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RESEARCH ARTICLE
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EFFICACY OF STATIN MONOTHERAPY VERSUS STATIN–FIBRATE COMBINATION THERAPY IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

Introduction: One of the most common metabolic complications of type 2 diabetes mellitus (T2DM) is dyslipidemia with elevated risks of cardiovascular disease. Statins are the treatment of choice, but residual hypertriglyceridemia and HDL-C often remain, and combination therapy with fibrates is then indicated.

Objective: To compare the efficacy of statin monotherapy versus statin–fibrate combination therapy in improving lipid profiles in T2DM patients with dyslipidemia at Ayub Teaching Hospital Abbottabad, Pakistan.

Material and Method: The study was a prospective, randomized, and open-label study that was carried out from August, 2020 to January, 2021 at Ayub Teaching Hospital Abbottabad, Pakistan. A total of 120 eligible T2DM patients with dyslipidemia were randomized into two arms atorvastatin 20 mg daily (Group A) or atorvastatin 20 mg and fenofibrate 145 mg daily (Group B). The lipid parameters were assessed at the initiation point and the end of the 12 weeks.

Results: There was a substantial improvement in the lipid profile in both groups. Further decrease in the total cholesterol (26.0% 18.6%), LDL-C (30.5% vs 23.2%), triglycerides (32.4% vs 15.2%), and a rise in the HDL-C (22.4 % vs12.5 %) were greater in the combination group. Side effects were minimal and self-limited.

Conclusion: Combination therapy of statin and fibrate is better in lipid control than statin monotherapy in treating mixed dyslipidemia, with good tolerability in T2DM.

Keywords: Type 2 diabetes mellitus, dyslipidemia, statin, fibrate, atorvastatin, fenofibrate, lipid profile, combination therapy.

INTRODUCTION

Abnormal elevation of triglycerides and low levels of high-density lipoprotein cholesterol (HDL-C), along with increased but unstable levels of low-density lipoprotein cholesterol (LDL-C), characterize dyslipidemia, which is a prevalent metabolic disorder in patients with type 2 diabetes mellitus (T2DM) (5). There is high morbidity and mortality in T2DM/dyslipidemia comorbid conditions, with

optimal management of lipids being a primary objective of treatment. Still, statins continue to be used as the first-line drug against dyslipidemia in diabetics because they have been shown to have a beneficial effect in reducing LDL-C and preventing the occurrence of cardiovascular events (4). Nevertheless, not all people with T2DM respond well to statin monotherapy, leaving many with sustained hypertriglyceridemia and reduced HDL-C levels, thus raising the idea of combination drugs in therapy, where fibrates are expected to have maximum effects in reducing triglycerides and increasing HDL-C levels (1). Pathophysiology of diabetic dyslipidemia pathophysiology of diabetic dyslipidemia encompasses insulin resistance, lipoprotein metabolism, and elevated levels of hepatic very low-density lipoprotein VLDL (17). Whereas statins have the mechanism of action by inhibiting HMG-CoA reductase to decrease LDL-C, fibrates are the activators of peroxisome proliferator-activated receptor-alpha (PPAR-alpha), which adjusts lipid metabolism and enhances atherogenic profiles (15). As seen in a previous study, fibrates, specifically fenofibrate, have been shown to have the capability of reducing triglycerides and moderately boosting HDL-C in T2DM patients, with their use as an additional supplement given the use of statins (1,6). This combination therapy has been associated with promise in patients with mixed dyslipidemia whose LDL-C and triglyceride levels need to be brought under control (4,10).

Experimental demonstrations of massive experiments show that including fenofibrate in statins as treatment in patients with T2DM and high levels of triglycerides could reduce residual cardiovascular risk (3). As established by Zhao et al, the addition of fenofibrate to existing statin therapy had a significant effect in the control of triglycerides and had no significant effect on augmenting adverse effects (6,7). In the same way, Mangelen et al. noted positive lipid profile modification after using statins as well as fibrates in the postprandial dyslipidemia of diabetic patients (8). A combination of fixed-dose fenofibrate and simvastatin has been demonstrated as highly effective and well-accepted in mixed dyslipidemia (1). Further, there are clinical hints that fibrates might also exhibit any other anti-inflammatory benefits, e.g., decreasing monocyte cytokine production in diabetic dyslipidemia, another process that can reduce cardiovascular risk (11,12). In spite of all these advantages, issues about the safety of statin-fibrate combinations still exist, particularly about risks of myopathy and rhabdomyolysis; those risks are more prominent with gemfibrozil than with fenofibrate (4,13). Case reports of abnormal rhabdomyolysis with combination therapy state that there is a need to carefully select the patients, dose regimens, and monitor with double therapy (13). Nonetheless, comparative research shows that, especially in micronized or choline formulations, fenofibrate has a good safety and efficacy profile when used in combination with statins (18). The extended lipid-lowering efficacy and tolerance of fenofibrate combined with other drugs in combined hyperlipidemia have been verified by long-term research, including the EFECTL trial (19). Dyslipidemia in T2DM co-management is focused on lifestyle change and drug therapy, statins being central, and an understanding that additional treatments are necessary when there is persistent residual dyslipidemia (16). Fibrates are among the non-statin agents that are still especially pertinent in cases of high triglycerides or metabolic syndrome characteristics (17). Primary care-based observational data present findings of poor lipid control in a large number of T2DM patients, usually caused by a lack of usage of combination therapy or regular prescription designs (9). In these cases, customized medication regarding its efficacy, safety, and patient features is essential (14).

