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ORIGINAL ARTICLE

Comparison between High-Dose Pitavastatin and Moderate-Dose Pitavastatin combined with Ezetimibe on LDL-C Levels in Type II Diabetics.

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ABSTRACT… Objective: To compare pitavastatin 4 mg (high dose) with pitavastatin 2 mg (moderate dose) and ezetimibe combination on LDL-C in type II diabetics. **Study Design:** Observational study. **Setting:** National Medical Center (NMC) and PNS Shifa Hospital. **Period:** January to June 2022. **Material & Methods:** Fifty diagnosed type II diabetics on metformin, 25 in the monotherapy group (group A) and 25 in the combination therapy group (group B). Glycosylated hemoglobin and lipid profile tests were conducted in labs pre therapy and 3 months post therapy. LDL-C levels were recorded and compared. **Result:** Average LDL-C level drop of 13.51% occurred in the monotherapy group and 17.48% in the combination therapy group. Chi square test showed that LDL-C target levels (< 130 mg/dl) were reached in 33% patients in the monotherapy group and in 64% patients in the combination group. **Conclusion:** Pitavastatin monotherapy and combination therapy both lowered LDL-C levels, however, combination therapy with ezetimibe lowered levels by a greater degree and in a larger number of people.

Key words: Ezetimibe, Hyperlipidemia, LDL-C, Pitavastatin, Type II Diabetes.

INTRODUCTION

Hyperlipidemia is a common comorbidity in patients with type II diabetes mellitus that occurs as a consequence of insulin resistance. When tissues stop responding to insulin, levels of the enzyme lipoprotein lipase drop and the breakdown of lipids in the blood decelerates, thus giving rise to atherosclerosis.[1] In addition, LDL-C receptor generation by the liver is reduced, thereby further raising LDL-C levels in the blood. Center for disease control and prevention labels LDL-C as the 'bad cholesterol' because it makes individuals vulnerable to advanced cardiovascular and cerebrovascular disease that can prove fatal.[2] A national survey was conducted in Pakistan for 1.5 years to determine the prevalence of elevated lipid levels in diabetics. The results showed that 4000 out of 10000 people had elevated LDL-C.[3] LDL-C quantity can rise with or without disrupting measures of other important lipids, namely, triglycerides and HDL-C. Pitavastatin is the most recently introduced member of first line treatment drug class, HMG CoA Reductase inhibitors; it is available in the lowest effective concentrations.

A study has documented that it is well-tolerated at conventional doses with notable side effects in only a few people.[4] Yet another study has reported that bringing down LDL-C by around 39 mg/dl can promote over 20% reduction in the risk of cardiovascular disease, which is a major benefit.[5] Ezetimibe is a lipid absorption inhibitor and acts by preventing intestinal cholesterol from entering the blood stream by blocking the carrier NPC1L1.[5] Im et al also reported that pitavastatin combination with ezetimibe is more effective than monotherapy in reducing the incidence of acute coronary syndrome; however, they used different pitavastatin doses (1-4 mg/day) during the trial to bring down LDL-C levels.[5]

Literature search was performed using Google

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Scholar and the keyphrases, pitavastatin high dose in diabetics, pitavastatin intermediate dose and ezetimibe in diabetics, comparison of pitavastatin high dose with pitavastatin intermediate dose and ezetimibe from 2018 to the current year, but documented studies on high dose pitavastatin and moderate dose pitavastatin with ezetimibe combination in type II diabetics on metformin was not found.The objective of this study was to compare pitavastatin 4 mg (high dose) with pitavastatin 2 mg (moderate dose) and ezetimibe combination on LDL-C in type II diabetics.

