As monotherapy both metformin and pioglitazone have comparable glycemic effects, however pioglitazone increased insulin sensitivity more than metformin from week 4 through week 52, as assessed by QUICKI.³ As an insulin sensitizer, pioglitazone is superior to metformin.

In comparison to gliclazide, though HbA_{1c} reduction was similar (0.79%), there was a greater reduction in fasting blood glucose (- 1.0 mmol/l vs - 0.7 mmol/l) with greater reductions in insulin levels and insulin resistance, and continuous decrease in fasting blood glucose over one year, which was not seen with gliclazide.⁴ Gliclazide is considered to be the safest and most preferred of the sulfonylureas, and pioglitazone has stood its ground in comparison.

As an add-on to patients uncontrolled with metformin

and sulfonylurea, pioglitazone (30 mg.) compared to sitagliptin (100 mg.), achieved comparable improvements in overall glycemic control, with greater reductions in fasting plasma glucose (35.7 vs 22.7 mg/dL), and a significant decrease in hs-CRP, albeit at a higher weight gain.⁵ Sitagliptin is cardio-vascular and weight neutral, whereas pioglitazone reduces cardio-vascular risk with comparable efficacy. The weight gain caused by pioglitazone can be taken care of by enforcing life-style modification, which remains an essential part of diabetes management.

In Indian patients, pioglitazone (15 mg) was found to significantly reduce HbA_{1c} from mean 8.34 to 7.78%, FPG from mean 172.6 to 143.8 mg% and PPG from mean 222.9 to 204 mg% at the end of two years, and was safe & well-tolerated.⁶ This observational study reflects the experience of most of the clinicians in our country.

Durability

Pioglitazone was found to be superior in achieving maximum reduction in HbA_{1c} & FPG in the shortest time, with greater durability at end of four years in Japanese patients with T2DM, as compared to other oral glucose-lowering drugs.⁷

In another retrospective cohort study in 20,070 patients, who were newly treated with a SU / DPP-4i / TZD, the risk of failure with dual therapy at one year was 15% with SU, 23% with DPP-4i, & 8% with TZD. Corresponding failure rates at 2 years were 26%, 38% & 12% respectively. Adding a TZD to metformin was associated with a reduced hazard (aHR 0.45; 95% CI :0.41-0.50) and resulted in the most durable glycemic response.⁸ Pioglitazone proved to be superior to both sulfonylureas and DPP-4 inhibitors, as far as durability of glycemic response is concerned. It also proved to be superior to Sitagliptin in both durability and reducing HbA_{1c} levels in drug-naïve patients.⁹

It also provides effective lowering of HbA_{1c} by 0.5 – 1.5% and durable glycemic control in combination with other oral anti-diabetic drugs and insulin.¹⁰

In addition, it also resulted in 70% reduction in risk of developing T2DM in the ACT NOW study for prevention of diabetes.¹¹

Addressing the Core Defect of Insulin resistance

Insulin resistance, which is seen in >80% of Indian patients ("The Thin Fat Indian"), manifests as endogenous glucose overproduction and reduced insulin mediated glucose uptake in both the adipose tissue and skeletal muscles. It

is a very strong independent predictor of cardiovascular events including myocardial infarction and stroke.¹² Both metformin & pioglitazone increase insulin suppression of endogenous glucose production and fasting plasma glucose clearance, but only pioglitazone also improves insulin-mediated glucose uptake at all levels.¹³

Pleiotropic Effects

Pioglitazone increases HDL-c, decreases LDL-particle size and non-HDL cholesterol, decreases fasting triglycerides & plasma free fatty acids, without having any effect on the total cholesterol and LDL-c, leading to favourable CV outcomes.¹⁴

Unlike metformin, it reduces inflammatory cytokines like MMP-9, CRP, PAI-1, TNF-alpha, etc. and increases the vascular-protective adipokine - adiponectin levels as shown in the PICOOMB Study.¹⁵

Pioglitazone provides consistent reductions in both systolic and diastolic blood pressure in the range of 3-5 mm at end of one year therapy.¹⁶

These effects translate into improved endothelial function, reduced carotid intima-media thickness, and improvements in stenosis after stent angioplasty as seen in various clinical trials. It also improves the circulating levels and functional activity of angiogenic endothelial progenitor cells, an independent predictor of CV events and death.¹⁷ Moreover, significant positive effects were seen in various organs and CV risk markers.