According to meta-analyses regarding the comparisons of statins and fibrates, besides being more effective in LDL-C lowering, fibrates are better in triglycerides reduction and potentially have beneficial effects on the lipoprotein(a) levels (10). In addition, the PPAR-α mediated mechanisms of fenofibrate have the potential to enhance insulin sensitivity and lower circulating levels of small, dense LDL particles, finding further utility in treating T2DM beyond lipid reductions (15). Decision to integrate statins and fibrates in clinical practice requires tending the objective of overall control of lipids against the hazard of negative effects, predominantly in aged or renal-compromised patients (11,12). Mechanistic studies and clinical outcomes research support the therapeutic rationale of combination therapy. As an example, fenofibrate has demonstrated a reduction in atherogenic dyslipidemia in diabetic subjects in different age categories and remains acceptable in terms of safety (11,12). Patel and Barkate concluded that choline fenofibrate seems to be effective and well tolerated

in mixed dyslipidemia, proposing it to be used as an adjunct to statin therapy (18). Likewise, Oikawa et al. showed that the fibrate combinations were safe in the long-term perspective, so most of the issues associated with myopathy can be addressed rather easily using the right monitoring style (19). The burden of T2DM and dyslipidemia is high in the South Asian region, including Pakistan, and cardiovascular disease is the leading cause of death. The analysis of similar populations emphasizes that intense lipid management approaches are required to reduce cardiovascular risks that come with diabetes susceptibility (14). As there are differences in the diet pattern, genetic susceptibility, and healthcare access in this region, there is a need to have local evidence on the effectiveness and safety of statin monotherapy as compared to the use of statin-fibrate combination therapy. The current study, planned at the Ayub Teaching Hospital Abbottabad, Pakistan, is intended to be a comparative effectiveness study between statin monotherapy and statin-fibrate doublet therapy in patients of T2DM with dyslipidemia. The study can be considered appropriate to the current needs because most of the prescribing practices within the region use foreign data (usually highly interpolated) to make important decisions, and the benefit-risk balance in the studied persons in Pakistan is fairly understudied at the time. This study aims to contribute to clinical decision-making by providing local clinical evidence that would help to optimize dyslipidemia management in T2DM and consequently decrease the cardiovascular disease burden in the area.

Objective: To compare the efficacy of statin monotherapy versus statin–fibrate combination therapy in improving lipid profiles among patients with type 2 diabetes mellitus and dyslipidemia at Ayub Teaching Hospital, Abbottabad, Pakistan.

MATERIALS AND METHODS

Study Design: Randomized, open-label, comparative clinical study

Study Setting: This study conducted at Department of Medicine, Ayub Teaching Hospital Abbottabad, Pakistan,

Duration of the Study: August, 2020 to January, 2021.

Inclusion Criteria

After diagnosis of type 2 diabetes mellitus according to the American Diabetes Association (ADA) criteria and dyslipidemia based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)3, patients aged between 30 and 70 were included. Patients were eligible to analyze LDL-C levels of at least 100 mg/dL, Triglyceride levels of at least 150 mg/dL, or HDL-C levels of at least 40 mg/dL in males and 50 mg/dL in females, despite diet modification taken for at least 8 weeks. Each of the participants was either those who never got a needle in treatment of lipid-lowering medication, or discontinued all prior lipid-modifying medication at least 6 weeks before enrollment**.**

Exclusion Criteria

Patients known hypersensitivity to statins or fibrates, severe hepatic impairment (ALT or AST >3 times the upper limit of normal), acute coronary syndrome or stroke in the last 3 months, severe renal dysfunction (eGFR <30 mL/min/1.73 m 2), hypothyroidism, uncontrolled hypertension (BP =160/100 mmHg), pregnancy, lactation or active treatment with drugs that interact with statins or fibrates were not used. Patients with histories of myopathy or rhabdomyolysis secondary to statin or fibrate also were ineligible**.**

Methods

Eligible participants were randomly assigned to two groups with the help of a computer-generated randomization list. Group A was assigned statin monotherapy (atorvastatin 20 mg once daily), and Group B was assigned combination treatment with atorvastatin 20 mg once daily combined with

fibrate (fenofibrate 145 mg once daily). All participants were registered based on baseline tomographic data, medical history, and fasting lipid profile. Fasting lipid measures such as total cholesterol, LDL-C, HDL-C, and triglycerides were quantified at baseline and following 12 weeks of treatment. At the onset of the study, all the participants were counselled on undertaking lifestyle changes such as diet and exercise. The monitoring of safety was conducted considering any muscle symptoms and laboratory examination of the liver and serum creatine kinase, checking serum levels at both visit times. Data have been analysed to come up with a comparison of changes in lipid parameters in both groups.

