EFFECT OF PIOGLITAZONE ON SERUM HIGH DENSITY LIPOPROTEIN (HDL) LEVELS OF TYPE-2 DIABETICS

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ABSTRACT

Objective: To study effect of Pioglitazone on serum high density lipoprotein levels in patients with type 2 diabetes mellitus.

Study Design: Single blind randomized controlled trial

Place and Duration of Study: Department of medicine, Combined Military Hospital Multan from 1st Feb 2011 to 30th July 2012.

Material and Methods: A total of 276 already diagnosed patients of diabetes mellitus type 2 between age of 30-80 years, presenting to the outpatient department of Combined Military Hospital Multan were selected. Type 2 diabetic patients were allocated group A or B using random allocation. Base line blood sugar fasting (BSF), glycosylated hemoglobin (HbA1c), high density lipoprotein (HDL) levels were taken. Group A was treated with Pioglitazone along with other hypoglycemic agents while group B was treated with only hypoglycemic agents and multivitamin tablets were added as placebo.After 12 weeks of treatment, serum HDL levels were measured to analyze effect of pioglitazone on serum HDL levels.

Results: Pioglitazone group showed significant improvement in the serum HDL levels from baseline HDL 46.38 + 6.44mmol/L to 49.80+ 5.86 mmol/L after 12 weeks of therapy, (p = 0.001).

Conclusion: Pioglitazone when used in combination with other oral hypoglycemic agents has a beneficial effect on the serum HDL levels of the diabetics.

Keywords: Diabetes Mellitus, High density lipoprotein, Pioglitazone.

INTRODUCTION

Type 2 Diabetic patients commonly have lipid abnormalities[1]. These changes are characterized by elevated triglycerides and decreased HDL cholesterol[2]. The pattern of lipid abnormalities in diabetics differ in various races and the commonest dyslipidemia in type 2 diabetic local population is low HDL[3]. Decreased HDL levels may occur in up to 81% of type 2 diabetics in Pakistani population[4]. Decreased HDL cholesterol has been identified as a major independent risk factor for coronary artery disease[5].

Pioglitazone is a thiazolidinedione derivative approved for the treatment of type 2 diabetes mellitus. Pioglitazone acts by binding to Peroxisome proliferator activated receptor (PPAR-γ) which is a nuclear receptor affecting cellular function by nuclear transcription[6]. Besides the glucose lowering effect of Pioglitazone, the inhibition of lipolysis and adipocyte differentiation results in changes in the lipid metabolism. The effects include a decrease in triglyceride (TG) levels, increased high density lipoproteins (HDL)[7]. The lipid effects of this drug have been studied in the west showing baseline serum HDL mean 50.6 (±11.9) in general diabetic population on Sulfonylureas and /or Metformin and 54.4 (±13.4)[8] for those diabetics taking Pioglitazone. Data regarding the lipid effects of Pioglitazone in the Pakistani population is lacking. Considering one of the most common dyslipidemia in type 2 diabetic Pakistani population is decreased HDL, studies on this drug may prove it to be more beneficial in our people. The results of this study may benefit the patients by better HDL profile and decreased cardiovascular complications in such patients.

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Received: 24 Jul 2013; revised received: 27 Oct 2014; accepted: 10 Dec 2014

This study aims at determining the effect of Pioglitazone on serum HDL levels of type 2 diabetics in a subset of local population.