MATERIAL & METHODS

This study was conducted at NMC and PNS Shifa hospitals from January 2022 to June 2022. All males and females with type II diabetics and hyper (dys)lipidemia were identified in the given time period. The patients belonged to two groups, A= (Pitavastatin 4 mg OD), B= (Pitavastatin 2 mg OD-Ezetimibe 10 mg OD). The patients were sent to the labs of the respective hospitals for HbA1c and lipid profiles. They were identified as participants if they had diabetes and hyper (dys) lipidemia and were to be maintained on metformin and pitavastatin or metformin pitavastatin and ezetimibe. Their parameters were recorded. The patients were asked by their consultants to attend follow-up after three months. After 3 months of treatment glycosylated hemoglobin and lipid profile tests were re-ordered, parameters were recorded and compared to determine the superior therapy in type II diabetics with high LDL-C levels.

Statistical Analysis

Data was analyzed using SPSS 23. Kolmogorov-Smirnoff test was used to evaluate the normality of distribution. Frequencies and percentages of variables were recorded. McNemar test was used to assess intragroup pre and post therapy results in both clusters. Chi square was used to make overall intergroup comparisons. The p-value was considered statistically significant if < 0.05.

Ethical review was conducted by the institutional review board of Bahria University of Health Sciences Campus Karachi, ERC 85/2021 (21-Dec-2021).

RESULT

Demographics data of the sample is presented in percentages (Table-I). The sample consisted of 50 people, 25 in each group. There were 22 females and 28 males in the sample. The largest proportion of diabetics with high LDL-C were seen in the 36-45 year old group.

Factor	Total Sample	Therapies	
		Pitavastatin (Group A)	Pitavastatin-Ezetimibe (Group B)
Gender			
n	50	25	25
% Male	56	64	48
% Female	44	36	52
Age Group			
n	50	25	25
%25-35	8	12	4
%36-45	40	20	60
%46-55	34	44	24
%56-65	18	24	12

Table-I. Demographics of the sample

The proportion of patients with high and low LDL-C levels before and after treatment in the study clusters are presented in Figure-1. In both groups, there was a drop in the proportion of patients with LDL-C > 130 mg/dl after 3 months of therapy.

Average LDL-C level drop was 13.51% in Pitavastatin 4 mg (group A) and 17.48% in Pitavastatin 2 mg and ezetimibe combination (group B).

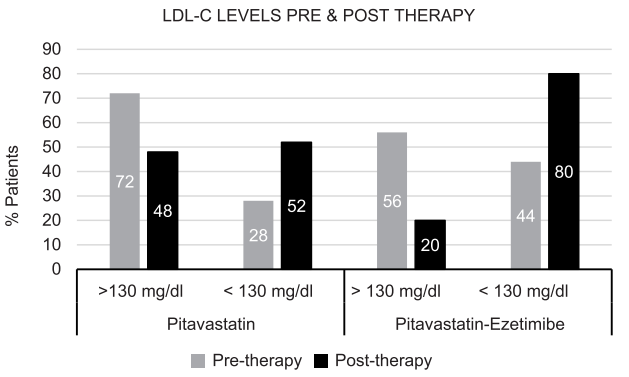

Figure-1. Patient proportions with LDL-C levels

Intragroup comparison was conducted using McNemar's test. Results showed that 7 (28%) patients had > 130 mg/dl LDL-C before therapy and < 130 mg/dl after therapy; 1 (4%) patient had < 130 mg/dl LDL-C level before treatment and > 130 mg/dl after it. The difference was not statistically significant in the proportion of diabetics pre and post therapy in the pitavastatin high dose group with p = .070.

In the pitavastatin moderate dose and ezetimibe group 10 (40%) patients had > 130 mg/dl LDL-C levels before therapy and < 130 mg/dl levels after therapy; 1 (4%) patient had < 130 mg/dl LDL-C level before treatment and > 130 mg/dl after it. The difference was statistically significant in the proportion of diabetics pre and post therapy in the combination group with p = .012. Chi square test was conducted for intergroup comparison of LDL-C levels in diabetics. Difference between the two groups was statistically significant post-therapy, $x^2 = 4.367$, p = 0.037 (Table-II)

