Original Article

Therapies to Reduce Cholesterol and Glucose in Diabetics

Comparison of Therapies to Reduce Total Cholesterol and Glucose Levels in Type II Diabetics

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ABSTRACT

Objective: To compare the effectiveness of high dose pitavastatin and intermediate dose pitavastatin combined with ezetimibe in lowering total cholesterol (TC) in diabetic patients on metformin. Secondary endpoint is to compare glycosylated hemoglobin (HbA1c) levels after therapy.

Study Design: Observational / comparative study

Place and Duration of Study: This study was conducted at the NMC and PNS Shifa Hospitals from January 2022 to June 2022.

Materials and Methods: Patients diagnosed according to international guidelines were included in the study. Consultation was conducted by physicians; glycosylated hemoglobin and lipid tests were performed in pathology labs of the above-mentioned hospitals before and after intervention.

Results: Sample of 50 individuals was divided into two groups of 25 patients. HbA1c and TC levels were assessed before and after 3 months of therapy. TC was significantly higher in group A compared to group B after treatment ($U = 172.5$, $p = 0.006$). Mean TC after therapy dropped to 73.7±18 mg/dl, a change of 64.9% in group A and to 60.7±15.6 mg/dl, a 67.83% change in group B. HbA1c was marginally higher in group B compared to group A after therapy ($U = 311$, $p = 0.981$).

Conclusion: Metformin-pitavastatin (2 mg)-ezetimibe lowered TC levels significantly in type II diabetics compared to metformin-pitavastatin (4 mg) group. HbA1c dropped considerably in both groups, but the difference was not statistically significant.

Key Words: pitavastatin, ezetimibe, total cholesterol, type II diabetes, glycosylated hemoglobin, metformin.

Citation of article: Raza G, Jaffri MSA, Zehra S. Comparison of Therapies to Reduce Total Cholesterol and Glucose Levels in Type II Diabetics. Med Forum 2023;34(8):11-14 .doi:10.60110/medforum.340803.

INTRODUCTION

Dyslipidemia is a common comorbidity in type II diabetics. Elevated lipids lead to systemic diseases that can be fatal in the long run; most notable of these are cardiometabolic pathologies, comprising 32% cardiovascular diseases[1] and around 80% metabolic disorders[2.] Since dyslipidemia can exacerbate insulin resistance as well, it is important to monitor the incidence of advanced disease. Total cholesterol levels among other parameters are used to assess the risk of cardiometabolic disease in dyslipidemic patients.

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Received: January, 2023
Accepted: May, 2023
Printed: August, 2023

Levels of > 200 mg/dl place the patient at risk of systemic diseases. Cholesterol levels are considered normal at < 200 mg/dl, borderline high between 200-239 mg/dl and high at or above 240 mg/dl. Drugs such as statins have been credited with lowering lipid levels, however, dose, severity, length of intervention, compliance and lifestyle changes can impact occurrence and recurrence of dyslipidemia. It is important to assess whether these first line therapies can impact future cardio-metabolic markers, such as total cholesterol in diabetics with dyslipidemia. Zhang et al (2021) reported that metformin affects lipid levels by inhibiting the production of sterol regulatory element binding protein and inducing a positive effect on the synthesis of LDL receptors[3.] Another effect that metformin can induce is through the activation of AMP kinase that is a major regulator of blood glucose and lipid levels, however, the actual way that it accomplishes this is still not known[4,5]. Whereas, HMG CoA reductase inhibitors apply a straightforward effect for reduction of cholesterol through inhibition of conversion of mavelonic acid to cholesterol[6]. Pitavastatin is a comparatively recent statin that has shown a marked reduction in lipid levels at lower doses and fewer side effects compared to older, more commonly prescribed statins. Moroi et al (2020) compared atorvastatin and pitavastatin in hypercholestrolemic patients and stated

that no differences were observed in lipid profiles and side effects at 10mg and 2mg doses respectively, however, pitavastatin had a more profound effect on the incidence of cardiovascular disease. Ezetimibe is a lipid absorption inhibitor that acts by blocking Neiman Pik C1 Like 1 protein, a transporter that carries cholesterol from the intestine into the blood stream to be metabolized; however, it is only used in combination therapy[7]. A review by Miao et al (2019) reported eight studies showed that the statin-ezetimibe combination lowered the incidence of cardiovascular and cerebrovascular disease by lowering cholesterol levels to a greater extent in type II diabetics compared to statin monotherapy, however, the studies included different statins as well as pitavastatin and different doses including low, intermediate and high doses of all the statins[8]. Lee (2020) investigated combination of pitavastatin 2 mg and 4 mg on the Korean population with impaired fasting glucose and reported that the reduction of total cholesterol was higher in the high dose group[9]. The objective of this study is to compare the effectiveness of high dose pitavastatin and intermediate dose pitavastatin combined with ezetimibe in lowering TC levels in type II diabetics on metformin. The secondary endpoint is to compare HbA1c levels after therapy.

