TO EVALUATE THE EFFECTS OF PITAVASTATIN ON GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS WITH HYPERCHOLESTEROLEMIA WHO WERE PREVIOUSLY BEING TREATED WITH ATORVASTATIN

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ABSTRACT

Objective: To evaluate the effects of Pitavastatin on glycemic control in patients with Type 2 Diabetes Mellitus with hypercholesterolemia who were previously being treated with Atorvastatin.

Study Design: The present study was a prospective and cross-over study.

Place and Duration of Study: At Combined Military Hospital Sialkot from 15th September 2018 to 15th December 2018.

Material and Methods: A total of 103 patients of Diabetes Mellitus and Hypercholesterolemia who were previously treated with Atorvastatin for at least 12 weeks were enrolled for the study. 52 patients were then switched treatment from Atorvastatin to Pitavastatin and defined as the A to P group and treated to maintain a goal of LDL-C <100 mg/dL. In the same period the rest of 51 patients were continued with Atorvastatin treatment defined as the A to A group and the dose of Atorvastatin was maintained at the same level. Serum lipid profiles and Blood Samples were obtained between 0600 hours and 900 hours after overnight fast. HbA1c levels were recorded at enrolment (baseline), and after 3 months of pitavastatin or atorvastatin treatment. HBA1c and Lipid profile were analyzed.

Results: There were no statistically significant differences in the baseline BMI, HDL-C, triglycerides or HbA1c among the two groups. Age, and duration of diabetes were significantly different among the two groups.A significant improvement in HbA1c was found in the baseline HbA1c (p=0.001) in the A to P group. At the end of the study HbA1c was lower with pitavastatin treatment than with atorvastatin treatment in A to P group.

Conclusion: Pitavastatin in comparison to Atorvastatin treatment had more favorable effects on glucose metabolism level measured as reduction in HBA1c levels in patients with type 2 Diabetes Mellitus.

Keywords: Glycemic control, Statin, Type 2 diabetes mellitus, Lipid Profile.

INTRODUCTION

Patients with type 2 diabetes are at higher mortality due to cardiovascular diseases, and low-density lipoprotein (LDL) cholesterol is the most important predictor of the onset of cardiovascular disease in these patients. It has been repeatedly proven that Atorvastatin, an inhibitor of 3-hydroxy-3- methylglutaryl coenzyme A reductase, reduces the risk of cardiovascular disease in patients with type 2 diabetes regardless of being the primary or secondary prevention[1,2]. Pitavastatin a relatively new statin which is marginally metabolized by cytochrome P450 isoenzymes, and has a powerful LDL cholesterol lowering has effects similar to Atorvastatin[3]. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial, it was highlighted that a higher frequency of new-onset type 2 diabetes was found in patients receiving Atorvastatin 80 mg/day (hazard ratio [HR] 1.37, 95% confidence interval [CI] 1.08–1.75) as compared with those who received a placebo4. Statins are frequently prescribed for patients with diabetes and dyslipidemia, therefore the effect of statins on glycemic control in patients with type 2 diabetes is a major concern to the treating physicians. Although research is still ongoing Pitavastatin has been reported to reduce the risk of new-onset diabetes in patients with impaired glucose tolerance by 18%[5,6]. At the same time two prospective studies reported no deterioration in

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glycemic control in patients with metabolic syndrome and type 2 diabetes after 1 year treatment with Pitavastatin[7,8]. A recent study reported a higher incidence of new-onset diabetes in patients receiving Pitavastatin compared with simvastatin[9]. Many serial studies have demonstrated adverse effect on glycemic control with Atorvastatin in patients with type 2 diabetes[10-13]. Yamakawa *et al* reported a significant increase in glycated hemoglobin (HbA1c) in patients with diabetes receiving Atorvastatin treatment for 3 months , whereas only a minimal change in HbA1c in patients receiving Pitavastatin[14]. Takano *et al*[15] reported a similar adverse influence on HbA1c with Atorvastatin treatment for 3 months (6.8 ± 0.9% to 7.2 ± 1.1%, $p<0.001$). Similarly some studies did not show any favorable effects of Pitavastatin compared with Atorvastatin[16]. Therefore the effect of Pitavastatin on glycemic control remains controversial due to the conflicting data. There have been no studies so far that have evaluated the effect of Pitavastatin on glycemic control as the primary end-point. Surprisingly in our setup no studies have been carried out to evaluate the effect of Pitavastatin on glycemic control let alone to compare its effects on glycemic control with Atorvastatin. Similarly no comparison has been drawn between the use of Pitavastatin and Atorvastatin in patients with Diabeteis Mellitus with hyperchlosterlomia. Similarly there is no published data to compare the different statins regarding their effect on Insulin resistance in patients of Diabetes Mellitus.

