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A retrospective multi-centric study evaluating the effectiveness and safety of pioglitazone combination therapy in Indian type 2 diabetic patients

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ABSTRACT

To evaluate the effectiveness and safety of pioglitazone combination therapy in patients with type 2 diabetes. A retrospective multi-centric study was conducted in adult type 2 diabetic patients on pioglitazone combination therapy across seven centres. Percentage of patients achieving glycemic control (HbA1C level < 7%) with pioglitazone combination therapy was the primary efficacy endpoint. Safety was evaluated by recording adverse events. 602 patients (58.0 % male; 42 % female) with mean age of 56.0 (±10.65) were enrolled in the study. Family history of diabetes was present in 41.5 %patients. Pioglitazone was commonly prescribed in combination with metformin and glimepiride (24.8%).The mean duration of pioglitazone combination therapy was 3.36 (±2.29) years. Comorbid conditions such as hypertension and dyslipidemia were present in 48.7% and 48.5% patients respectively in this study. Proportion of patients with HbA1c ≥7% decreased from 85.2% to 53.5% after pioglitazone therapy. 1.6% reduction in mean HbA1c was observed after pioglitazone therapy (8.8% to 7.2%). Reduction in mean fasting plasma glucose and postprandial plasma glucose was 45.2 mg/dl (169.5 mg/dl to 124.3 mg/dl) and 61.5 mg/dl (246.8 mg/dl to 185.3 mg/dl) respectively, after pioglitazone therapy.. There was no safety events observed with the use of pioglitazone based therapies. Pioglitazone combination therapy is found to be effective and safe in adult type 2 diabetes Indian patients.

Keywords: Pioglitazone, retrospective study, Indian patients

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a global health problem with significant contribution from India. Currently, 66.8 million people with diabetes live in India.[1] South Asians have higher proportion of insulin resistance compared to Caucasians even at earlier age group.[2] Progressive deterioration of pancreatic β cells lead to hyperglycaemia and subsequent complications.[3]These pathophysiological characteristics suggest a need of anti-diabetic agent which can reduce insulin resistance and arrest the decline of beta cell functions for the effective management of type 2 diabetes mellitus. Type 2 diabetes mellitus treatment is usually initiated with metformin monotherapy. Failure or reduced response to monotherapy over the period of time requires addition of drugs with different mechanism of action.

Pioglitazone, an oral hypoglycaemic drug increases insulin sensitivity, reduces hepatic gluconeogenesis and increases peripheral glucose uptake.[4,5] It also has a positive effect on beta cell functions in patients with diabetes. It reduces demands of insulin secretion and preserve pancreatic beta-cell function.[6] The overall mechanism of action of pioglitazone suggests both central (on pancreas) and peripheral actions in effective controlling blood glucose levels. Considering these benefits, pioglitazone play a vital role in the management of type 2 diabetes mellitus in combination therapy with other antidiabetic agents.

In clinical practice, patients diagnosed with high glycosylated haemoglobin (HbA1c) are started with pioglitazone therapy in a combination regimen. However, there is limited data from real world setting on use of pioglitazone combination therapy especially for the long term duration in Indian patients. Hence the objective of our study was to evaluate the long term effectiveness and safety of pioglitazone combination therapy in type 2 diabetes patients.

MATERIALS AND METHOD

Study settings:

In this retrospective multicentric study, data was collected from physicians prescribing pioglitazone combination therapy for diabetes management for minimum of one year. Adult (≥ 18 years of age) type 2 diabetic patients on pioglitazone combination therapy were included in the study. Patients with type 1 diabetes mellitus, gestational diabetes, diabetes insipidus, or renal glycosuria, those with a history of bone fracture or osteoporosis, congestive heart failure, hepatic impairment, diabetic ketoacidosis, or any other condition prior to start of pioglitazone combination therapy were excluded from the study. The total duration of study was approximately 12 months. The study was initiated in April 2015.