	LDL-C Levels	Pitavastatin (n=25)	Pitavastatin & Ezetimibe (n=25)	x^2	P
Pre-therapy	> 130 mg/dl	18	14	1.389	0.239
	< 130 mg/dl	7	11		
Post-therapy	> 130 mg/dl	12	5	4.367	0.037*
	< 130 mg/dl	13	20		

Table-II. Intergroup comparison of LDL-C Levels
*Statistically significant

DISCUSSION

High levels of cholesterol in type II diabetics can cause advanced systemic diseases, as well as aggravation of insulin resistance. LDL-C levels are extremely important in diabetics, as lipolysis in the blood is reduced because of insulin resistance. Therefore, it is important to compare efficacies of different drugs and combinations to manage hyperlipidemia. In this study, Pitavastatin high dose was compared with Pitavastatin moderate dose and ezetimibe to assess which therapy lowers LDL-C levels in most type II diabetics. The results showed that pitavastatin moderate dose and ezetimibe combination lowered LDL-C in a larger proportion of patients and the results were statistically significant.

Pitavastatin acts by disrupting cholesterol synthesis through inhibition of HMG CoA Reductase.[6,7] Whereas ezetimibe blocks the NPC1L1 protein from transporting cholesterol into the circulation.[8] Combination adjusts LDL-C metabolism efficiently because it blocks cholesterol synthesis and removes large lipid molecules from the blood. Pitavastatin blocks HMG CoA Reductase and inhibits cholesterol production, whereas ezetimibe keeps intestinal cholesterol from entering the bloodstream by blocking NPCILI transporter; the cholesterol remains in the digestive system and is expelled. According to Barter (2018), increasing the dosage, switching members of the same class or using other anti-hyperlipidemic drugs in combination can further lower LDL-C levels.[9] He compared efficacy rate of pitavastatin in the Japanese REAL CAD trial with statin trials in Caucasians and concluded that high dose of pitavastatin is beneficial in patients with a high risk of atherosclerotic cardiovascular disease.[9] Miao et al (2019) conducted meta-analysis of eight studies to assess the efficacy of five statins of differing doses, including pitavastatin on the incidence of cardiovascular and cerebrovascular disease. The comparison was done for statin monotherapy and combination with ezetimibe in type II diabetics. They concluded that statins combined with ezetimibe produced better results compared to monotherapy.[10] A group of researchers from Japan investigated the effects of pitavastatin monotherapy and pitavastatin combination therapy with ezetimibe in individuals with ST segment elevation myocardial infarction. They enrolled over 1700 patients to conduct a case control study and discovered that pitavastatin-ezetimibe combination proved much better than pitavastatin monotherapy.[11] Jeong et al (2022) conducted a phase III trial on Korean men and women to discover whether pitavastatin monotherapy or its combination with ezetimibe reduced lipid levels in patients with primary

hypercholesterolemia. Moderate and high doses of the statin were compared in combination with ezetimibe. They found that the combination therapies reduced LDL-C levels more than 50% in the enrolled patients.[12] In the present study, average LDL-C drop was 13.51% in the high dose pitavastatin group and 17.48% in the moderate dose and ezetimibe combination group after 3 months of therapy. The limitations of this study include a restricted time frame and therefore, inability to record the effects of different durations of therapies, on LDL-C levels, past 3 months. There was lack of relevant literature discussing the effects of pitavastatin and its combination with ezetimibe on LDL-C levels and on comparison of pitavastatin dosages in type II diabetics on metformin.

CONCLUSION

Combination therapy of moderate dose pitavastatin and ezetimibe proved beneficial in reducing LDL-C by a greater percentage and in a larger proportion of type II diabetics on metformin compared to high dose Pitavastatin.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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1	Ghazal Raza	Concept, Data acquisition, analysis & interpretation, Manuscript drafting, Final approval, Accountable for work.	
2	Talea Hoor	Concept, Revision, Final approval, Accountable for work.	
3	M. Kamran Yusuf	Concept, Revision, Final approval, Accountable for work.