TO COMPARE THE EFFECTS OF PITAVASTATIN ON INSULIN RESISTANCE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS WITH HYPERCHOLESTEROLEMIA WHO WERE PREVIOUSLY BEING TREATED WITH ATORVASTATIN

Shahid Abbas, Muhammad Nadir Khan*, Naseer Ahmed Samor, Humzah Abbas***, Rahmeen Pervaiz Khan****, Javeria Kamran*****

Combined Military Hospital, Sialkot Pakistan, *Army Cardiac Center, Lahore Pakistan, **Pakistan Naval Ship (PNS), Shifa Karachi Pakistan, ***HBS Medical College, Islamabad Pakistan, ****Shifa Medical College, Islamabad Pakistan, *****Armed Forces Institute of Cardiology/ National Institute of Heart Disease (AFIC/NIHD)/National University of Medical Sciences (NUMS), Rawalpindi Pakistan

ABSTRACT

Objective: To compare the effects of Pitavastatin on Insulin Resistance in patients with type 2 diabetes mellitus with hypercholesterolemia who were previously being treated with Atorvastatin.
Study Design: Prospective, comparative cross-sectional study.
Place and Duration of Study: Combined Military Hospital Sialkot, from Sep 2018 to Dec 2018.
Methodology: Our study was a prospective, comparative cross-sectional study, formulated to evaluate the effects of statins on Insulin resistance. A total of 52 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. Serum lipid profiles and blood samples were obtained after overnight fast. Insulin resistance was calculated at the start of study for atorvastatin and after 3 months of shifting to Pitavastatin.
Results: At initiation of the study no statistically significant differences were found in the baseline BMI, HDL-C, triglycerides or HbA1c. Homeostatic Model Assessment of Insulin Resistance (HOMA_IR) was employed to calculate Insulin resistance at the start of study and after 3 months of shifting to Pitavastatin. There was a significant reduction in Insulin resistance (p=0.031) after three months of shifting the patient from Atorvastatin to Pitavastatin.
Conclusion: Pitavastatin treatment in comparison to Atorvastatin had statistically significant reduction in Insulin resistance in patients with type 2 Diabetes Mellitus.

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

INTRODUCTION

It is an established fact that coronary heart disease is one of the main concerns of all patients of type 2 diabetes mellitus and a number of risk factors have a profound effect on the disease progression and the incidence of complication in these patients. Low density lipoprotein (LDL) cholesterol is the most significant modifiable risk factor of the cardiac mortality in patients with type 2 diabetes mellitus[1]. Statins are frequently used worldwide and have established role in preventing cardiovascular events. Atorvastatin when used as a lipid lowering agent significantly reduces the cardiac mortality in patients with type 2 diabetes[2,3]. The relatively newstatin, Pitavastatin having a complex molecule (figure). It is partially neutralized by cytochrome P450 isoenzymes, and has a LDL cholesterol-lowering effect that is quite similar to Atorvastatin[4], but has a potential to increase HDL-C levels[5]. As statins are frequently administered todiabetics with deranged lipid levels the effect of statins on glucose metabolism in patients with type 2 diabetes is an issue of major interest. It was quite alarming when in various trials a deleterious effect on glucose metabolism was highlighted with atorvastatin and simvastatin[6,7]. Although research is still ongoing it has been documented that Pitavastatin reduces the onset of diabetes in patients with impaired glucose tolerance[8,9]. M.J. Chapman reported that Pitavastatin has a positive effect on glycemic control evident by stable levels of glycated hemoglobin and insulin

Correspondence: Dr Shahid Abbas, Interventional Cardiologist and Medical Specialist, CMH Sialkot Pakistan
Email: shahabbas0@gmail.com

in diabetic patients[10]. It is evident with these conflicting reports that different statins must have different effect on risks of diabetes and glycemic levels. Therefore the effect of Pitavastatin on glucose metabolism remains controversial due to the conflicting data. Initially a few reports revealed that statin treatments was associated with insulin resistance culminating as a potential risk of developing new onset diabetes[11]. A recent meta analysis of mega-scale randomized control trials on Pitavastatin was analyzed but deteriorating effects on glucose metabolism and diabetes onset were not seen[12]. A large number of patients with Diabetes Mellitus have associated hypercholesteremia making them more susceptible to cardiovascular adverse events. Both hypercholesterolemia and type 2 diabetes are associated with the onset of cardiovascular events, the information that insulin-resistance is aggravated and the onset of diabetes is accelerated with statin treatment was alarming and an urgent need to reassess the safety of statins was required. Current data does not provide a clear explanation of the role of statins on glycemic parameters. There is some evidence that Pravastatin and Pitavastatin are the two statins least associated with worsening insulin resistance. However, a proven explanation and complete association between statins and diabetes mellitus risk has not yet been clarified.

