EFFECT OF PIOGLITAZONE ON LIPID PROFILE IN TYPE 2 DIABETIC PATIENTS

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ABSTRACT

Objective: *To determine the effect of pioglitazone on lipid profile in type 2 diabetic patients treated and followed up for three months after initiation of therapy.*

Methodology: *This hospital based quasi-experimental study was conducted in the medical B unit, Lady Reading Hospital Peshawar from July 2008 to June 2009. A total of 161 patients with type 2 diabetes mellitus were included in this study using convenient (non-probability) sampling. Clinical and laboratory evaluation of all the patients were done to note the change in lipid profile after the use of 30 mg pioglitazone. Continuous variables such as age and lipid profile (triglycerides; Low Density Lipoprotien[LDL]; High Density Lipoprotien[HDL]; cholesterol) at baseline and after 3 months time were expressed as mean ± S.D. Paired sample t-test was used to analyze the mean difference in pre-post lab investigation by SPSS version15.*

Results: *Out of the 161 patients, 79(49.1%) were males and 82(50.9%) were females. The mean age of the sample was 51.2±11.33 years. Triglycerides decreased from 219.2±34.4 to 189.2±33.7 mg/dl with a mean difference of 29.9 mg/dl ($p<0.001$). Total cholesterol changed from 201.4±29.8 to 203.2±28.9 mg/dl with a mean difference of 1.8mg/dl ($p<0.001$). LDL changed from 153.7±21.1 to 154.7±20.7 mg/dl with a mean difference of 0.9 mg/dl ($p<0.001$). HDL increased from 37.2±2.9 to 41.5±3.1 mg/dl with a mean difference of 4.3 mg/dl ($p<0.001$).*

Conclusions: *Pioglitazone was found to have beneficial effects on lipid profile. It significantly reduced the levels of triglycerides and increased levels of HDL cholesterol in patients with Type 2 diabetes.*

Key Words: *Diabetes mellitus, Lipid profile, Pioglitazone, Metabolic syndrome*

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INTRODUCTION

Diabetes mellitus (DM) is a syndrome with disordered metabolism. It is characterized by inappropriate hyperglycemia due to either an absolute or relative deficiency of insulin secretion and/or insulin resistance[1].

Type 2 diabetes is a major public health issue. Its prevalence worldwide was estimated to be approximately 150 million in 2000, and this is predicted to double by 2025[2].

The major part of this numerical increase will occur in developing countries. There will be a 42% increase, from 51 to 72 million, in the developed countries and a 170% increase, from 84 to 228 million, in the developing countries. In the developing countries the majority of people with diabetes are in the age of 45-65 years[3].

An increasing prevalence of Type 2 diabetes mellitus is mainly due to the rising prevalence of obesity and physical inactivity[4]. Both excess body fat and physical inactivity predispose to Type 2 diabetes[5].

The tremendous rise in the prevalence of diabetes will almost certainly be associated with a similar increase in the long-term complications that are associated with diabetes. Both metabolic susceptibility and complication predisposition are genetically determined, but this genetic expression is significantly influenced by environmental factors.

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Diabetes is also one of the strongest causal risk factors for cardio-vascular disease (CVD) in the Pakistani population[6]. Complication rate in diabetes is very high in Pakistan[7]. In Pakistan 19.8% of the diabetics were shown to be suffering from coronary artery disease (CAD), 6.2% had suffered a major cerebrovascular event whereas 2.1% had a diabetic foot[8]. Another study has revealed that 25% of those that present to healthcare facilities in Pakistan with diabetes suffer from retinal complication[6,9].

Pioglitazone is an oral antihyperglycaemic agent for the treatment of type 2 diabetes. It is a member of the thiazolidinedione (glitazone) class, which also includes troglitazone (now discontinued) and rosiglitazone. Pioglitazone acts as an insulin sensitizer[10]. At a molecular level, TZDs activate peroxisome proliferator-activated receptor gamma (PPAR), a ligand-activated nuclear transcription factor that modulates the expression of a number of genes coding for proteins involved in glucose and lipid metabolism[11]. PPARγ receptors are most strongly expressed in adipose tissue and in the vascular wall, with secondary benefits on insulin sensitivity in skeletal muscle and liver[11].