MATERIAL AND METHODS

These randomized controlled trials were carried out in department of medicine, Combined Military Hospital Multan, from 1st Feb 2011 to 30th July 2012. Diagnosed Patients of diabetes mellitus type 2 between age of 30-80 years of both genders presenting to the outpatient department for regular follow-up and glycemic control were included in the study. Total 276 patients were included in the study through non-probability convenienced sampling technique. Informed written consent was taken from all enrolled patients and permission from hospital ethical committee was sought. Those using statins in past 08 weeks, HbA1c > 10.5%, ketoacidosis, renal failure, congestive cardiac failure, pregnant females, current smokers, non-compliant to treatment, Body Mass Index (BMI) > 30 kg/m², acute or chronic hepatitis were excluded from the study. Sample size was calculated using WHO sample size calculator for comparing two means, taking confidence interval of 95%, power of the test 80%. Thorough history was taken and clinical examination performed. Patients previous treatment records and follow up proformas were checked for compliance and treatments received in the past 3 months. Patients were allocated group A or B using random allocation based on computer generated table of random numbers with 138 subjects in each group. Fasting Blood Glucose levels, glycosylated hemoglobin (HbA1C) and baseline serum HDL levels were taken after an overnight fast of 10 hours. All 276 patients were using various hypoglycemic agents namely, metformin, acarbose, sulfonylureas, insulin therapy. Group A was started on Pioglitazone 15mg once daily along with other hypoglycemicagents (which the patient was already taking). Patients were followed up on regular monthly basis and necessary adjustments made in the dosages to control sugar levels. Dose was adjusted (15-45mg once daily) depending on the fasting blood sugar levels on fortnightly visits subsequently.

Group B was started on multivitamin tablet as a placebo along with other hypoglycemic agents namely, metformin, acarbose, sulfonylureas, insulin therapy except pioglitazone. Dose of hypoglycemic agents was adjusted according to the fasting blood glucose levels. After 12 weeks of treatment, again

Table-1: Base line Characteristics of study group.

	Pioglitazone group (n=138)	Control group (n=138)	*p*-value
Age in years (mean ±SD)	54.43 ± 9.66	53.62 ± 9.57	0.76
BMI (kg/m²) (mean ±SD)	25.09 ±2.85	25.15 ± 2.88	0.42
Medications n (%)			
Sulfonylurea	70 (50.7%)	67 (48.5 %)	0.31
Metformin	90 (65.2%)	127 (92%)	0.51
Acarbose	28 (20.2 %)	25 (18.1%)	0.23
insulin	10 (7.2%)	15 (10.8%)	0.11
Gender (male/female)n	66/72	65/73	0.45
HbA1c % (mean ±SD)	7.15 ± .66%	7.15 ± .65%	0.87
BSF (mmol/l) (mean ±SD)	6.452 ±.674	6.549 ± .687	0.49
Serum HDL (mg/dl(mean ±SD)	46.38 ±6.45	45.93 ± 6.43	0.73

Table-2: Clinical characteristics of study group at 12 weeks of treatment.

	Pioglitazone group n=138	Control group n=138	*p*-value
BMI (kg/m²) (mean ±SD)	25.10 ± 2.81	25.11 ± 2.86	0.78
HbA1c % (mean ±SD)	7.25 % ± .76	7.11 % ± .55	0.45
BSF (mmol/l) (mean ±SD)	6.95 ± .77	6.64 ± .65	0.87
Serum HDL (mg/dl) mean (SD)	49.80 ± 5.86	45.73 ± 5.97	0.001*

*statistically significant

serum HDL levels were taken after an overnight fast of 10 hours. Patients in both the groups were followed up for 3 months. Samples were also taken for glycosylated hemoglobin to assess the blood glucose control over the preceding 3 months. Serum HDL levels were determined in the 10 hour fasting serum samples taken by laboratory technician. Patients were asked to sit on a chair and roll up their sleeves above elbow. Venous blood samples were collected using full aseptic measures and samples were transported to Pathology laboratory for analysis. Serum HDL level estimation was done by a timed endpoint method using HDLD reagent. DXC 600 automated analyzer was used. The results were verified by pathologist. GLU reagent was used to measure serum glucose levels using DXC-600 automated analyzer. All the data had been entered in computer software Statistical Package for Social Sciences (version 17.0). Mean and standard deviation (SD) were calculated for all the quantitative variables i.e. age, BMI, glycosylated hemoglobin, fasting blood sugar and serum HDL levels. Frequency and percentage was used to express qualitative variables. Stratification was done to control effect modifiers like age, gender and BMI. Comparison between groups was done independent samples t test, difference between before and after treatment values were analysed using paired t test. A p value < 0.05 was considered significant.