In our setup no studies have been carried out to evaluate the effect of Pitavastatin on glycemic levels let alone to compare its effects on glucose metabolism with Atorvastatin. Similarly no comparison has been drawn between the use of Pitavastatin and Atorvastatin in patients with diabetes mellitus with raised cholesterol levels. Furthermore there is no published data to compare the different statins regarding their effect on Insulin resistance in patients of diabetes mellitus. To complicate the issue a large number of statins are available in the market with a large range of therapeutic dosage and are being used extensively.

With this background and considering the paucity of data in our population regarding this important issue we decided to formulate this study. The present study aimed at evaluating the effect of Pitavastatin on Insulin resistance in patients with type 2 diabetes who were being previously treated with Atorvastatin.

METHODOLOGY

Combined Military Hospital Sialkot is a 600 bedded hospital and patients with Diabetes Mellitus and hypercholesterolemia occupy the main chunk of medical outpatient load. Our study was a prospective, comparative cross-sectional study, formulated to evaluate the effects of statins on Insulin resistance. A total of 52 patients of diabetes mellitus and Hypercholesterolemia who were previously being 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. We excluded patients with type 1 diabetes mellitus, those with deranged hepatic and liver functions and those who were Insulin dependent. During the study period all patients had interactive counseling with regard to lifestyle modifications and a detailed proforma 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 version 25 (IBM SPSS Inc., Chicago, IL, USA). Serum lipid profiles and Blood Samples were obtained after overnight fast. Blood sugar fasting, Insulin levels and Lipid profile were analyzed at SELECTRA (ELI TECH Netherland). Insulin resistance was calculated by Homeostatic Model Assessment of Insulin Resistance (HOMA_IR) 13 at the start of study and after 3 months of shifting to Pitavastatin. All statistical analysis was carried out in an unbiased and professional environment using SPSS software version 25 (IBM SPSS Inc., Chicago, IL, USA). Special laboratory staff was utilized for ensuring a chain of sample collection from the out patients or the wards and collaboration was established between the patients undergoing the study and the laboratory to facilitate the process of investigations and data collection. No financial

or administrative services from any pharmaceutical source were utilized for sample collection, investigations, data collection or their interpretation to obtain reliable and efficient results. Similarly strict privacy and confidentiality was ensured at all levels till the completion of results.

RESULTS

At initiation of the study, No statistically significant differences were found in the baseline BMI, HDL-C, triglycerides or HbA1c. There was a statistically significant difference in age and duration of diabetes among the patients at enrolment (table-I).

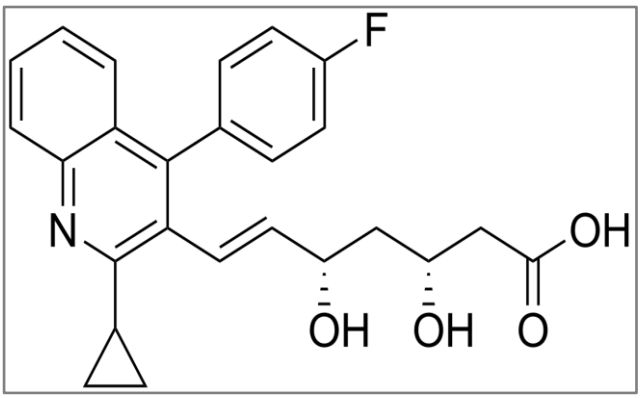

Figure: Pitavastatin molecule.

The *p*-values were calculated by the Kruskal–Wallis test except for gender. Patients who continued atorvastatin / Pitavastatin treatment; BMI, body mass index; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol.

