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Comparative Study of Lipid and Glycemic Effects of Pioglitazone, Rosiglitazone with Glibenclamide in Patients with Type 2 Diabetes and Dyslipidemia

S.D. Inbaraj and I . Glory Josephine

Department of Pharmacology, Sree Balaji Medical College and Hospital,
Bharath University, Chromepet, Chennai-600044, India

Abstract: *Objective:* To evaluate the lipid and glycemic effects of Thiazolidinedione group of drugs (Pioglitazone, Rosiglitazone) in Type 2 diabetic patients with dyslipidemia.Methodogy: After ethical clearance and informed consent Type 2 diabetic patients with dyslipidemia attending the diabetic out patient clinic of Diabetology unit of Voluntary health services hospital.Chennai were screened and 45 patients selected for the study according to WHO criteria for diabetes and National cholesterol Education program guidelines for dyslipidemia. Each group consisting of 15 patients viz., Group I: Received Glibenclamide 5 mg/day. Group II: Received Pioglitazone 15 mg/day. Group III: Received Rosiglitazone 4 mg/day. Estimation of serum Total Cholesterol and HDL Cholesterol,Triglycerides,VLDL, Blood glucose,SGOT,S.GPT levels were estimated. Anthropometric evaluation and clinical parameters also evaluated. Results and discussion: Pioglitazone group showed significant reduction ($p < 0.05$) in fasting and post prandial blood glucose level at 12th week of study when compared with sulphonylurea group. Reduction in total cholesterol level. 16% in pioglitazone, 4% in rosiglitazone and 1% in sulphonylurea group. Serum Triglycerides showed significant reduction ($P< 0.001$) in Rosiglitazone group when compared to sulphonylurea group at 12th week of the study. HDL cholesterol level showed significant increase ($p < 0.001$) in pioglitazone group when compared to sulphonylurea group in 8th week and 12th week of the study. LDL cholesterol level showed significant reduction ($p < 0.05$) in pioglitazone group when compared to the Rosiglitazone group at 12th week of the study. When compared to pioglitazone, Rosiglitazone showed considerable reduction ($p < 0.05$) at 4th and 8th week of the study. Liver enzymes study showed significant increase in SGOT and SGPT levels ($p < 0.001$) in pioglitazone as well as rosiglitazone group. Conclusion:Thiazolidinediones group of oral antidiabetic drugs shows hypoglycemic as well as favourable lipidemic effects on type 2 diabetic patients. Among the two glitazones, pioglitazone showed more favourable effects of increasing HDL cholesterol. Hence this group of drugs may be considered for use in the early stage of Type 2 diabetes judiciously to tide over the insulin resistance, hyperglycemia and dyslipidemia and thereby to prevent cardiovascular morbidity.

Key words: Glitazones · Pioglitazone · Hypolipidemia · Insulin Resistance

INTRODUCTION

Diabetes mellitus is a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrates, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both [1]. The important metabolism affected by diabetes is the lipid metabolism which has the potential to develop atherosclerosis and cardiovascular complications.

The prevalence of type 2 diabetes is increasing rapidly and it is destined to become one of the world's most important and costly disease[2]. India tops the word with largest number of patients. Presently India has 32 million diabetic subjects and this will increase further to 57 million by 2025[3].

Type 2 diabetes patients often have other atherosclerotic risk factors such as dyslipidemia, obesity (Central obesity) hypertension, etc. [4].

Corresponding Author: Domnic Inbaraj, Department of Pharmacology, Sree Balaji Medical College and Hospital, Bharath University, Chromepet, Chennai-600044, India.

Coronary artery disease is two to three times more frequent in type 2 diabetes when compared to non diabetic individuals [5].

The treatment available for Type 2 diabetes are Insulin and oral hypoglycemic agents such as sulphonylureas, biguanides, Thiazolidinediones, meglitinide analogues and (Glucosidase inhibitors). Out of these agents thiazolidinedione group of drugs possess beneficial effects on lipids apart from hypoglycemic effect [6]. There is no adequate studies carried out to establish the beneficial lipidemic effect of thiazolidinediones in south Indian population, hence this study was carried out to evaluate the effects of two thiazolidinediones viz. Pioglitazone and Rosiglitazone in comparison with sulphonylurea, (Glibenclamide).

Methodology: The ethical clearance and permission from voluntary Health Services Hospital, Taramani was obtained to conduct the study at the Diabetes Department from March 2005 for a period of 12 weeks.

