Role of Pioglitazone on glycemic control and its effect on lipid profile in type 2 diabetics

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ABSTRACT

The effect of *pioglitazone* on glycemic control in type 2 diabetics was analysed in the present study. The study groups consisted of 220 type 2 diabetic patients (110 males, 110 females) and 220 age and sex matched type 2 diabetic subjects treated with *pioglitazone* (110 males, 110 females). The levels of blood glucose, urea, creatinine, HbA_1c were found to be significantly decreased by pioglitazone treatment. Lipid status was also found to be normalised by *pioglitazone therapy* in type 2 diabetics. Hence pioglitazone can be used more often in patients with type 2 diabetes, because they offer excellent glycemic control as well as decrease in insulin resistance and reductions in cardiac risk factors associated with the insulin resistance.

Key words: Type 2 diabetes mellitus; pioglitazone*;* glycemic control.

INTRODUCTION

Type 2 diabetes mellitus is a heterogeneous group of disorders usually characterized by variable degrees of insulin resistance, impaired insulin secretion and increased glucose production.

Insulin resistance typically becomes worse with the progression of diabetes because of dysregulation of lipid and carbohydrate metabolism. Impaired β-Cell function in these patients as evidenced by altered pulsatility of insulin release, loss of first phase insulin release and reduced insulin release in response to a glucose load plays an important role in the expression of the disease. Finally increased hepatic glucose output correlates well with the fasting plasma glucose levels and is the primary cause of fasting hyperglycemia in type 2 diabetes (Defronzo et al., 1992).

The medication class of thiazolidinedione (TZD) was introduced in the late 1990s as an adjunctive therapy for diabetes mellitus (type 2) and related diseases. TZDs are a new class of drugs that act primarily by improving insulin sensitivity in different target tissues such as liver, skeletal muscle and adipose tissue. They are potent synthetic ligands for PPAR-γ activation. They have been shown to improve glycemic control in patients with type 2 diabetes and appear to have favourable direct effect on other components of the insulin resistance syndrome.

EXPERIMENTAL

The study subjects were recruited from in and around Thanjavur. All the study subjects gave written informed consent prior to study enrolment. The study population consisted of four groups belonging to the age group of 40-70 years.

Group I

This consists of two hundred and twenty freshly diagnosed type 2 diabetic patients who were not under mediation for the disease previously.

Group II

This consists of 220 known type 2 diabetic subjects receiving *pioglitazone* along with sulphonylureas for 6 months.

Serum, plasma and whole blood were utilized for glycemic and lipid studies. Blood Sugar was assayed using 0 - Toluidine method (Fongs et al., 1970). Blood urea was estimated using Diacetyl monoxime method (Harold Varley, 1988). Serum creatinine was assayed using Folin Wu tungstic acid method (Harold Varley, 1988). Glycosylated haemoglobin (HbA$_{1C}$) was determined by colorimetry (Parker *et al.*, 1981).

The serum cholesterol levels were estimated by Zlakitis - Zak Boyle method (Zak and Amer, 1951). Triglyceride (TG) was estimated by the method of Rice (Ramnik Sood, 2009). The high-density lipoprotein (HDL) cholesterol was estimated by Hybenga and Pileggi method (Burstein *et al.*, 1970). Free fatty acid (FFA) was estimated by colorimetric method (Falhoff *et al.*, 1973).

RESULTS AND DISCUSSION

The study deals with the effect of *pioglitazone* on glycemic control in type 2 diabetic patients. The results of the present study suggest that *pioglitazone* therapy in type 2 diabetic patients decreases fasting and postprandial plasma glucose levels by improving hepatic and peripheral muscle tissue sensitivity to insulin. The mechanism of the antidiabetic action of *pioglitazone* involves activation of insulin receptors and /or high affinity PPAR- γ.

Pioglitazone treatment improved fasting and postprandial glycemia principally via inhibition of gluconeogenesis (Gastadelli et al., 2007). *Pioglitazone* has been shown to decrease glucomeogenesis (Nishimura et al., 1997) and to inhibit expression of key genes involved in gluconeogenesis (Way *et al.*, 2001).

Pioglitazone treatment produces significant decrease in urea and creatinine levels in type 2 diabetic patients as shown in group II (Table 1). *Pioglitazone* serves as a potential therapeutic agent for diabetic nephropathy that may prevent glomerular dysfunction independent of their insulin sensitizing action through the inhibition of the DAG-PKC-ERK pathway.

In patients with type 2 diabetes, the level of HbA$_{1C}$ was significantly decreased by *pioglitazone* therapy. In a 26 meek clinical trial by (Aronoff *et al* , 2000) comparing *pioglitazone* monotherapy in a dose range of 15-45 mg day with placebo in patients with type 2 diabetes , *pioglitazone* treatment resulted in significant improvements in glycosylated hemoglobin and fasting plasma glucose and

Table 1: Glycemic characteristics of study subjects

Groups	Treatment	Fasting blood sugar (mg/dl)	Postprandial blood sugar (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)	HbA1c (%)
I	Type 2 diabetic subjects	203.80± 40.134[b]	323.18± 87.95 [b]	68.47± 15.70 [b]	3.24± 1.439 [b]	9.26± 1.742 [b]
II	Pioglitazone treated type 2 diabetic subjects	97.277± 10.92 [d]	138.31± 19.90 [d]	23.99± 6.36 [d]	1.062± 0.250 [d]	5.11± 0.803 [d]

Values were expressed in mean ± SD (n=220). Values not sharing a common superscript significantly differ at   P < 0.01 (paired sample 't' test)

appeared to confer additional benefit with respect to lipid parameters and fasting insulin.

Pioglitazone significantly decreases cholesterol, low-density lipoprotein (LDL) cholesterol, TG and FFA levels and increases HDL cholesterol as given in Table 2. *Pioglitazone* directly affect adipose tissue by enhancing differentiation of preadipocytes into mature adipocytes and the regulation of gene expression in adipose tissue leading to the coordinated regulation of lipid metabolism. Investigations into the mechanisms of plasma TG lowering showed that abolition of hypertriglyceridemia by *pioglitazone* involves removal of TG from very low-density lipoprotein (VLDL) particles and decreased hepatic TG production.

Table 2: Lipid characteristics of study subjects

Groups	Treatment	Total cholesterol (mg/dl)	Triglyceride (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	FFA (mg/dl)
I	Type 2 diabetic subjects	249.92± 20.41[b]	271.83± 46.73 [b]	20.932± 8.85 [b]	160.02± 18.52 [b]	1060.86± 175.375 [b]
II	Pioglitazone treated type 2diabetic subjects	164.88± 12.141[d]	94.06± 9.59 [d]	63.07± 12.29 [d]	80.30± 11.063[d]	519.49± 72.209 [d]

Values were expressed in mean ± SD (n = 220) . Values not sharing a common superscript significantly differ at P < 0.01 (paired sample 't' test)

The anti - diabetic efficacy of *piogitazone* correlates well with their rank order of binding affinity to PPAR-γ. Hence it is inferred that most of the anti - diabetic effects of *pioglitazone* result from PPAR-γ mediated regulation of adipocyte gene expression and the subsequent improvement in adipose physiology.

CONCLUSION

Hence *pioglitazone* can be considered as a very attractive candidate for first line glycemic management and prevention of primary and secondary adverse outcomes in patients with metabolic syndrome, cardio diabetes and type 2 diabetes mellitus.

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