The primary data including all blood levels were documented on individual specimen proforma and the serial results were endorsed after 3 months of atrovastatin treatment and then after 12 weeks of Pitavastatin medication. At the same time data was also entered in separate flow charts for documentation and comparison. Homeostatic Model Assessment of Insulin Resistance (HOMA _IR) was employed to calculate Insulin resistance at the start of study for atrovastatin and after 3 months of shifting to Pitavastatin. There was a significant reduction in Insulin resistance (p= 0.031) after three months of shifting the patient from Atorvastatin to Pitavastatin, (table-II).

There was a statistically significant reduction in Insulin resistance in patients with type 2 diabetes mellitus after treatment with Pitavastatin in comparison to Atorvastatin.

There was no association between the reduction of insulin resistance and reduction of LDL cholesterol. No serious adverse effects were observed in all the study patients.

Table-I: Comparison of baseline Demographics and lab investigations amongst Atrovastatin group and Pitavastatin group.

Variables	*p*-value
Age (years)	0.003
Duration of diabetes (years)	0.052
Gender (male)	0.432
BMI, baseline (kg/m²)	0.672
BMI, at 3 months (kg/m²)	0.454
Creatinine (mg/dL)	0.007
ALT (U/L)	0.455
Baseline TC (mg/dL)	0.664
Baseline LDL-C (mg/dL)	0.001
Baseline TG (mg/dL)	0.634
Baseline HDL-C (mg/dL)	0.088
Baseline HbA1c (%)	0.745

Table-II: Comparison of insulin resistance 03 monthspost atrovsatatin and pitavastatin.

	Mean	SD	SE Mean	*p*-value
03 Months post Atrovastatin	1.643	0.5416	0.0758	0.031
03 Months post Pitavastatin	1.578	0.4505	0.0631	

DISCUSSION

Diabetes mellitus is a metabolic disease with deleterious 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 may also be a causative factor. Well controlled lipid level sare essential in the

prevention of diabetic complications so effective statin therapy should be beneficial in diabetics with dyslipidemia. In the past three decades, there has been new insight in the pathophysiology of unstable atherosclerotic plaques leading to a better awareness regarding acute coronary event. The significance of clotting cascade, lipid disorders, inflammation and their interplay has been researched at micro-levels, resulting in new diagnostic and therapeutic strategies for treatment of patients with acute coronary syndrome. Arai H, *et al* showed that early aggressive LDL cholesterol treatment yielded reduction of coronary atherosclerotic burden in diabetic patients with acute cardiac event[14]. Pitavastatin, an agent developed in Japan, was primarily used in Asian countries, and its usage has gradually spread over the globe. Although Atorvastatin and Pitavastatin have similar efficacy for managing lipid disorders[15,16]. Pitavastatin has shown to reduce LDL-C and increase HDL-C in patients. Atorvastatin on the other hand has shown to only reduce LDL-C levels, but not had any effect on HDL-C in patients with diabetes mellitus[17]. Various studies have explored the effects of Pitavastatin on glucose metabolism compared with other statins, but the results so far were statistically insignificant[18]. There is direct evidence that the beneficial effect of Pitavastatin on glucose metabolism is independent of its lipid reduction ability and can be helpful to the type 2 diabetic patients on statin therapy. Several pathological mechanisms have been postulated to explain the potential risk of diabetes in patients receiving statins. The Beta cell inflammation due to statin-induced inhibition of cholesterol synthesis finally results in apoptosis and death of the Beta cell and decreased Insulin secretion[19]. Insulin resistance is also attributable to many other factors including inhibitory effect of statins on hydroxymethylglutaryl - CoA reductase, isoprenoid synthesis, calcium (Ca^{2+}) release, glucose transport and calcium mediated pancreatic insulin secretion[20]. It has been postulated that lipophilic and hydrophilic statins may have different effects on glucose metabolism[21]. PROVE-IT TIMI 22 trial revealed that although Atorvastatin and Pravastatin were both associated with a small increase in HbA1c, Atorvastatin exhibited significant increase in the risk for developing diabetes mellitus[22]. Studies comparing the efficacy of Pitavastatin with Atorvastatin in type 2 diabetic patients showed equal potential of LDL-C reduction, but contrary to Atorvastatin, Pitavastatin had no significant effect on glucose metabolism[23].