Patient Screening: Type 2 diabetic patients with dyslipidemia attending the diabetic outpatient clinic were screened and selected for the study according to WHO criteria for diabetes and National cholesterol Education program guidelines for dyslipidemia [1].

Inclusion Criteria:

- Type 2 diabetic patients with dyslipidemia.
- Total cholesterol (200 mg/dl.)
- Serum Triglycerides (200 mg/dl.)
- HDL cholesterol (≤40 mg / dl)
- LDL-cholesterol (100 mg/dl)
- VLDL-cholesterol (50 mg / dl)
- Adult males or females more than 30 yrs. and less than 60 yrs,
- Newly diagnosed patients or patients who were not on any anti-diabetic, or lipid lowering drugs for the past 2 months were included.

Exclusion Criteria:

- Pregnant Ladies, Breast feeding mothers and those who intent to become pregnant.
- Hepatic Dysfunction, previous recent history of Jaundice, alcoholic liver disease
- Hypersensitivity to any drugs
- Congestive cardiac failure
- Renal dysfunction
- Edematous conditions
- Alcoholism

Informed Consent: Informed consent in the prescribed form was obtained from all patients included in the study. Study period 12 weeks from march 2005.

Study Design A prospective randomized comparative study.

Study Centre Diabetes Research Institute, Voluntary Health Services Hospital, Taramani, Chennai.India.

Study Protocol: 45 type 2 diabetic patients with dyslipidemia were selected as per WHO criteria [1] and 2001 National Cholesterol Education Program Guidelines (NCEP) [13]. They were divided into 3 groups each consisting of 15 patients.

Group I: Received Glibenclamide 5 mg daily, 15 patients were included in this group, out of which 14 patients completed the study.

Group II: Received Pioglitazone 15 mg daily 15 patients were included in this group, out of which 13 patients completed the study.

Group III: Received Rosiglitazone 4 mg daily 15 patients were included in this group, out of which 13 patients completed the study.

Observations of Patients Included in the Study

Clinical Assessment: All subjects were interviewed about the history of alcohol abuse, smoking and panchewing. Family history of diabetes, hypertension, IHD. Past history of hypertension, coronary heart disease, associated illness like retinopathy, nephropathy and neuropathy were enquired and recorded.

All patients were measured height, weight waist circumference, waist-Hip ratio and BMI. Blood pressure measurements were made for all patients. Patients had initial blood pressure more than 130/85 mm Hg were treated with ACE inhibitors (T. Enalapril 2.5 mg/day).

All the three groups received exercise and diet counseling by qualified dietician and physiotherapist at Diabetes department. All the patients were instructed to follow the prescribed diet throughout the study.

Laboratory Analysis

Serum Lipid Profile Estimations: Serum Lipid Profile estimations were made at the Laboratory Department of Pharmacology and Environmental Toxicology
DR. A.L.M.P.G.I.B.M.S. Institute, Taramanai.

Table 1: Showing the demographic profile of the patients participated in the study

	Glibenclamide	Pioglitazone	Rosiglitazone	
n	15	15	15	
Sex				
Male	8	6	10	
Female	7	9	5	
Age (years)	48.47 ± 5.4	48.13 ± 3.6	47.40 ± 3.0	
Duration of Diabetes (years)	3.9 ± 4.4	3.2 ± 3.8	4.0 ± 4.6	
Body weight (kg)	67.2 ± 5.1	65.4 ± 4.8	64.1 ± 5.2	
BMI (Kg / m^2)	27.58 ± 3.84	26.07 ± 3.95	24.12 ± 1.76	
WHR	0.94 ± 0.54	0.94 ± 0.08	1.03 ± 0.17	
Diet				
Non Vegetarians	69	411	510	33%67%
Associates Illness				
Systemic Hypertension	54	63	34	31%24%
Diabetic Neuropathy	21	1-	3-	135
Family H/O Diabetes:				
Both parent DM	316	527	215	22%8%40%
(weight > 4kg)	10	20	11	
Social status				
Rich	2	1	0	6%
Middle Class	10	9	11	67%
Poor	3	5	4	27%
Educational Status				
Uneducated	123	114	132	80%20%
Smoking	2	3	1	13%

Serum lipid profile blood samples were collected from patients after overnight fasting and analysed by the following methods.

Methods

Estimation of Total Cholesterol and HDL Cholesterol: The total cholesterol and HDL cholesterol estimation were done by CHOD/POD method [14] using Liquistar Cholesterol Kit from Star diagnostics Pvt. Ltd.

Triglycerides Estimation: The triglycerides estimation was done by CHOD/POD method [15] using Liquistat Kit by Bio Lab diagnostics.