Available data from patient records was collected retrospectively to determine the effectiveness and safety of pioglitazone combination therapy. The following data were collected from the patients records: demographic data (age, gender, weight, height, body

mass index [BMI], diabetes history (years), family history, history of previous anti-diabetic treatments prior to the start of pioglitazone combination therapy, history of glucose levels (fasting plasma glucose [FPG], postprandial glucose [PPG] and HbA1c values prior and post pioglitazone combination therapy. Percentage of patients achieving glycemic control (HbA1C level < 7%) in last one year of starting pioglitazone combination therapy was the primary efficacy endpoint. The safety was determined by recording any significant safety issues.

Statistical analysis:

No formal sample size calculation was done as this a retrospective study. All statistical analyses including summary tables, listings and figures were generated using Statistical Analysis System. The continuous variables were summarized descriptively in terms of number of observations (n), mean and standard deviation. The categorical data was presented in terms of frequencies and percentages.

Ethics approvals:

The study protocol was approved by ethics committee before initiation of study. The study was conducted in accordance with local regulatory requirements, the principles of the Declaration of Helsinki, International Conference on Harmonization - Good Clinical Practice (ICH-GCP) and Indian GCP guidelines as applicable.

RESULTS AND DISCUSSION

Study Participant Profiles:

The study included available data of 602 type 2 diabetes adult patients from seven centres. A total of 58% patients were male while 42% were female. Other demographic characteristics of the study participants are shown in table 1.

Table 1: Demographic Characteristics (N=602)

Parameter	Mean (±SD)
Age (years)	56 (10.65)
Weight (kg)	68 (12.2)
Height (cm)	160.2 (9.01)
Non-obese(BMI<30 kg/m^2)	25 (2.78)
Obese(BMI≥30 kg/m^2)	33.2 (3.61)

Out of 602 patients, 112 (18.6%) patients were obese while 490 (81.4%) patients were non-obese. Family history of diabetes was noted in 250 (41.5 %) patients in our study. Out of this, 110 (44 %) patients had a history of father being diabetic and 118 (47.2%) patients had history of mother being diabetic.

Out of all patients, 48.7% (n = 293) and 48.5 %(n =292) had hypertension and dyslipidemia, respectively. The other comorbid conditions noted were coronary heart disease (4.3%), chronic kidney disease (1.3%), chronic obstructive pulmonary disease (1.0 %), stroke (0.5

%), and tuberculosis (0.2 %). Overall, 163 (27.1 %) patients reported two chronic comorbid conditions whereas 27 (4.5 %) patients reported three. Out of patients with two chronic co-morbid conditions, 143 (87.7 %) had dyslipidemia and hypertension.

The percentage of patients with co-morbidities is shown in table 2.

Table 2: Co-morbidities in study participants

Condition n (%)	Subjects (n=602)
Dyslipidemia	292 (48.5%)
Hypertension	293 (48.7%)
Coronary heart disease	26 (4.3%)
Chronic kidney disease	8 (1.3%)
Chronic Obstructive Pulmonary Disease (COPD)	6 (1.0%)
Stroke	3 (0.5%)
Tuberculosis	1 (0.2%)

Overall, 38.7% patients were on pioglitazone combination therapy for 1 to 2 years while 14.2%, 38.4% and 14.5% patients in the study used pioglitazone combination therapy for 2 to 3, 3 to 4 and 4 to 5 years, respectively.

Glimepiride plus metformin plus pioglitazone [149 (24.8%)] was the most commonly used combination followed by metformin plus pioglitazone [89 (14.8%)], metformin, glibenclamide plus pioglitazone [66 (11.0%)] and gliclazide, metformin plus pioglitazone [42 (7.0%)]. The other combinations used in the study patients are shown in table 3.