MATERIALS AND METHODS

This article is based on data collected for a clinical trial. The investigation was conducted between January 2022 and June 2022. The patients were grouped as follows: A= Metformin-Pitavastatin 4 mg B= Metformin-Pitavastatin 2 mg-Ezetimibe. Blood tests were conducted in PNS Shifa hospital, NMC pathology labs and parameters were recorded. Lab parameters included glycosylated hemoglobin (HbA1c), total cholesterol (TC). Data was collected at initial visit and at three months follow-up. Drug effects on TC levels were compared in patients with history of type II diabetes and dyslipidemia on metformin. Patients were diagnosed according to International Diabetes Federation (IDF) guidelines for type II diabetes, HbA1C levels > 6.4% and American Heart Association (AHA) guidelines for dyslipidemia, total cholesterol (TC) ≥ 200 mg/dl, Low-density lipoprotein (LDL-C) ≥130 mg/dl, high-density lipoprotein cholesterol (HDL-C) <40 mg/dl, or triglyceride ≥150 mg/dl or being under treatment with statins. AHA guide (2018) also states that adults with diabetes should be started on intermediate dose statins and as the risk of heart disease increases, the dose of statins should also be increased[11]. The subjects included males and females, aged 25-65 years who signed consent forms. The settings of the study included Internal Medicine Departments of NMC hospital and PNS Shifa hospital. The patients were educated about the importance of the study and were asked to sign consent forms; those who did were included in the study. Excluded patients had systemic comorbidities, were pregnant and lactating, on oral hypoglycemic medicines except metformin, taking insulin, older than 65 years, taking calcium channel blockers, thyroxine or antibiotics, as these drugs are likely to interact with pitavastatin. Ethical review was conducted by the institutional ethical review committee; approval letter no: ERC 85/2021. Drug doses included Metformin 500 mg BD, Pitavastatin 4 mg OD, Pitavastatin 2 mg OD and Ezetimibe 10 mg OD.

Statistical Analysis: Data is examined using SPSS version 23. Normality of distribution is assessed through Kolmigrov Smirnoff test. Descriptive statistics are reported as frequencies (%) and mean ± standard deviation. The intragroup evaluation of efficacy is conducted through Wilcoxon Signed Rank test. Intergroup comparison is assessed by Mann Whitney U test. The p-value is considered statistically significant at < 0.05.

RESULTS

Table 1 shows lab and demographic data. The sample consisted of 50 people, 25 in each group. The largest proportion of diabetics with high total cholesterol were seen in the 46-55 year cluster.

Table No. 1: Demographic and lab characteristics of the sample

Factor	Therapies	
	Metformin-Pitavastatin (n=25)	**Metformin-Pitavastatin-Ezetimibe (n=25)**
Gender		
	25	25
n (%) Male	16(64)	12(48)
n (%) Female	9(36)	13(52)
Age (years)	48.92 ± 8.96	46 ± 7.71
HbA1c (%)	7.93±2.26	8.08±1.77
TC (mg/dl)	209.98±71.93	188.71±43.7

Table No. 2: Wilcoxon Signed Rank Test for group A.

Param-eters	Pre-therapy		Post-therapy		Ties
	N (%)	**Mean Ranks**	**N (%)**	**Mean Ranks**	**N (%)**
TC	3(12)	9.67	21(84)	12.90	1(4)
HbA1c	3(12)	6.33	20(80)	12.85	2(8)

In 3 people, TC was high after treatment and low before treatment. In 21 people, TC dropped after therapy. In 1 patient TC did not change after treatment ($z = -3.457$, $p = 0.001$).

In 3 people, HbA1c was high after therapy and low before therapy. In 20 people, HbA1c dropped after therapy. In 2 patients HbA1c did not change after treatment ($z= -3.628$, $p < 0.001$).

Table No. 3: Wilcoxon Signed Rank Test for group B.

Param-eters	Pre-therapy		Post-therapy		Ties
	N (%)	Mean Ranks	N (%)	Mean Ranks	N (%)
TC	1(4)	10.00	24(96)	13.13	0(0)
HbA1c	5(20)	8.50	19(76)	13.55	1(4)

In 1 patient, TC was high after treatment and low before treatment. In 24 people, TC dropped after therapy. There were no ties after treatment in this group ($z = -4.103$, $p < 0.001$).