RESULTS

The age of the study population ranged from 30 to 80 years. Mean age of the patients in group A was 54.43 ± 9.66 years and mean age in group B was 53.62 ± 9.57. In group A, the mean Serum HDL levels at presentation was 46.38 ±6.45 mg/dl, in group B it was 45.93 ± 6.43 mg/dl. Clinical and demographic characteristics of study group are described in table-1.

In group A, mean serum HDL, 3 months after treatment was 49.80 ± 5.86 mg/dl and the mean in group B was 45.73 ± 5.97 mg/dl, with significant difference(p=0.001).There were no significant differences of BMI, BSF, Hba1c levels between group A and group B. Group A showed significant increase in HDL levels (p=0.001) at 12 weeks of therapy but in group B there was no change in HDL at 12 weeks (p= 0.26).

DISCUSSION

Diabetic population has shown increased incidence of dyslipidemia[10]. This makes these patients more vulnerable to diabetic complications. So understanding the lipid abnormalities that affect your population group and having tools and measure to correct them becomes more important. Decreased serum HDL levels is one of the commonest lipid abnormality encountered in Pakistani diabetic population[3]. Pioglitazone is a relatively newer treatment modality in Pakistan and very little work had been done on it, particularly in our population. Pioglitazone has shown many beneficial effects in the treated diabetic population and better serum HDL profile is one of major benefits derived from this therapy. Patients with Diabetes Mellitus frequently encounter dyslipidemia or deranged lipid profile therefore, a drug which not only improves glycemic control but has added benefits becomes important and drug of choice. This drug has a relatively safe side effect profile therefore most of the patients tolerated the therapy well[11].

This aspect of dyslipidemia has been studied very less in our population but is gaining large attention in the world. The results of the study clearly show that there is statistically significant improvement in serum HDL profile in patients treated with Pioglitazone. In this study, patients in both the groups belonged to either gender or the age group included 30-80 years. Statistically significant results were seen as improvement in serum HDL levels of the group treated with Pioglitazone.. Test of significance revealed p-value of<0.05(0.0001). Since most common dyslipidemia is deranged HDL levels, this drug can be more beneficial in our population.

Pioglitazone is currently approved as a third line therapy. But in patients who show marked lipid abnormalities this may be used earlier[12]. Also for those patients in which HDL remains low despite treatment, Pioglitazone

may offer an effective alternative to standard treatment for better metabolic profile. Similar results were seen in a Japanese study though there is much difference in the ethnic buildup, lifestyles and diet of the two population groups13. Tamio T, et all conducted a randomized controlled trial involving 92 patients and compared the effects of Pioglitazone therapy with Glibenclamide in terms of serum lipid profile[14]. This study indicated a statistically significant improvement in serum HDL profile. From baseline HDL mean 50.6(±11.9 mg/dl) improved to 54.4 (±13.4mg/dl). The change from baseline was 3.8 (± 8.2)[15].

In a review of the clinical data, Kelley[14] (2007) found that Pioglitazone has a modest improvement in the serum HDL levels in the Diabetic population. In another landmark PROACTIVE trial (Prospective pioglitazone Clinical Trial In macrovascular Events) , Wilcox R et al ,shared similar results and showed improvement in HDL levels but found an association with heart failure. None of our patients reported or presented with heart failure during the treatment[17].

Dormandy et al[16], (2005) studied this drug with cardiovascular event as endpoints and found it to not only improve serum HDL levels but also decrease cardiovascular mortality.

CONCLUSION

Pioglitazone is one of the better treatment options available for the treatment of diabetes. This drug improves the serum HDL levels in these patients and thus offers a decrease in diabetic complications and an improved survival.

CONFLICT OF INTEREST

The authors of this study reported no conflict of interest.

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