Table 3: Common combinations used in study patients

Combination used	N=602 (%)
Glimepiride + Metformin + Pioglitazone	149 (24.8%)
Metformin + Pioglitazone	89 (14.8%)
Metformin + Glibenclamide + Pioglitazone	66 (11.0%)
Gliclazide+ Metformin + Pioglitazone	42 (7.0%)
Metformin + Pioglitazone + Glimepiride + Voglibose	27 (4.5%)
Metformin+Pioglitazone+Voglibose	15 (2.5%)
Metformin+Pioglitazone+Glibenclamide+Glimepiride	14 (2.3%)
Pioglitazone+Glibenclamide	14 (2.3%)
Metformin+Pioglitazone+Glipizide	13 (2.2%)

Concomitant medications:

Anti-dyslipidemic drugs and antihypertensive drugs were the most commonly prescribed concomitant medications. A total of 288 (47.8%) were on lipid modifying agents. Of all lipid modifying agents, atorvastatin was prescribed in 165 (57.3 %) patients.

For hypertension, Renin-Angiotensin Aldosterone System (RAAS) blockers were prescribed in 234 (38.9 %) patients. Telmisartan (133 [56.8 %]) was the most common agent used in this study. Other common medications were beta blockers (86 [14.3 %]) and calcium channel blockers (57 [9.5%]).

Effectiveness of pioglitazone and its combination on glycemic control:

1.6% reduction in mean HbA1c was observed after pioglitazone therapy (8.8% to 7.2%). Reduction in mean fasting plasma glucose and postprandial plasma glucose was 45.2 mg/dl (169.5 mg/dl to 124.3 mg/dl) and 61.5 mg/dl (246.8 mg/dl to 185.3 mg/dl) respectively, after pioglitazone therapy (Table-4).

Out of 602 patients, the proportion of patients with HbA1c ≥7 % decreased from 85.2 % to 53.5 %, after pioglitazone therapy.

Table: 4 Effect of pioglitazone therapy on glycemic control

% (N=602)	Before Initiating Pioglitazone Therapy	After Pioglitazone Therapy
Fasting blood glucose		
▪ N	518	303
▪ Mean	169.5	124.3
▪ SD	62.41	41.76
▪ Range (Min.: Max.)	(73.0:535.0)	(62.0:312.0)
Post Prandial plasma glucose (PP)		
▪ N	598	376
▪ Mean	246.8	185.3
▪ SD	87.24	60.73
▪ Range (Min.: Max.)	(58.0:722.0)	(70.0:506.0)
HbA1C		
▪ N	579	368
▪ Mean	8.8%	7.2%
▪ SD	1.78	1.29
▪ Range (Min.: Max.)	(5.0:15.9)	(0.6:13.3)

Complication of Diabetes (N=602):

Diabetic neuropathy was noted in 145 (24.1%) patients in our study. Diabetic nephropathy, diabetic retinopathy, erectile dysfunction and diabetic foot ulcers were noted in 76 (12.6%), 39(6.5%), 13 (2.2%) and 12 (2.0%) patients respectively. The percentage of patients with other complications is shown in figure 1.