Clinical Trial Data

The PROactive trial, a prospective, randomized, double-blind, secondary prevention study in 5,238 patients (50% with previous MI, 25% with previous stroke & 25% with previous peripheral arterial disease), showed that pioglitazone (45 mg) in addition to optimized care, significantly reduced CV death plus non-fatal MI & non-fatal stroke (HR 0.82 [95% CI 0.70-0.97]) in 3 years follow-up period. It reduced subsequent MI by 28%, acute coronary syndrome by 38% and second stroke by 48%.¹⁸

In the CHICAGO trial, pioglitazone decreased the progression of carotid intima-media thickness (surrogate marker for future CV events) in 462 patients, over 18 months compared with glimepiride.¹⁹

In the PERISCOPE (Pioglitazone effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) study, coronary intravascular ultrasonography in 360 patients with T2DM & CAD, showed a lower rate of progression of atherosclerosis in patients treated with pioglitazone as compared to glimepiride.²⁰

In the DIABAMON project, a meta-analysis investigating the safety of glucose-lowering agents, showed that pioglitazone reduced the risk of CV events by 9% and MI by 10%, with no relation to heart failure.²¹

In the QUARTET studies, consistent lowering of albumin-creatinine ratio (predictor of CKD and future CV events)

was observed with pioglitazone, unlike with metformin or sulfonylurea.²²

In a retrospective analysis of 5,290 diabetic patients on dialysis, there was a reduction of risk for all-cause mortality by 35% in patients on pioglitazone, which increased to 47% in patients who received pioglitazone without insulin.²³

In a meta-analysis of 19 RCTs with pioglitazone, enrolling 16,390 patients with a study-drug treatment duration ranging from 4 months to 3.5 years, death, MI, or stroke occurred in 4.4% receiving pioglitazone and in 5.7% receiving control therapy (HR 0.82 [95% CI 0.72-0.94]; P = 0.005).²⁴

In a recent trial (IRIS – Insulin Resistance Intervention after Stroke) in 3,876 patients with ischemic stroke or TIA, with no history of diabetes but presence of insulin resistance (HOMA-IR score >3.0), were treated with pioglitazone (45 mg./day) with a follow-up for 4.8 years. It decreased the risk of diabetes by 52% (HR 0.48, 95% CI 0.33-0.69, P>0.0001), while also reducing the risk of subsequent ischemic events, without any evidence of cancer risk.²⁵

In an open cohort study in 469,688 patients with T2DM aged 25-84 years, between 1st April 2007 and 31st January 2015, for the risk of heart failure, cardiovascular disease and all cause mortality, compared to metformin monotherapy, the adjusted hazard ratio for pioglitazone was 0.74 (0.38 to 1.42) for heart failure, 1.03 (0.69-1.54) for cardiovascular disease and 1.38 (1.04-1.83) for all cause mortality, which was much more favourable as compared to sulfonylureas, insulin and gliptins. This study proves the safety and superiority of pioglitazone over other anti-diabetic drugs.²⁶

Safety Concerns

Risk of adverse events are weight gain, oedema, congestive heart failure, bone fractures, macular oedema and a possible link with bladder cancer.