In 5 people, HbA1c was high after therapy and low before therapy. In 19 people, HbA1c dropped after therapy. In 1 patient HbA1c did not change after treatment ($z= -3.072$, $p = 0.002$).

Table No. 4: Mann Whitney U test

	Parameters	Group	Mean Rank	Sum of Ranks
Post-therapy	TC	A	31.10	777.50
		B	19.90	497.50
	HbA1c	A	25.44	636.00
		B	25.56	639.00

Table 4 shows that mean TC after therapy dropped to 73.7±18 mg/dl, a change of 64.9% in group A and to 60.7±15.6 mg/dl, a 67.83% change in group B. HbA1c was marginally higher in group B compared to group A after therapy ($U = 311$, $p = 0.981$). TC was significantly higher in group A compared to group B after treatment ($U = 172.5$, $p = 0.006$).

DISCUSSION

Metabolic diseases, such as type II diabetes can lead to a myriad of health issues, including dyslipidemia that cause conditions of the heart, liver and kidneys. Therefore, researchers should keep investigating useful combinations of drugs in this group. Total cholesterol levels are used to predict the occurrence of cardiometabolic issues and the present study has utilized this parameter along with glycosylated hemoglobin to assess the efficacy of therapies in patients with diabetes and dyslipidemia.

The present study showed that metformin-pitavastatin (4mg) combination reduced TC in a considerable proportion of type II diabetics. Metformin-pitavastatin (2mg)-ezetimibe combination lowered TC levels in a higher percentage of the sample. Both therapies brought about change and lowered the risk of cardiometabolic disease in a significant number of patients, with the metformin-pitavastatin (2mg)-ezetimibe group displaying more positive results and the intergroup difference between the therapies was statistically significant. Both combinations also reduced HbA1c significantly, however neither of the combinations was superior to the other in case of blood glucose levels.

A double blind, multi-center trial was conducted in Japan that included division of 293 people with high cholesterol levels into four groups; one group was given 2 mg pitavastatin, the second group was given 4 mg pitavastatin, the third group was given 2 mg pitavastatin and 10 mg ezetimibe and the fourth group was given 4 mg pitavastatin and 10 mg ezetimibe. The drugs were taken once daily by the groups for three months. The investigators concluded that combination therapies lowered TC and other lipid parameters extensively as compared to groups that were prescribed only pitavastatin[10]. Similar results were seen in our study. Sahebkar et al (2021) conducted a review of the effects of pitavastatin on patients with hypercholesterolemia and concluded that pitavastatin is the safest statin that lowers total cholesterol and triglycerides considerably and has few side effects[11] as was discovered in our study. A cross over trial conducted in Pakistan included 103 patients with diabetes type II and hypercholesterolemia. All patients were treated with atorvastatin for three months, then 52 were switched to pitavastatin and the rest were continued on atorvastatin. This study showed that 2 mg pitavastatin lowered HbA1c significantly compared to 10 mg atorvastatin, however TC dropped to almost the same extent in both groups[12]. Our study showed significant reductions in HbA1c and TC in both groups. Cai et al (2023) conducted a review of nine clinical trials that included 2586 patients with coronary heart disease. Lipid profiles were assessed after combination therapy with pitavastatin and ezetimibe. Results showed TC with standard mean difference of -0.84 95% CI (−1.10 to −0.59) and lowering of other lipid parameters as well[13]. Mandumpal et al (2021) reported that metformin may be beneficial in dyslipidemics on statins because these drugs can induce dose dependent new onset diabetes mellitus in Asians, the elderly and individuals with a type II diabetes family history. The mechanisms behind this benefit involve promotion of apoptosis and inflammation control[14]. However, Jeong et al (2019) discovered that the occurrence of new onset diabetes mellitus (NODM) did not depend on pitavastatin dose; the incidence of NODM was low and similar between doses[15]. This study showed reduction of blood glucose levels in a large proportion of patients, however a very small number showed higher levels of HbA1c after therapy in both groups. A Korean study compared high and intermediate dose pitavastatin in patients with impaired fasting glucose and hypercholesterolemia. They reported that high dose pitavastatin brought down total cholesterol by a greater margin than 2mg pitavastatin. They concluded that over 10% of patients in 4 mg pitavastatin group and around 14% people in the 2 mg group developed NODM within one year of the study. Mustafa et al (2018) did not find a statistically significant difference when they compared the effects of metformin and its combination with statins on lipid and glycemic indices. They also reported improved conditions in both groups of overweight patients with type II diabetes mellitus in line

with this study. A review of 47 studies concluded that each time pitavastatin dose was doubled, it reduced TC by a greater percentage than before[16]. Further research should be conducted on this issue with other oral hypoglycemic drugs.