Estimation of Low Density Lipoprotein (LDL) and Very Low Density Lipoprotein (VLDL): The estimation of LDL and VLDL cholesterol was done by Friedwald calculation method [16].

Friedwald Calculations

$$VLDL = \frac{\text{Triglyceride}}{5}$$

LDL = Total cholesterol-(HDL + VLDL)

Blood Glucose Estimation: The effect of sulphonylurea, pioglitazone and Rosiglitazone on glycemic level is assessed by 8 hrs fasting blood glucose and 1½ hrs post prandial blood glucose levels at baseline, 4 wks, 8 wks and 12 wks interval.

Method: Blood glucose estimations were analysed by GOP / PAP enzymatic method at the laboratory of Voluntary Health Services Hospital.

Serum Transaminase (SGOT SGPT) Estimation: Serum SGOT, SGPT analysis were made for all the 3 groups of patients at Laboratory of voluntary health services hospitals by Kinetic / IFCC method.

All the above parameters were analyzed at baseline and at the end of 4th week and 12th week of the study.

Statistical Analysis: In three groups of patients treated with sulphonylurea, pioglitazone and Rosiglitzone-biochemical values of fasting blood sugar (FBS), Post prandial blood sugar (PPBS), Lipid profile namely total cholesterol (TC), Triglycerides (TGL), High density lipoprotein (HDL), Low density lipo protein (LDL) and very low density lipoprotein (VLDL), Liver enzymes namely SGOT, SGPT are expressed as mean and standard deviation.

The mean difference between sulphonylurea, pioglitazone and rosiglitazone group were analysed individually as baseline, 4th week, 8th week and 12 th week by one way analysis of variance. F-test.

The mean difference between individual groups like sulfonylurea Vs pioglitazone, sulphonylurea vs rosiglitazone, pioglitozone Vs Rosiglitazone were analysed using Tukey-Kramer multiple comparison test.

RESULTS

Biochemical Parameters

Hypoglycemic Effects: All three groups showed reduction in fasting and post prandial blood glucose levels. Pioglitazone group showed significant reduction ($p< 0.05$) in fasting and post prandial blood glucose level at 12th week of study when compared with sulphonylurea group. Among the pioglitazone and rosiglitazone group there is no significant difference.

Blood Sugar (FBS, PPBS) (mg / dl)

Effect on Lipids

Total Cholesterol: There is no significant reduction in total cholesterol level when compared between individual groups. However there is apparent reduction in total cholesterol level. 16% in pioglitazone, 4% in rosiglitazone and 1% in sulphonylurea group.

Serum Triglycerides: Serum Triglycerides showed significant reduction ($P < 0.001$) in Rosiglitazone group when compared to sulphonylurea group at 12th week of the study and moderate reduction ($P< 0.01$) at 8th week of study. However there is no significant effect when compared to pioglitazone group.

HDL Cholesterol: HDL cholesterol level showed significant increase ($p < 0.001$) in pioglitazone group when compared to sulphonylurea group in 8th week and 12th week of the study, when compared to the Rosiglitazone group, pioglitazone group showed significant increase in HDL level ($p < 0.001$) at 12th week of study.

HDL Cholesterol (mg / dl)

LDL Cholesterol: LDL cholesterol level showed significant reduction ($p < 0.05$) in pioglitazone [8] group when compared to the Rosiglitazone group at 12th week of the study. When compared to pioglitazone, Rosiglitazone showed considerable reduction ($p < 0.05$) at 4th and 8th week of the study.

LDL Cholesterol (mg /dl)

VLDL-cholesterol: VLDL cholesterol level showed significant reduction ($p<0.001$) in Rosiglitazone group when compared to the sulphonylurea group at 12th week of the study. When compared to Pioglitazone, Rosiglitazone showed considerable reduction ($p<0.05$) at 4th and 8th week of the study.

Table 5: Blood glucose levels in 3 groups of patients

	0 wks		4 wks		8 wks		12 wks	
Drugs	FBS	PPBS	FBS	PPBS	FBS	PPBS	FBS	PPBS
Group								
Sulphonylurea n = 15	149.47 ± 20.760	242.60 ± 30.622	136.87 ± 14.846	225.33 ± 25.826	129.14 ± 14.076	216.64 ± 19.397	119.79 ± 9.932	196.07± 19.731
Group II								
Pioglitazone n=15	161.07 ± 19.426	251.93 ± 30.628	148.53 ± 17.079	237.80 ± 27.125	237.80 ± 14.618	221.71 ± 25.563	117.46 ± 5.797	196.38*±23.715
Group III								
Rosiglitazone n=15	149.40 ± 15.810	257.93 ± 25.186	141.21 ± 15.453	247.43 ± 25.509	130.15 ± 11.495	234.85 ± 25.563	122.08 ± 7.08	217.92±21.895
No. of patients	45		44		41		40	