Pioglitazone treatment also reduces hepatic and muscular fat, resulting in increased insulin sensitivity in these tissues[12,13].

Interventions such as reducing low-density lipoprotein (LDL)-cholesterol, controlling blood pressure, angiotensin converting enzyme (ACE) inhibitors and aspirin have been shown to lower CV morbidity and mortality in DM. In a 10-year, epidemiological follow-up study of patients with T1DM who participated in the Diabetes Control and Complications Trial (DCCT), lower rates of CVD were observed in the group initially randomized to intensive glucose control. Neither the UKPDS nor the DCCT was powered to detect a reduction in CVD, however. Thus, while these data suggest that improved glycemic control may itself decrease CVD, there remain many unanswered questions. In particular, it is not known whether newer classes of drugs for T2DM such as the thiazolidinediones (TZDs) will have beneficial effects and only a few studies are done or are underway to answer this question and one of the most recent one is the PROactive study[14].

Many patients with type 2 diabetes have an abnormal lipid profile characterized by increased triglycerides and decreased high density lipoproteins HDL-C. Although low density lipoproteins LDL-C levels are similar to non-diabetic patients, there is an increase in small, dense LDL-C particles[15,16]. LDL-C is a well-known risk factor for cardiovascular disease, and the primary target for statin treatment; however, it is appreciated that hypertriglyceridemia, low HDL-C and increases in small, dense LDL-C particles are also important risk factors[17-19], highlighting the management of all components of the lipid profile in patients with type 2 diabetes[20,21].

There is emerging evidence that pioglitazone treatment is associated with more favorable lipid changes[22]. Although the effects of pioglitazone on HDL-C and triglycerides are 'fibrate-like', the current literature does not provide compelling evidence that pioglitazone has any significant physiological or clinical PPARα activity[23-26].

The objective of this study was to determine the effect of pioglitazone 30 mg/day on lipid profile (serum total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides) in type 2 diabetic patients treated and followed up for three months after initiation of therapy.

METHODOLOGY

This Hospital based Quasi-experimental study was conducted in the medical B unit and on out-patient department days of medical B unit, Lady Reading Hospital Peshawar, from July 2008 to June 2009. The sampling technique was non probability, convenience sampling.

Permission from Hospital Ethical Committee was taken prior to data collection. Informed consent was taken from all the patients. Patients selected for study were interviewed through a pre-designed proforma. Personal particulars, presenting complaints, treatment taken for diabetes, duration of diabetes, family history of diabetes mellitus and any previous hospitalization(s) were recorded.

A total of 161 patients with type 2 diabetes mellitus were included in this study. Inclusion criteria was all adult patients with type 2 diabetes mellitus who have normal blood pressure (<130/85mm hg), age of 30 years or above and regular in monthly follow up. All patients with diagnosed Type 1 diabetes mellitus were excluded. The patients fulfilling the criteria were enrolled in the study. They were then admitted to the medical unit for proper assessment and education regarding diabetes and its complications. This, although initially was thought to be done at out-patient department, but found to be difficult due to the heavy number of the patients and the fasting serum levels of various parameters of the study.

After having the detailed evaluation and excluding all those patients who were found to have any contraindication to pioglitazone (i.e., congestive heart disease, chronic liver disease and renal failure), the risk/ benefit ratio was discussed

with all patients including effects and side effects of the medication. All were informed that this class of drug is basically used as an insulin sensitizer to enhance sensitivity of the body tissues to insulin and dyslipidemias is a major concern in patients with type 2 diabetes, and pioglitazone may or may not have harmful effect on lipid profile, so the primary benefit as insulin sensitizer is there, we are evaluating the secondary effect on lipid profile.

All patients underwent complete physical examination looking for complications of diabetes. Presence of retinopathy was defined on fundoscopic examination or on a history of laser therapy. Height in meters and weight in kilograms with clothes on and without shoes was recorded. Body mass index (BMI) was calculated as weight in Kg/Height in meters square.

Investigations carried out were fasting venous blood was sampled from an ante-cubital vein from all patients for the measurement of blood glucose levels, HbA1c and serum lipid profile. Fasting blood sugar was tested by Elitech kit method. Serum lipid profile was tested by Boerhinger kit method at the baseline and 3 months after the initiation of therapy. Urine routine examination was carried out, again a routine test for diabetic patients not having direct relation to the present study.