Even though a weight gain of about 3-5 kg. has been seen in many studies, paradoxically, it was associated with an improved survival in a post hoc analysis of the PROactive population (HR per 1% weight gain : 0.96[0.92-1.00] P=0.037).²⁷

Oedema, which has been seen in about 5% patients with monotherapy or in combination with other oral drugs, and in about 10% patients when combined with insulin, possibly due to decreased urine sodium excretion, increased plasma renin & aldosterone levels, increased vasodilation & vascular permeability, rarely leads to withdrawal of pioglitazone. Despite these adverse effects, the incidence of heart failure and mortality rates is less with pioglitazone. However, it should not be used in patients with heart failure (> NYHA 1), despite some benefits suggested by various outcome trials.²⁸

Most studies have shown an increased risk of bone fractures with the glitazones especially in post-menopausal women, but the major evidence is from the use of rosiglitazone. A randomized control trial conducted

218 in 86 people with T2DM or IGT with pioglitazone 30 mg./day for one year, did not show any significant changes in either bone mineral density or bone turnover.²⁹ However, it is prudent to avoid pioglitazone in post-menopausal women and in those with low bone density.

Glitazones use have shown increased risk of Diabetic macular oedema, especially when combined with insulin, however the risk can be mitigated by the concurrent use of ACE inhibitors & aspirin.³⁰ Regular eye check-up should be the norm in patients on pioglitazone.

Diabetes, per se, has been associated with increased risk of various cancers of the liver, pancreas, ovary, colorectum, lung, bladder and breast (HR 1.25[95% CI 1.19-1.31].³¹ Interestingly, a recent study in > 60,000 patients with T2DM, showed that use of pioglitazone was associated with a significantly decreased risk of liver cancer (OR 0.83 [95% CI 0.72-0.95]), and colorectal cancer (adjusted OR 0.86 [95% CI 0.79-0.94].³²

However, there have been number of conflicting studies regarding the link with bladder cancer, possibly because of flaws and inherent bias in most of the studies, which has been the major bone of contention. In a very recent large, pooled multipopulation analysis, data collated on 1.01 million persons over 5.9 million person-years showed 3248 cases of bladder cancer, with 117 exposed cases and a median follow-up of 4.0 to 7.4 years. After adjustment for age, calendar year, diabetes duration, smoking, no evidence for any association was found between cumulative exposure to pioglitazone and bladder cancer in men (RR 1.01; 95% CI 0.97-1.06) or in women (RR 1.04; 95% CI 0.97-1.11).³³

In another study, conflicting data has been presented, with increased risk of bladder cancer with pioglitazone, in a population based cohort study (HR 1.63; 95% CI 1.22-2.19).³⁴

In view of such conflicting data, one can assume that there may be a weak link with bladder cancer, and one has to remain vigilant about this adverse event.

Comments

Pioglitazone is a cheap and effective drug, and from the point of benefit-risk ratio, it has a confirmed cardiovascular risk protection with a dubious link to bladder cancer, with odds heavily favoring its use. Moreover, in a developing country like ours with more than 70 million diabetics, cost and affordability plays a significant role in long-term compliance.

It has not only proved its efficacy as compared to other oral drugs, but has also shown greater durability of glycemic response. Moreover, its pleotropic effects, of being lipid friendly and in reducing the inflammatory cytokines, gives it a distinct edge over other oral anti-diabetic drugs, No wonder, it is still retained as a second-line option in all the guidelines (ADA/ EASD/ AACE/ IDF).

More so, in our scenario, where insulin resistance is the predominating culprit, pioglitazone would be the ideal drug along with metformin in the early stages of T2DM,

giving us a therapeutic window of 5-7 years, to achieve early glycemic control and obtain the benefits of “Legacy Effect”. It is believed that in comparison to the western population, we are unable to compensate for insulin resistance with insulin secretion to the same extent.

More important is to know, when not to use this drug – in post-menopausal women & those with low bone density, in heart failure (> NYHA 1), in elderly patients > 75 years at risk of heart failure, and in patients with active bladder cancer or history of bladder cancer.

Like the intelligent use of any drug, it is prudent to be pharmaco-vigilant and judiciously select the patients. Ofcourse, patient education about the benefit-risk ratio is of paramount importance. If, one wants a rose, then one should learn to accept the thorns along with it !