With this background and considering the paucity of data in our population regarding this important issue we decided to formulate this study. The aim of the present study was to evaluate the effect of HMG CoA reductase inhibitor Pitavastatin, on glycemic control in patients with type 2 diabetes who were previously being treated with Atorvastatin.

MATERIAL AND METHODS

Combined Military Hospital Sialkot is a 600 bedded and patients with Diabetes Mellitus and hypercholesterolemia occupy the main chunk of medical outpatient load. The present study was a prospective and cross-over study designed to evaluate the distinct effects of statins on HbA1c. A total of 105 patients of Diabetes Mellitus and Hypercholesterolemia who were previously treated with Atorvastatin for at least 12 weeks were enrolled for the study carried out for 3 months (from 15 September 2018 to 15 December 2018) at Combined Military Hospital Sialkot. 52 patients were then switched treatment from Atorvastatin to Pitavastatinand defined as the A to P group and treated to maintain a goal of LDL-C <100 mg/dL. In the same period from 15th September 2018 to 15th December 2018, the rest of 51 patients were continued with Atorvastatin treatment defined as the A to A group and the dose of Atorvastatin was maintained at the same level. Two patients did not report after signing the consent form and were not included in the study. We also excluded patients aged younger than 20 years, those with type 1 diabetes mellitus, those with major organ failure and those who were Insulin dependent. During the study period all patients received interactive counseling with regard to lifestyle modifications including

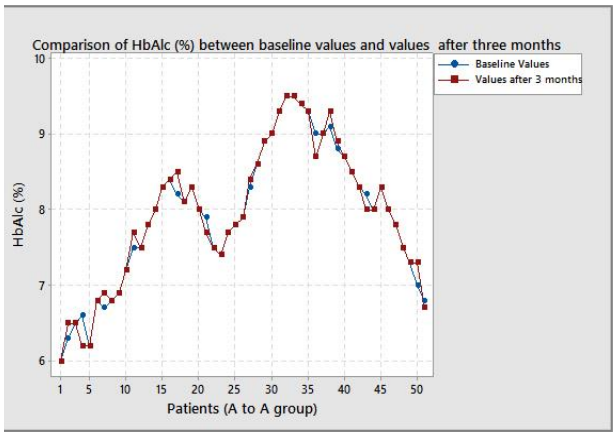

Figure-1: A to A group.

Table: Baseline Values & Values after 3 months (*p*-value 0.637).

Sample	n	Mean	SD	SE Mean
Baseline Values	51	7.929	0.920	0.129
Values after 3 months	51	7.937	0.923	0.129

SD: Standard deviation, SE Mean : Standard Error Mean

exercise and diet and a detailed Performa was filled from each patient covering the necessary variables. Data was expressed as means ± standard deviation for continuous variables and as frequencies for categorical variables using SPSS software version 25 (IBM SPSS Inc., Chicago, IL, USA). Serum lipid profiles and Blood Samples were obtained between 0600 hours and 900 hours after overnight fast. HbA1c levels were recorded at enrolment (baseline), and after 3 months of Pitavastatin or Atorvastatin treatment. HBA1c and Lipid profile were analyzed at SELECTRA (ELI TECH Netherland). In the A to P group, the dose of treatment was converted either from Atorvastatin 5 mg daily to Pitavastatin 1 mg daily, or from Atorvastatin 10 mg daily to Pitavastatin 2 mg daily respectively. For patients in the A to A group, the dose of Atorvastatin was maintained at the same level. Among the 103 patients, 67 (43 in the A to P group and 24 in the A to A group) did not change or adjust the dosage of their antidiabetic agents during the 3 months of the study period. Changes in glucose control after stat in treatment were studied in these patients. Changes in lipid and HbA1c levels between baseline and 3 months, were assessed using the Wilcoxon signed-rank test. Differences in lipid and HbA1c levels between the patients treated with Pitavastatin 1 mg or 2 mg daily at baseline, and 3months were examined using the Mann–Whitney U-test. We adjusted for age, body mass index (BMI), and high-density lipoprotein cholesterol (HDL-C) using partial correlation. All statistical tests were carried out at a two- tailed significance level of 0.05 using SPSS software version 25 (IBM SPSS Inc., Chicago, IL, USA). Special collaboration was established between the patients undergoing the study and laboratory staff to facilitate the process of investigations and data collection.