The study sample was started on 30 mg of pioglitazone per day along with the previous oral medication they were using for diabetes and followed up for 03 months. After having done baseline biochemical values, the patients were discharged from the hospital and these investigations were repeated after three month to monitor any effect of pioglitazone on lipid profile. The compliance was ensured by checking the empty blisters of the medication.

Data collected included variables like age, gender, HbA1c and lipid profile values. Data storage, processing and analysis were computer based. Computer soft ware, SPSS version 15, was used. The study variables that were included were age, gender, fasting lipid profile values (including trigycerides (TG), total cholesterol (TC), high density lipoproteins(HDL) and low density lipoproteins(LDL) at the base line and after initiation of therapy.

Descriptive statistical analysis was employed. Lipid profile values are presented in percentages, mean $\pm$ SD. A p-value ≤ 0.05 was considered significant.

RESULTS

Out of 161 patients who were enrolled in the study 79 were males and 82 were females.

Age of the patients ranged from 30 to 75 years. Mean age of the patients was 51.20 year ±SD.

Majority of the patients were overweight (about 84.5%) while 6.2% were in the obese class and only 9.3% were in the normal group.

Out of the 79 males triglycerides decreased from 215.3± 36.17 to 185.38± 35.06 with a mean difference of 29.9 ($p<0.001$). Total cholesterol changed from 203.37±29.49 to 205.2±28.6 with a mean difference of 1.8 ($p<0.001$). LDL-C Changed from 154.42±20.61 to 155.37±20.32 with a mean difference of 0.9 ($p=0.002$). HDL-C Changed from 37.48±3.02 to 41.86±3.16 with a mean difference of 4.3 ($p<0.001$).

Out of the 82 females triglycerides changed from 223.1± 32.57 to 193.05± 32.14 with a mean difference of 30.1 ($p<0.001$). Total cholesterol changed from 199.5±30.34 to 201.22±29.37 with a mean difference of 1.7 ($p<0.001$). LDL-C Changed from 153.09±21.51 to 154.12±21.27 with a mean difference of 1.1 ($p=0.003$). HDL-C Changed from 36.94±2.77 to 41.22±2.91 with a mean difference of 4.2 ($p<0.001$).

Table 1: Mean comparison of pre and post Pioglitazone treatment results

Variables	Baseline Mean ± S.D	After 3 Months Mean ± S.D	Mean Difference	P-Value
HbA1c	8.8 ± 1.1	7.9 ± 0.7	0.88	< 0.001
Triglycerides	219.2 ± 34.4	189.2 ± 33.7	29.98	< 0.001
Total Cholesterol	201.4 ± 29.8	203.2 ± 28.9	1.81	NS
LDL-C	153.7 ± 21.1	154.7 ± 20.7	0.99	< 0.001
HDL-C	37.2 ± 2.9	41.5 ± 3.1	4.32	< 0.001

DISCUSSION

The number of male patients approximated that of female patients in our study i.e., 50.9% males and 49.1% females which was a chance finding as convenient sampling was used in the study and other possible explanation is that the number of male patients attending the hospital out patient department and even the number of admitted male patients to the medical units are more compared to the female patients in this hospital, although studies conducted in Pakistan and Turkey has found high prevalence of type 2 diabetes in women[27,28].

Average age of the patients in our study was 51.2 years which is closer to the study conducted by khatib et al in India in year 2008 in which majority of the diabetic patients were in the age group of 51-60 years[29].

Approximately ten percent of the Pakistani population is considered obese. Obesity is one of the major risk factors behind hypertension, diabetes and CAD[30].

The reasons for the increased risk of CVD among patients with DM are not completely understood but it is likely that both traditional and non-traditional risk factors play a role. Among the various factors which are now well understood are hypertension, dyslipidaemias and insulin resistance. There are still more which are coming up like chronically elevated inflammatory biomarkers, abnormalities in fibrinolysis and platelet activation.