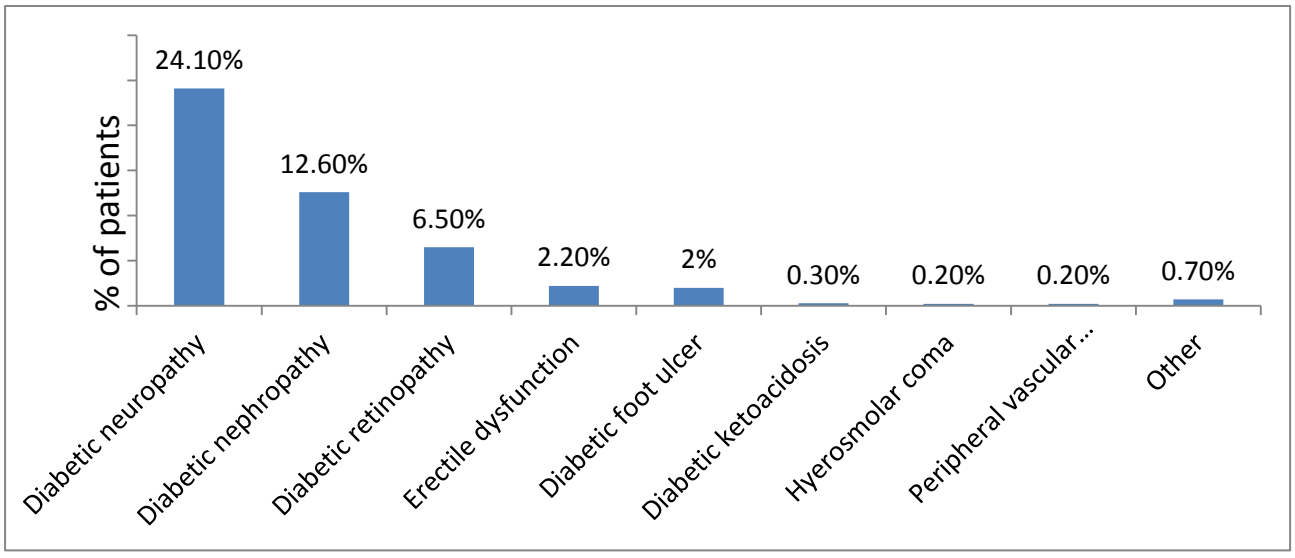

Figure 1: Complications in the study patients

DISCUSSION:

Diabetes is a global concern, more so in India and is now increasingly seen even in younger population[7]. It is known that the elderly people have higher risk of diabetes. However, the incidence of diabetes at early age is increasing due to stress, poor dietary habits, sedentary lifestyle etc.[7] The mean age of our study population was 56 years while another recent study in India had reported a mean age of 52.9 years.[8] South Asians have reported an early onset of diabetes and they are more insulin resistant compared to Caucasians, though similar BMI levels were reported in both populations.[2] In our study, about 20% patients were less than 38 years of age at onset which suggests early occurrence of diabetes in Indian patients.

Asian Indians have reduced insulin sensitivity compared to Caucasians subjects.[9] In addition economic growth, lifestyle changes and dietary pattern also contribute to the rising prevalence in younger population. [10]

Family history of diabetes is a known risk factor for type-2 diabetes. Various studies have shown high prevalence of diabetes among people with a family history in parents or siblings. The prevalence of diabetes in family members with history of diabetes in father, mother and both were 6.48%, 10% and 14.94% respectively.[11] In our study, the history of diabetes among parents was more common compared to previously reported study.[11]

Hypertension and dyslipidemia were the commonest comorbidities present in almost 49% of the type 2 diabetes patients in this study. Our findings are in concurrence with another study from India which has shown an overall prevalence of hypertension of 49% in patients with type 2 diabetes.[12] The prevalence of dyslipidemia was in fact lower in our study as compared to a previous study in India.[12] Neuropathy is a common complication in diabetes patients. In our study diabetic neuropathy (24.1%), nephropathy (12.6%) and retinopathy (6.5%) were the three most common complications. A recent Indian study has shown that among known cases of diabetic neuropathy, prevalence of painful and painless neuropathy is 49.1% and 50.9% respectively. This could be attributed to the prolonged exposure to high blood pressure causing nerve damage, which in turn may result in different types of neuropathies.[13]

Another large cross sectional study from India showed prevalence of peripheral sensory neuropathy and nephropathy to be 37% and 20% respectively.[14] Both these observations underlie high occurrence of microvascular complications in type-2 diabetes patients. Strict and sustained control of hyperglycemia is critical in preventing or delaying such complications. On one hand the availability of plethora of antidiabetic agents offers choices of therapy, however, it also adds to the dilemma while selecting one agent over the other. Presence of comorbidities requires treatment with other drugs. Drug interactions potential should be considered while selecting antidiabetic medicine. Antidiabetic drug should not

have interaction with other drugs used for the treatment of comorbid conditions. Apart from effect on glycemic parameters, thiazolidinedione have beneficial non-glycemic effects including on dyslipidemia.[15]