RESULTS

There were no statistically significant differences in the baseline BMI, HDL-C, triglycerides or HbA1c among the two groups. Age and duration of diabetes were significantly different among the two groups (table-I). Higher baseline levels of total cholesterol and LDL-C were observed in the patients in the A to P compared with the patients in the A to A group (table-I). In the A to P group, there were no significant differences in total cholesterol, LDL-C or triglycerides after changing to Pitavastatin treatment. No increase in HDL-C was found in A to P group. In the A to A group, there was no significant change in the levels of HbA1c, total cholesterol, LDL-C, triglycerides, HDL-C or triglycerides/HDL-C at 3 months of the observation period (fig-1). A significant improvement in HbA1c was found in the baseline HbA1c (p=0.001) in the A to P group (fig-2). At the end of the study HbA1c was lower withPitavastatin treatment than withAtorvastatin treatment in A to P group (table-II). In the A to P group, there was no significant difference between the patients taking Pitavastatin 1 mg daily and 2 mg daily in the lipid profile at baseline, and at 3 months. No serious adverse effects were observed in all study patients including the two dropout cases.

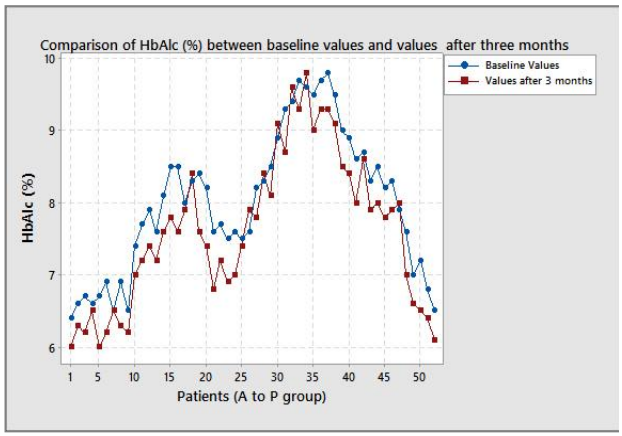

Figure-2: A to P group.

Table: Baseline Values & Values after 3 months (p-value 0.001).

Sample	N	Mean	SD	SE Mean
Baseline Values	52	7.996	0.978	0.136
Values after 3 months	52	7.610	1.044	0.145

SD: Standard deviation, SE Mean : Standard Error Mean

DISCUSSION

In the past 3 decades, there has been new insight on the pathogenesis of atherosclerosis and complicated and vulnerable plaques leading to a better understanding of acute coronary syndromes. The role of thrombosis, lipid metabolism, inflammation and their interplay has been investigated at the cellular and molecular levels, resulting in important new diagnostic and therapeutic strategies for treatment of patients with acute coronary syndrome. Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome (JAPAN-ACS) study showed that early intensive LDL cholesterol-lowering therapy resulted in the regression of coronary plaque volume in type 2 diabetic patients with acute coronary syndrome[17]. Though Pitavastatin 2 mg and Atorvastatin 10 mg are equally effective in improving LDL-C, total cholesterol, and triglycerides[18,19], Pitavastatin has been reported to have the effects of decreasing LDL-C and increasing HDL-C in both patients with or without diabetes. Atorvastatinon the other hand has been reported to only have an effect on lowering LDL-C, but not on increasing HDL-C in both patients with or without diabetes[20]. Pitavastatin increases the production of apolipoprotein A1 in Hep G2 cells at lower concentrations as compared with Atorvastatin[21]. Pitavastatin has been shown to facilitate an increase in HDL-C through stimulating lipoprotein lipase activity in 3T3-L1 preadipocytes more potently than Atorvastatin[22]. Pitavastatin on the other hand did not impair the differentiation and maturation of 3T3-L1 preadipocytes, and suppressed GLUT-4 expression when used at clinical concentrations[23] Teramoto *et al*[24] reported that the effect on increasing HDL-C was more prominent in patients with HDL-C levels less than 40 mg/dL at baseline. Diabetes mellitus is a metabolic disease with explicit effects on coronary vascular system leading to many of its complications.Various studies have shown that patients with diabetes mellitus have accelerated atherosclerotic vascular disease, and its understanding has resulted in new diagnostic and therapeutic approaches. In recent years it was highlighted that lipid changes may not only be a result of impaired glucose metabolism but also causing themasglycemic control is also important in the prevention of

Table-I: Baseline Demographics of 340 patients with type 2 diabetes in the three groups divided by statin treatment.