In a 5 years retrospective comparison of Atorvastatin, Pravastatin and Pitavastatin on glycemic control in patients with type 2 diabetes (LIVES) with hypercholesterolemia Pitavastatin showed significant reduction in HbA1c[24]. Similarly in a relatively recent study, patients with dyslipidemia were given Pitavastatin and there were no significant changes in glucose metabolism in 3 months[25]. A similar trial of Pitavastatin and Pravastatin on patients with the metabolic syndrome who had multiple additive risk factors for diabetes also had no effect on glucose metabolism over 6 months in. In the line of this precedence our study revealed that patients of diabetes mellitus with hypercholesteremia when shifted from Atorvastatin to Pitavastatin there was significant reduction of Insulin resistance. The present study identified that patients with diabetes mellitus had reduction in insulin resistance with Pitavastatin treatment in comparison to Atorvastatin. In addition to that the present study also exhibited that the documented changes in HbA1c did not correlate with changes in other variables like LDL cholesterol, age, BMI, and HDL-C; as there were no differences in their levels between Pitavastatin and Atorvastatin treated groups. Pitavastatin had a favorable effect on glucose metabolism which was not linked to variations in cholesterol levels between Pitavastatin and Atorvastatin therapy. This not only justifies the preference of Pitavastatin over the other statins in patients of Diabetes with Hypercholesterolemia but indirectly proves the superiority of Pitavastatin on other statins in patients predisposed to diabetes mellitus. Therefore it is in order to state that multicenter randomized trials are required to have a comparison of Pitavastatin with other statins in

the community of patients with diabetes mellitus and hypercholesteremia. If the findings confirm the superiority of Pitavastatin over other statins regarding glycemic control then a change of trend of statin therapy is required for immaculate management of type 2 diabetic patients.

LIMITATION OF STUDY

The limitations of the present study were a relatively short study period, and the lack of correlation with pancreatic function and association with insulin levels / resistance. Further multi centertrials with a larger study population are required to establish the effects of Pitavastatin treatment for a longer duration of time. A lot of diabetic patients are being managed with Insulin and the beneficial effects of Pitavastatin have not been studied in this vast group.

CONCLUSION

Pitavastatin treatmentin comparison to Atorvastatin had statistically significant reduction in Insulin resistance in patients with type 2 Diabetes mellitus.

The risk of new-onset diabetes varies substantially among various clinical trials evaluating the efficacy and safety of statins; with only JUPITER and PROSPER trials exhibiting statistically significant increases in the potential for type 2 diabetes. There is ample evidence that patients predisposed to diabetes mellitus have significant risk of developing type 2 diabetes mellitus with statin therapy. At the moment statins are now used with the corollary that this increased risk for diabetes is outweighed by the cardiovascular risk reduction. However with the current data pour-ing in it is required that a preference pattern among various statins should be formulated based on weighing the risks and benefits for individualizing the treatment plan for each patient.