Pioglitazone has shown favourable effect on plasma high-molecular-weight adiponectin concentrations in patients with metabolic syndrome.[16] In type-2 diabetes mellitus, pioglitazone as monotherapy, or in combination with metformin, or sulphonylurea has shown improvement in serum lipid profile.[5] proving its beneficial effect in diabetes patients with dyslipidemia. Absence of significant drug interactions makes pioglitazone a suitable agent to combine with others in the management of type 2 diabetes mellitus. These evidences underlie the importance of pioglitazone in the management of type 2 diabetes mellitus.

In this study metformin, sulfonylureas or combination of both, voglibose and vildagliptin were used in the past before initiating pioglitazone. Asian Indians have more insulin resistance[9] which may need drug with additional benefits in type 2 diabetes patients. Pioglitazone's glycemic benefits and effect on cardiovascular risk facts and arteriosclerosis[5] makes it a better choice in these patients.

According to the Research Society for the Study of Diabetes in India recommendations,[17] metformin is the first line therapy for the management of type-2 diabetes, unless contraindicated. A recent national diabetes registry showed metformin as the most commonly used anti-diabetic medication in India.[8] Thiazolidinedione is recommended to be added to metfomin if blood glucose target is not achieved. In our study, 24.8% of patients were prescribed pioglitazone along with glimiperide and metformin. Triple drug therapy of pioglitazone, glimepiride and metformin is commonly used in India due to efficacy and potential to offer improved compliance. Moreover, drugs acting on different pathways may provide more beneficial effects in diabetes patients. Pioglitazone increases insulin sensitivity,[5] while glimepiride increases insulin release[18] and metformin acts by multiple mechanisms including increased glucose uptake into skeletal muscle and adipocytes. [19] The second most commonly used combination was metformin plus pioglitazone. The use pioglitazone combination therapy ranging between one to ten or more years in this study points towards good tolerability and sustained efficacy of pioglitazone

In addition to its glucose lowering potential, antioxidant effect of pioglitazone may help in better outcome by improving insulin resistance and reducing diabetic complications.[20,21] Pioglitazone is a peroxisome proliferator activated receptor (PPAR) gamma agonist. In addition, it also causes minor activation of PPAR alfa which is linked to reduction of triglyceride level, anti-inflammatory action and beneficial effect on atherosclerosis.[22]In the

CHICAGO study (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone), pioglitazone reduced carotid-intima medica progression, compared with glimepiride.[23,24] In the PERISCOPE trial, pioglitazone has shown to be significantly improve the cardiovascular risk factors and result in lower progression of coronary atherosclerosis compared with glimepiride.[25]Analysis of the Pioglitazone In Prevention Of Diabetes (PIPOD) and Troglitazone In Prevention Of Diabetes (TRIPOD) study showed that pioglitazone arrested the decline of beta cell function and also maintained the stability of beta cell function.[6] Pioglitazone showed a reduction in hs-CRP by 18% after three days of treatment and increased insulin sensitivity and adiponectin levels too.[26]

The "Asian Indian Phenotype" with unique abnormalities consisting of increased insulin resistance, higher waist circumference, lower adiponectin and higher high sensitive C-reactive protein (hs-CRP) levels increases the risk of diabetes and premature coronary artery disease.[27,28] Insulin resistance being a prevalent impairment even in normal weight Asian Indians,[29] pioglitazones are commonly used in diabetes treatment. Considering the unique profile of Indian diabetic patients and benefits offered by pioglitazone, it can be an ideal agent in the management of diabetes in the Indian set-up. Triple drug therapy of pioglitazone metformin and sulfonylurea has been found to be effective in Indian patients receiving insulin. This therapy offers benefits of early and sustained reductions in fasting glucose levels and reduced HbA1c levels resulting in less requirement of total insulin dose. Thus, the triple drug therapy can improve insulin-mediated glucose utilization because of enhanced insulin sensitivity.[30] Pioglitazone therapy also reduces hs-CRP level in patients with diabetes.[31]