In conclusion, the proportion of patients that benefited from the therapies was statistically significant in both groups. However, combination of metformin-pitavastatin 2 mg-ezetimibe showed much lower TC levels in almost all patients after 3 months of therapy.

CONCLUSION

Metformin-pitavastatin (2mg)-ezetimibe lowered TC levels significantly in type II diabetics compared to metformin-pitavastatin (4mg) group. HbA1c dropped considerably in both groups, but the difference was not statistically significant.

Author's Contribution:

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Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovasc Diabetol 2018;17(1).
2. Zerga AA, Bezabih AM. Metabolic syndrome and lifestyle factors among type 2 diabetes mellitus patients in Dessie Referral Hospital, Amhara region, Ethiopia. PLoS One 2020;15(11): e0241432.
3. Zhang Y, Wang H, Xiao H. Metformin actions on the liver: Protection mechanisms emerging in hepatocytes and immune cells against NASH-related HCC. Int J Mol Sci 2021;22(9):5016.
4. Lin SH, Cheng PC, Tu ST, Hsu SR, Cheng YC, Liu YH. Effect of metformin monotherapy on serum lipid profile in statin-naïve individuals with newly diagnosed type 2 diabetes mellitus: a cohort study. Peer J 2018;6(e4578): e4578.
5. 6.Bu Y, Peng M, Tang X, Xu X, Wu Y, Chen AF, et al. Protective effects of metformin in various cardiovascular diseases: Clinical evidence and AMPK-dependent mechanisms. J Cell Mol Med 2022;26(19):4886–903.
6. Maltês S, Lopes LR. Novas perspetivas no tratamento farmacológico da miocardiopatia hipertrófica. Rev Port Cardiol (Engl Ed) 2020;39(2):99–109.
7. Moroi M, Nagayama D, Hara F, Saiki A, Shimizu K, Takahashi M, et al. Outcome of pitavastatin versus atorvastatin therapy in patients with hypercholesterolemia at high risk for atherosclerotic cardiovascular disease. Int J Cardiol 2020;305:139–46.
8. Miao XY, Liu HZ, Jin MM, Sun BR, Tian H, Li J, et al. A comparative meta-analysis of the efficacy of statin-ezetimibe co-therapy versus statin monotherapy in reducing cardiovascular and cerebrovascular adverse events in patients with type 2 diabetes mellitus. Eur Rev Med Pharmacol Sci 2019;23(5):2302–10.
9. Lee HY, Han KH, Chung WB, Her SH, Park TH, Rha SW, et al. Safety and efficacy of pitavastatin in patients with impaired fasting glucose and hyperlipidemia: A randomized, open-labeled, multicentered, phase IV study. Clin Ther 2020;42(10):2036–48.
10. Tsujita K, Yokote K, Ako J, Tanigawa R, Tajima S, Suganami H, et al. Efficacy and safety of pitavastatin/ezetimibe fixed-dose combination vs. Pitavastatin: Phase III, double-blind, randomized controlled trial. J Atheroscler Thromb 2023; advpub:64006.
11. Sahebkar A, Kiaie N, Gorabi AM, Mannarino MR, Bianconi V, Jamialahmadi T, et al. A comprehensive review on the lipid and pleiotropic effects of pitavastatin. Prog Lipid Res 2021;84(101127):101127.
12. Abbas S, Khan MN, Samore NA, Abbas H, Khan RP. 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. Pak Armed Force Med J 2019;69:S91-6.
13. Cai R, Chang C, Zhong X, Su Q. Lowering of blood lipid levels with a combination of pitavastatin and ezetimibe in patients with coronary heart disease: A meta-analysis. Cardiovasc Innov Appl 2023;7(1). http://dx.doi.org/10.15212/cvia.2023.0004
14. Mandumpal Chacko S, Thambi Thekkekara P. Combined effect of metformin and statin. In: Akhtar J, Ahmad U, Badruddeen, Khan MI, editors. Metformin - Pharmacology and Drug Interactions. London, England: Intech Open; 2021.
15. Jeong HS, Hong SJ, Son S, An H, Kook H, Joo HJ, et al. Incidence of new-onset diabetes with 1 mg versus 4 mg pitavastatin in patients at high risk of developing diabetes during a 3-year follow-up. Cardiovasc Diabetol 2019;18(1):162.
16. Adams SP, Alaeiilkhchi N, Wright JM. Pitavastatin for lowering lipids. Cochrane Database Syst Rev 2020;6(7):CD012735.