REFERENCES

1. Haffner SM, Mykkanen L, Festa A, Burke JP, Stern MP, “Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive pre-diabetic subjects : implications for preventing coronary heart disease during the pre-diabetic state”. *Circulation* 2000; 101:975-980.
2. Unnikrishnan R, Sundramoorthy C, Deshpande N, Sarvothaman R, Sahay RK, Mehtalia S et al, “Eight cases of bladder cancer in pioglitazone users from India”. *J Assoc Physicians India* 2012; 60-66.
3. Roden M, Laakso M, Johns D, Widell M, Urguhart R, Richardson C, et al, “Long-term effects of pioglitazone and metformin on insulin sensitivity in patients with Type 2 diabetes mellitus”. *Diabet Med* 2005; 22:1101-6.
4. Perriello G, Pampanelli S, Di Pietro C, Brunetti P, “Comparison of glycemic control over 1 year with pioglitazone or gliclazide in patients with Type 2 diabetes”. *Diabet Med* 2006; 246-52.
5. Liu SC, Chien KL, Wang CH, Chen WC, Leung CH, “Efficacy and safety of adding pioglitazone or sitagliptin to patients with type 2 diabetes insufficiently controlled with metformin and a sulfonylurea”. *Endocr Pract* 2013; 19:980-8.
6. Balaji V, “Efficacy and safety of pioglitazone in type 2 diabetes in the Indian patients: Results of an observational study”. *Indian J of Endocr and Metab* 2013; 17:709-15.
7. Stringer F, DeJongh J, Enya K, Koumura E, Danhof M, Kaku K, “Evaluation of the long-term durability and glycemic control of fasting plasma glucose and glycosylated hemoglobin in Japanese patients with type 2 diabetes mellitus”. *Diabetes Technol Ther* 2015; 17:215-23.
8. Jil Mamza et al, “Important differences in the durability of glycemic response among second-line treatment options when added to metformin in type 2 diabetes : a retrospective cohort study”. *Annals of Medicine*, 10.3109/07853890.2016.1157263, pages 224-234, Published online : 16 Mar 2016.
9. Russel-Jones D, Cuddihy RM, Hanefeld M et al, DURATION-4 Study Group, “Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naïve patients with type 2 diabetes (DURATION-4): a 26 week double blind study”. *Diabetes Care* 2012; 35:252-258.
10. Derosa G, “Efficacy and tolerability of pioglitazone in patients with type 2 diabetes mellitus : comparison with