Sulphonylurea Vs Pioglitazone * p value < 0.05

Table 6: Showing HDL cholesterol levels

Drugs Gr.	0 wk	4 wks	8 wks	12 wks
Group I Sulphonylurea n = 15	21.20 ± 6.190	20.67 ± 3.976	21.57 ± 3.435	21.57 ± 3.322
Group II Pioglitazone n=15	21.73 ± 3.788	23.20 ± 3.075	27.64 ± 2.790***	42.54 ± 6.936***
Group III Rosiglitazone n = 15	21.47 ± 2.416	22.71 ± 2.091	23.54 ± 3.282	24.23 ± 3.270
No. of patients	45	44	41	40
***-Sulphonylurea Vs Pioglitazone	p value < 0.01			
*** Sulphonylurea Vs Rosiglitazone	p value < 0.001			

Table 7: Showing LDL Cholesterol levels

Drugs Gr.	0 wk	4 wks	8 wks	12 wks
Group I Sulphonylurea n = 15	142.27 ± 41.560	139.80 ± 34.252	142.43 ± 31.265	143.50 ± 29.341
Group II Pioglitazone n=15	169.20 ± 31.248	165.73 ± 31.671	149.21 ± 29.908	122.54 ± 26.819*
Group III Rosiglitazone n = 15	163.40 ± 33.983	162.36 ± 31.983	162.36 ± 31.833	151.85 ± 33.842
No. of patients	45	44	41	40
*-Pioglitazone Vs Rosiglitazone	p value < 0.05			

Table 8: Showing VLDL Cholesterol level

Drugs Gr.	0 wk	4 wks	8 wks	12 wks
Group I Sulphonylurea n = 15	44.40 ± 3.795	43.67 ± 4.639	44.29 ± 5.210	42.86 ± 3.959
Group II Pioglitazone n=15	49.27 ± 6.995	46.00 ± 5.451	42.21 ± 5.338	39.23 ± 5.615
Group III Rosiglitazone n = 15	42.33 ± 8.466	40.43 ± 6.711	36.46 ± 5.981*	34.85 ± 5.655***
No. of patients	45	44	41	40
*** Sulphonylurea Vs Rosiglitazone	p value < 0.01			
* Pioglitazone Vs Rosiglitazone	p value < 0.05			

Table 9: showing SGOT,SGPT levels

		0 wk		4 wks		8 wks		12 wks	
Groups	No. of Patients	FBS	PPBS	FBS	PPBS	FBS	PPBS	FBS	PPBS
Group I Sulphonylurea n = 15	15	17.60± 3.776	19.40 ± 3.832	18.27 ± 2.774	18.47 ± 2.774	17.14 ± 3.483	18.00 ± 3.0	17.71 ± 3.221	20.07 ± 4.665
Group II Pioglitazone n=15	15	20.67 ± 3.109	21.33 ± 2.664	25.67 ± 3.830	24.67 ± 3.830	29.93 ± 5.967	30.00 ± 5.533	35.31 ± 5.793***	37.23 ± 5.183***
Group III Rosiglitazone n=15	15	21.73 ± 2.520	22.67 ± 2.769	29.50 ± 4.468	28.79 ± 2.665	34.25 ± 10.402	36.85 ± 3.00	44.69 ± 3.838	42.46 ± 1.808
No. of patients		45		44		41		40	
***Sulphonylurea Vs Pioglitazone			p < 0.001						
***Sulphonylurea Vs Rosiglitazone			p < 0.001						
Pioglitazone Vs Rosiglitazone			p < 0.005						
Pioglitazone Vs Rosiglitazone			p < 0.001						

VLDL Cholesterol

Serum Transaminase: Liver enzymes study showed significant increase in SGOT and SGPT levels ($p < 0.001$) in pioglitazone as well as rosiglitazone group when compared to sulphonylurea group in 4th, 8th and 12th week of study. When compared to pioglitazone group, Rosiglitazone group showed moderate increase in SGOT, SGPT levels ($p < 0.01$) in 4th, 8th and 12th week of the study [9]

SGOT / SGPT

Clinical Parameters: The mean age in sulphonylurea group was 48.47 ± 5.4 years, Pioglitazone group was 48.13 ± 3.6 years and rosiglitazone group was 47.40 ± 3.0 years. Body mass Index (BMI) of patients showed 27.5 ± 3.8 in sulphonylurea group, 26.07 ± 3.9 in pioglitazone and 24.12 ± 1.7 in rosiglitazone group. The over all BMI indicates that all the patients are falling under the obesity range.