Lipid profile parameters of the study population showed promising results which will have greater impact in the future guidelines for management of diabetes. Total cholesterol of the study group changed from a mean baseline level of 201.4 mg/dl to 203.21 mg/dl, which though statistically significant was not a major shift and is also confirmed in other studies like the one conducted by Peters Harmel et al[31]. In the most recent and comprehensive analysis, which included data from 23 randomized controlled trials, pioglitazone was associated with a neutral effect on total cholesterol[32].

It must be mentioned here that some studies have found decreased total cholesterol by pioglitazone. These are by Boyle PJ et al[32] and Gegick CG et al[33] and similarly another study showing no effect of pioglitazone on total cholesterol conducted by Herz M et al[34].

This difference among various studies carries a lot of discussion behind it, it can be explained by normal variation over time in the values of total cholesterol on either side of the baseline values which is probably the case in our study or this can be due to the statistical tests or differences among the study samples baseline characteristics in various studies and last one is due the effect of other lipid lowering drugs which the patients were using concomitantly.

The effects of thiazolidinediones on triglycerides have been somewhat more impressive. Decreases in triglyceride levels have been observed more often with pioglitazone. Herz Met al[34], King AB et al[35], Boyle PJ et al[32], Gegick CG et al[33] and Peters Harmel et al[31]. in their studies have shown this effect of pioglitazone on triglyceride that it significantly decreased it and the other thiazolidinediones do not share this effect with pioglitazone, although the effect of pioglitazone on triglycerides are fibrate like, the current literature does not provide compelling evidence that pioglitazone has any significant physiological or clinical PPAR α activity.

Our study also found the same effect of pioglitazone on triglyceride levels which decreased from a mean baseline level of 219.27 mg/dl to 189.29 mg/dl over a period of twelve weeks which was a significant change with a P value of < 0.001. Pioglitazone treatment also decreased triglyceride significantly by 11% in the PROactive trial[14].

The effect on low density lipoproteins is again variable among various studies some showing having no effect while other showing decrease in LDL and still other showing even increase in the LDL but not significant, overall, pioglitazone is associated with a neutral to modest increase in LDL[36].

Herz M et al[34] found in their study that pioglitazone increased LDL over baseline by 7%. These changes were not significant when compared to placebo. King AB et al[35] also has similar finding in their study. We also found the same milder effect on the LDL with a change from mean level of 153.74 mg/dl to 154.73 mg/dl.

Another effect that was studied was that on the high density lipoproteins which are the beneficial lipids. The mean level of HDL at the start of the study was 37.20 mg/dl which improved to a level of 41.53 mg/dl after twelve weeks of pioglitazone use. It has been found that of the roughly half of all patients with coronary heart disease (CHD) who fail to achieve protection against events, despite being on an optimal regimen of statin therapy, over one third have low serum HDL-C levels. In fact, low HDL-C is a significant independent risk factor[37]. This is an important aspect in the management of risk factors in the management of diabetes mellitus, we found

in our study that almost all the patients were having a baseline HDL level at a lower level and pioglitazone has a very significant effect on HDL by raising it. We were unable to detect the difference in the gender regarding HDL. In the PROactive trial the investigators found an increase of 17% in HDL from the baseline. Similar increase was noted in other studies[31-35,38].

LIMITATIONS

It was a hospital based study and not a community based study. The duration of the study was shorter and the long term sustained benefits of pioglitazone can't be assessed. Sampling was not randomized.

CONCLUSION

From this study, it is concluded that Pioglitazone which is basically used as an insulin sensitizer had beneficial effects on lipid profile and significantly reduced the levels of triglycerides and increased levels of HDL cholesterol in patients with type 2 diabetes.

RECOMMENDATIONS

Risk factors assessment of all diabetic patients is one of the most important aspects of diabetes mellitus management. Pioglitazone has beneficial effects on the glycemic control and lipid profile of type 2 diabetic patients and should be added to the treatment regimen of type 2 diabetic patients who have no contraindications to its use.

To reconfirm and to establish the efficacy of pioglitazone in local type 2 diabetes, large double blind randomized control trials are needed.

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CONTRIBUTORS

AM conceived the idea, planned the study & drafted the manuscript. AT critically revised and approved the manuscript. IA, IA, ZA & MB helped in acquisition, interpretation and analysis of data. All the authors contributed significantly to the research that resulted in the submitted manuscript.