Group	A to A	A to P	*p*-value
N			
Age (years)	52.3 (38-72)	53.2 (34-73)	0.003
Duration of diabetes (years)	9.5 (7.2–14.9)	10.1 (6.2–14.7)	0.052
Gender (male)	65.5%	64.3%	0.432
BMI, baseline (kg/m^2)	25.4 (24.9-28.6))	25.4 (24.6-29.2)	0.672
BMI, at 3 months (kg/m^2)	26(25.2–28.4)	25.8 (22.9-28.7)	0.454
Creatinine (mg/dL)	0.74 (0.54–0.93)	0.78 (0.63–0.99)	0.007
ALT (U/L)	21.0 (15.7–32)	19.0 (15.0–23.0)	0.455
Baseline TC (mg/dL)	155.0 (140.0–174.0)	173.0 (152.0–199.0)	0.664
Baseline LDL-C (mg/dL)	88.0 (72.0–200)	101.0 (88.3–274.5)	0.001
Baseline TG (mg/dL)	110.0 (79.3–164.8)	111.0 (78.3–145.3)	0.634
Baseline HDL-C (mg/dL)	37.0 (26.0–48)	46.5 (34.3–36.0)	0.088
Baseline HbA1c (%)	7.4 (6.8–8.3)	7.4 (6.9–9.3)	0.745

The *p*-values were calculated by the Kruskal–Wallis test except for gender. A to A group, patients who continued atorvastatin treatment; A to P group, patients who were switched from atorvastatin to pitavastatin treatment. BMI, body mass index; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

diabetic vasculopathies, the effects of statins on glycemic control should be beneficial in diabetics with hypercholesterolemia. Several studies have analyzed the beneficial effects of pitavastatin on glucose metabolism compared with atorvastatin, but the reported effects were statistically insignificant[25]. The present study showed a more favorable effect for pitavastatin on glucose metabolism compared with atorvastatin, although the two statins are known to have similar LDL cholesterol-lowering effects[26]. Recent reported data reveals unfavorable effects of some lipophilic statins on glucose metabolism. Lipophilic statins can be stored into various organs, such as the pancreas, adipose tissue and muscle, altering glucose metabolism. Hydrophilic statins on the other hand are primarily metabolized only in the liver. Simvastatin, but not pravastatin, inhibits insulin secretion toodue to selective blockage of L-type calcium channels in rat pancreatic β- cells[27]. Still the effects of lipophilic statins on glucose metabolism remain controversial[28], and the present results showed a differential effect for distinct lipophilic statin on glucose metabolism. The present study identified that the patients with diabetes mellitushad reduction in HBA1c with Pitavastatin treatment in comparison to Atorvastatin. Though it is unclear that this improvement was due to improvement in relatively worse β-cell function and/or insulin resistance. It was shown recently that hypercholesterolemia can induce islet cholesterol accumulation in mice[29], and that exposure of β-cells to high cholesterol concentrations results in their dysfunction and death[30]. However, in the present study, the observed changes in HbA1c did not correlate with changes in LDL cholesterol and there were no differences in LDL cholesterol levels between pitavastatin and atorvastatin treatments. The results further suggest that the correlation between baseline HbA1c and improvements in HbA1c was independent of age, BMI, dose of Pitavastatin, and HDL-C. Pitavastatinhad a favorable effect on glucose metabolism independent of cholesterol metabolismas the observed changes in HbA1c did not correlate with changes in LDL cholesterol and there were no differences in LDL cholesterol levels between Pitavastatin and Atorvastatin treatments.

LIMITATIONS OF STUDY

The present study was limited by the relatively short observation period, and the lack of data on β-cell function and insulin resistance. Further large scale trials are required to assess the outcomes of long term clinical events from Pitavastatin treatment. It is not clear whether the HbA1c lowering effect of Pitavastatin would be similar in the diabetic patients who were treated more commonly with insulin, sulfonylurea and dipeptidyl peptidase-4 inhibitors.

CONCLUSION

Pitavastatinin comparison to Atorvastatin treatment had more favorable effects on glucose metabolism level measured as reduction in HBA1c levels in patients with type 2 Diabetes Mellitus. In terms of prevention of cardiovascular events, Pitavastatin seems to be the preferred statin for patients with type 2 diabetes.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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