Favourable effect of pioglitazone combinations on glycemic parameters (HbA1c, fasting plasma glucose and postprandial plasma glucose) was observed. Compared to baseline, increase in number of patients with <100 mg/dl fasting blood glucose and decrease in number of patients with postprandial plasma glucose <140 mg/dl was observed end of the study. A randomized, prospective study has shown significant reduction in fasting and postprandial blood glucose with pioglitazone, metformin and glimiperide combination therapy in Indian population.[32] Similarly another prospective, non-randomized trial has proved effectiveness of pioglitazone combination with other oral antidiabetic drugs in Indian type 2 diabetic patients in reducing glycemic parameters and also in controlling weight gain.[33] Moreover, pioglitazone improves cardiovascular risk factors more effectively compared with gliclazide and metformin.[34]

Various studies have shown effect of pioglitazone in reducing fasting and postprandial blood glucose.[32,33,34]

The number of patients having glycosylated haemoglobin (HbA1c) ≥ 7% decreased consistently in the study. A study from India showed significant (P < 0.0001) reduction in HbA1c levels with addition of pioglitazone in uncontrolled diabetes mellitus. Addition of pioglitazone 7.5 mg reduced Hb1Ac from 8.46% to 7.78% (0.68% reduction) while pioglitazone 15 mg reduced it from 8.34 to 7.78% (0.56% reduction).[33] In our study, the reduction in mean HbA1c was 1.6%, higher than a reported study.[33]

A 12 week therapy with fixed-dose triple drug combination of glimepiride, metformin, and 15 mg pioglitazone reduced HbA1c by 1.33% in another study among uncontrolled diabetes patients.[32] Our study observations support the results published in other studies with pioglitazone alone or combination.[33-35]

The renin-angiotensin-aldosterone system (RAAS) activity is elevated in diabetic nephropathies. Clinical trials in patients with diabetic nephropathy have shown that angiotensin II receptor blockers (ARB) and angiotensin-converting enzyme (ACE) inhibition have favourable effect on blood pressure and renal hemodynamics, The effect is independent of blood pressure-lowering effect in type 2 diabetes patients.[36] In our study, 38.9% patients used RAAS blockers. Angiotensin receptor blockers seem to be preferred over ACE inhibitors. Telmisartan was the most preferred RAAS blocker followed by olmesartan. Among ACE inhibitor, beta blocker and calcium channel blockers (CCBs), Ramipril, Metoprolol, and Amlodipine were the most preferred agents respectively.

Though there was no formal reporting of adverse reaction in the study, being a retrospective analysis, it seems that pioglitazone combinations therapy is found to be safe in patients of this study without any significant safety concern. An Indian study has shown no increased risk of bladder related abnormalities with pioglitazone use up to two years.[37] Another retrospective study evaluating 1111 pioglitazone users also showed no occurrence of urinary bladder cancer with pioglitazone use. [38]In our study few patients received pioglitazone therapy even more than 10 years and there was no report of urinary bladder cancer in any patient. Our findings are in accordance with these studies. Overall, the observation from Indian data shows long term use of pioglitazone combination therapy is effective and safe.

CONCLUSION:

This retrospective study indicates that pioglitazone combination therapy resulted in sustained glycemic improvement in Indian type 2 diabetic patients. Combination therapy with pioglitazone was found to be effective and safe in these patients. Pioglitazone, glimepiride plus metformin and metformin plus pioglitazone were the two most commonly used combination therapies in Indian context. Thus, considering the unique predisposition of Indians' susceptibility to type 2 diabetes, robust glycemic controlling agents and better insulin

sensitizer like pioglitazone, in combination therapy, can play a critical role in the management of type 2 diabetes.

DISCLAIMER:

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