These patients also having lipid abnormalities, hence there may be a correlation between obesity and lipid abnormalities in Type 2 diabetes mellitus. (WHR) waist Hip Ratio measured in all patients showed 0.94 ± 0.54 in sulphonylurea group, 0.94 ± 0.83 in pioglitazone group and 1.03 ± 0.01 in rosiglitazone group. These values indicate that there is central obesity is present in all the patients which confirms that these patients are prone to develop lipid abnormalities [17]. Bodyweight increased by 2 kgs in both pioglitazone and rosiglitazone groups at the end of 12th week of study.

DISCUSSION

The clinical parameters clearly showed increased BMI in almost all the patients suggesting the incidence of obesity in type 2 diabetic patients with dyslipidemia. This indirectly indicates that these patients may have insulin resistance. The WHR (Waist to hip ratio) measurement taken for all patients showed increased incidence of central obesity. This may be another clinical parameter which can be correlated with abnormal lipoprotein profile consistent with diabetic dyslipidemia.

Before starting treatment with drugs, all the patients were analysed about their dietary habits and exercise. The dietician in the diabetic department prescribed the appropriate individualized dietary advice. This was reviewed and assessed at every visit of the patient. 21 patients (46%) followed the exact dietary advices. 16 patients (35%) followed it satisfactory and remaining 8 patients (17%) did not follow the dietary advice. Like wise the patients followed the regular exercise (Brisk walking 30 mts / day) were 40%, intermittent walkers 42% and remaining 17%, did not follow any exercise. The patients followed the exercise and dietary advises were mostly from educated group. The patients who were smokers and alcohol abusers were instructed to stop before starting the study.

The dyslipidemia in Type 2 diabetes in characterized by a combination of increased serum triglycerides and decreased HDL-cholesterol and most often near normal LDL cholesterol. In this study the same was observed viz., increased triglycerides and reduced HDL levels, but LDL and VLDL levels were also increased in most of the patients. Serum triglyceride level decrease was confirmed in pioglitazone group, whereas conspicuous decrease with statistical significance observed with rosiglitazone group [10].

In contrary to the statement in the Text book of diabetes [18] 3rd edition, chapter 45:13 that rosiglitazone causes an increase in low density lipoprotein (LDL), such an increase was not seen in our study. In fact though not statistically significant a decrease was seen after 8th and 12th week of the study, while the other thiazolidinedione (Pioglitazone) has been found to decrease the LDL cholesterol significantly after 12th week of the study.

However in accordance to the same report [16], significant increase in HDL-cholesterol was found with pioglitazone group with statistical significance after 8th-12th weeks of the study. A favourable finding observed in this study is the significant decrease of VLDL cholesterol with rosiglitazone in 8-12 weeks. The difference in this regard between the thiazolidinediones studied could be due to the predominant effect of pioglitazone and rosiglitazone on PPARá and PPARä [11] respectively. The recently concluded PROactive study (PROspective pioglitazone clinical trial in macrovascular events) assess the effect of pioglitazone with anti-inflammatory and vascular properties, on the secondary prevention of macrovascular events in type 2 diabetes [12].

The hypoglycemic effects showed by the 3 groups of drugs without much difference except the pioglitazone group showed slight reduction in the 12th week of the study. A progressive increase in SGOT and SGPT levels were seen with both pioglitazone and rosiglitazone groups, however the values were found within the normal range. Though hepatotoxicity has not been reported with these two agents, a progressive increase in SGOT/SGPT values from 0-12 weeks is to be explored further to overcome the concern regarding hepatotoxicity.

There was a mean increase in body weight of 2 kgs for rosiglitazone and pioglitazone groups at the end of 12th week of the study, this may be due to fluid retension which may be disadvantageous in case of cardiac failure patients.

CONCLUSION

Thiazolidinediones group of oral antidiabetic drugs shows hypoglycemic as well as favourable lipidemic effects on type 2 diabetic patients. Among the two glitazones, pioglitazone showed more favourable effects of increasing HDL-cholesterol. Hence this group of drugs may be considered for use in the early stage of Type 2 diabetes judiciously to tide over the insulin resistance, hyperglycemia and dyslipidemia and thereby to prevent cardiovascular morbidity.

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