CONFLICT OF INTEREST

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

REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes–2012. Diabetes Care 2012; 35(Suppl-1): S11–S63.
2. Colhoun HM, Betteridge DJ, Durrington PN. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentrerandomised placebo-controlled trial. Lancet 2004; 364(9435): 685-96.
3. Maruyama T, Takada M, Nishibori Y, Fujita K, Miki K, Masuda S, Horimatsu T et al Comparison of preventive effect on cardiovascular events with different statins. Circ J 2011; 75(3): 1951-59.
4. Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: A multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). J Am Coll Cardiol 2009; 54(4): 293-302.
5. Sasaki J, Ikeda Y, Kuribayashi T, Kajiwara K, Biro S, Yamamoto K et al. A 52-week, randomized, open-label, parallel-group comparison of the tolerability and effects of pitavastatin and atorvastatin on high-density lipoprotein cholesterol levels and glucose metabolism in Japanese patients with elevated levels of low-density lipoprotein cholesterol and glucose intolerance. ClinTher 2008; 30(6): 1089-1101.
6. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): A multi centre randomised controlled trial. Drugs 2004; 64(Suppl-2): 43-60.
7. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: The IDEAL study: A randomized controlled trial. JAMA 2005; 294(19): 2437-45.
8. Preiss D, Seshasai SRK, Welsh P. Risk of incident diabetes with intensive dose compared with moderate- dose statin therapy. J Am Med Assoc 2011; 305(24): 2556-64.
9. Sattar N, Preiss D, Murray HM. Statin and risk of incident diabetes: A collaborative meta analysis of randomised statin trials. Lancet 2010; 375(9716): 735-42.
10. Chapman MJ, Orsoni A, Robillard P, Hounslow N, Sponseller CA, Giral P etal. Effect of high-dose pitavastatin on glucose homeostasis in patients at elevated risk of new-onset diabetes: Insights from the CAPITAIN and PREVAIL-US studies. Curr Med Res Opin 2014; 30(5): 775-84.
11. Baker WL, Talati R, White CM. Differing effect of statins on insulin sensitivity in non-diabetics: A systematic review and meta-analysis. Diabetes Res Clin Pract 2010; 87(1): 98-107.
12. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010; 375(9716): 735-42.
13. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28(7): 412-9.
14. Arai H, Hiro T, Kimura T. More intensive lipid lowering is associated with regression of coronary atherosclerosis in diabetic patients with acute coronary syndrome sub-analysis of JAPAN-ACS study. J Atheroscler Thromb 2010; 17(1): 1096-1107.
15. Maruyama T, Takada M, Nishibori Y. Comparison of preventive effect on cardiovascular events with different statins. Circ J 2011; 75(8): 1951–59.

16. Yokote K, Bujo H, Hanaoka H, Shinomiya M, Mikami K. Multicenter collaborative randomized parallel group comparative study of pitavastatin and atorvastatin in Japanese hypercholesterolemic patients collaborative study on hypercholesterolemia drug intervention and their benefits for atherosclerosis prevention (CHIBA study). Atherosclerosis 2008; 201(2): 345-52.
17. Budinski D, Arneson V, Hounslow N. Pitavastatin com-pared with atorvastatin in primary hypercholesterolemia or combined dyslipidemia. ClinLipidol 2009; 4(3): 291–302.
18. Yokote K, Saito Y. Influence of statins on glucose tolerance in patients with type-2 diabetes mellitus: subanalysis of the collaborative study on hypercholesterolemia drug intervention and their benefits for atherosclerosis prevention (CHIBA study). J Atheroscler Thromb 2009; 16(1): 297-98.
19. Sampson UK, Linton MF, Fazio S. Are statins diabetogenic? Curr Opin Cardiol 2011; 26(4): 342-47.
20. Koh KK, Sakuma I, Quon MJ. Differential metabolic effects of distinct statins, Atherosclerosis, 2011; 215(1): 1-8.
21. Ishikawa M, Namiki A, Kubota T. Effect of pravastatin and atorvastatin on glucose metabolism in nondiabetic patients with hypercholesterolemia, Intern Med 2006; 45(2): 51-5.
22. Sabatine MS, Wiviott SD, Morrow DA. High-dose atorvastatin asssociated with worse glycemic control: A PROVE-IT TIMI 22 substudy (Abstract), Circulation 2004; 110(Suppl-1): S834.
23. Gumprecht J, Gosho M, Budinski D. Comparative long-term efficacy and tolerability of pitavastatin 4 mg and atorvastatin 20-40 mg in patients with type 2 diabetes mellitus and combined (mixed) dyslipidaemia. Diabetes Obes Metab 2011; 13(11): 1047-55.
24. Teramoto TU, Urashima M, Shimano H. A large-scale survey on cardio-cerebrovascular events during pitavastatin (LIVALO tablet) therapy in Japanese patients with hypercholesterolemia. Jpn Pharmacol Ther 2011; 39: 789-803.
25. Sponseller C, Stemder S, Zhu B. Neutral effects of pitavastatin and pravastatin on fasting plasma glucose over 12 weeks in elderly patients with primary hyperlipidemia or mixed dyslipidemia, Poster presented at the 7th World Congress on Prevention of Diabetes and its Complications (WCPD 2012) 2012; 11-14.