- other oral antihyperglycemic agents". *Drugs* 2010; 70:1945-1961.
11. DeFronzo RA, Tripathy D, Schwenke DC et al, "ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose intolerance". *N Engl J Med* 2011; 364:1104-1115.
 12. Bonora E, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L, et al, "HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects : prospective data from the Verona Diabetes Complications Study". *Diabetes Care* 2002; 25:1135-41.
 13. Natali A, Ferannini E, "Effects of metformin and thiazolidinediones on suppression of hepatic glucose production and stimulation of glucose uptake in type 2 diabetes : a systematic review". *Diabetologia* 2006; 49:434-41.
 14. Van Wijik JP, de Koning EJ, Martens EP, Rabelink TJ. "Thiazolidinediones and blood lipids in type 2 diabetes". *Arterioscler Thromb Vasc Biol* 2003; 23:1744-1749.
 15. Hanefeld M, Pfutzner A, Forst T, Kleine I, Fuchs W. "Double-blind, randomized, multicentre, and active comparator controlled investigation of the effect of pioglitazone, metformin, and the combination of both on cardiovascular risk in patients with type 2 diabetes receiving stable basal insulin therapy : the PIOCMB study. *Cardiovasc Diabetol* 2011; 10:65.
 16. Derosa G, Fogari E, Cicero AF, et al. "Blood pressure control and inflammatory markers in type 2 diabetes patients treated with pioglitazone or rosiglitazone and metformin". *Hypertens Res* 2007; 30:387-394.
 17. Schernthaner G. "Pleiotropic effects of thiazolidinediones on traditional and non-traditional atherosclerotic risk factors". *Int J Clin Pract* 2009; 63:912-929.
 18. Dormandy JA, Charbonnel B, Eckland DJ, et al. "Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial". *Lancet* 2005; 366:1279-1289.
 19. Mazzone T, Meyer PM, Feinstein SB, et al. "Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial." *JAMA* 2006; 296:2572-2581.
 20. Nissen SE, Nicholls SJ, Wolski K, et al PERISCOPE Investigators. "Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes : the PERISCOPE randomized controlled trial." *JAMA* 2008; 299:1561-1573.
 21. Peter Boyle, Boniol M, Koechlin A, et al. "Safety of glucose lowering medication: The diabetes adverse event monitor (DIABAMON) project: II cardio-vascular disease." *Diabetes* 2013; 1405-P:A367.
 22. Schernthaner G, Mathews DR, Charbonnel B, Hanefeld M, Brunetti P, Quartet [corrected] Studu Group. "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.
 23. Brunelli SM, Thadhani R, Ikizler TA, Feldman HI. "Thiazolidinedione use is associated with better survival in haemodialysis patients with non-insulin dependent diabetes." *Kidney Int* 2009; 75:961-968.
 24. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. "Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus : a meta-analysis of randomized trials." *JAMA* 2007; 298:1180-1188.
 25. Silvio E, Inzucchi, Catherine M Viscoli, Lawrence H, Young Karen L Furie, Mark Gorman, Anne M Lovejoy, et al. "Pioglitazone Prevents Diabetes in Insulin-Resistant Patients with Cerebrovascular Disease". *Diabetes Care* 2016 Jul 27, DOI: 10.2337/dc16-0798.
 26. Julia Hippisley-Cox, Carol Coupland. "Diabetes treatments and risk of heart failure, cardiovascular disease, and all cause mortality : cohort study in primary care". *BMJ* 2016; 354:i3477.
 27. Doehner W, Erdmann E, Cairns R, et al. "Inverse relation of body weight and weight change with mortality and morbidity in patients with type 2 diabetes and cardiovascular co-morbidity : an analysis of the PROactive study population". *Int J Cardiol* 2012; 162:20-26.
 28. Standl E, Schnell O, McGuire DK. "Heart Failure Considerations of Antihyperglycemic Medications for Type 2 Diabetes". *Circulation Research* 2016; 118:1830-43.
 29. Andrew Grey, Mark Bolland, Sheryl Fenwick, Anne Horne, Grey gamble, Paul L Drury, et al. "The skeletal effects of pioglitazone in type 2 diabetes or impaired glucose tolerance : a randomized controlled trial". *European Journal of Endocrinology* 2014; 170:255-62.
 30. Idris I, Warren G, Donnelly R. "Association between thiazolidinedione treatment and risk of macular oedema among patients with type 2 diabetes". *Arch Intern Med* 2012; 172:1005-11.
 31. Emerging Risk Factors Collaboration, Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, et al. "Diabetes mellitus, fasting glucose, and risk of cause-specific death". *N Eng J Med* 2011; 364:829-41.
 32. Chang CH, Lin JW, Wu LC, Lai MS, Chuang LM, Chan KA. "Association of thiazolidinediones with liver cancer and colorectal cancer in type 2 diabetes mellitus". *Hepatology* 2012; 55:1462-1472.
 33. Levin D, Bell S, Sund R, Hartikainen SA, Toumilehto J, Pukkala E, et al. "Pioglitazone and bladder cancer risk : a multipopulation pooled, cumulative exposure analysis". *Diabetologia* 2015; 58:493-504.
 34. Marco Tuccori, Kristian B Filion, Hui Yin, Oriana H Yu, Robert W Platt, Laurent Azoulay. "Pioglitazone use and risk of bladder cancer : population based cohort study". *BMJ* 2016; 352:i1541.