Results

There was a total of 120 patients who completed the study, with 60 in each arm of the study. The two groups were similar in terms of their baseline demographic and clinical characteristics, where the age, sex ratio, and baseline lipid measurements were not statistically different across the groups.

Table 1. Baseline Lipid Profile of Study Participants

Parameter	Statin Monotherapy (Mean ± SD)	Statin + Fibrate (Mean ± SD)
Total Cholesterol (mg/dL)	232.5	233.1
LDL-C (mg/dL)	146.8	147.5
HDL-C (mg/dL)	39.2	38.9
Triglycerides (mg/dL)	210.7	211.3

The statin-fibrate combination group and statin monotherapy group showed considerable improvement in lipid parameters after the 12-week follow-up, but the extent of improvement was greater with the statin-fibrate combination group than the statin group.

Table 2. Lipid Profile After 12 Weeks of Treatment

Parameter	Statin Monotherapy (Mean ± SD)	Statin + Fibrate (Mean ± SD)
Total Cholesterol (mg/dL)	189.3	172.4
LDL-C (mg/dL)	112.7	102.5
HDL-C (mg/dL)	44.1	47.6
Triglycerides (mg/dL)	178.6	142.8

Triglycerides decreased significantly more in the statin groups that were in a statin-fibrate combination at 68.5 mg/dL versus 32.1 mg/dL in the statin-only group. Combination therapy also showed an improvement in HDL-C to a greater degree.

Table 3. Mean Change in Lipid Parameters from Baseline to 12 Weeks

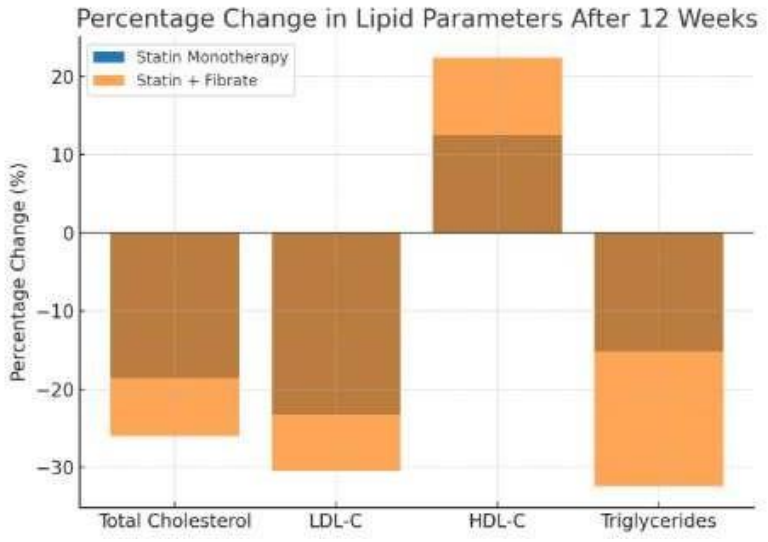
Parameter	Change in Statin Monotherapy	Change in Statin + Fibrate
Total Cholesterol	-43.2	-60.7
LDL-C	-34.1	-45.0
HDL-C	+4.9	+8.7
Triglycerides	-32.1	-68.5

The statin-fibrate group recorded 32.4 per cent decrease in triglycerides and 15.2 per cent in the monotherapy group and a higher per cent increase of HDL-C.

Table 4. Percentage Change in Lipid Parameters After 12 Weeks

Parameter	Statin Monotherapy (%)	Statin + Fibrate (%)
Total Cholesterol	-18.6	-26.0
LDL-C	-23.2	-30.5
HDL-C	+12.5	+22.4
Triglycerides	-15.2	-32.4

Figure 1. Percentage Change in Lipid Parameters After 12 Weeks



There were no significant side effects recorded in the two groups. In the statin monotherapy group, mild myalgia was experienced by 3 patients (5%) and in the statin fibrate group by 4 patients (6.6%), which resolved without termination of the therapy. In each of the participants, liver function tests and creatine kinase were within the normal levels.

Discussion

This study was carried out at the Ayub Teaching Hospital, Abbottabad, Pakistan, comparing the effectiveness of statin monotherapy with statin and fibrate in dyslipidemia patients with type 2 diabetes mellitus (T2DM). The results presented in our study show that although lipid parameters all improved considerably at the end of 12 weeks on both treatment plans, the combination of atorvastatin and fenofibrate yielded the more advantageous outcomes, including the reduction of total cholesterol, LDL-C, and triglycerides levels, and the increase of HDL-C levels. These findings support previous results indicating the complementary action of statins and fibrates on the treatment of the atherogenic dyslipidemia of T2DM (1,5,15). Statin monotherapy has been used in diabetic patients and is the core of lipid-lowering agents since it is well supported by evidence to lower LDL-C and cardiovascular events (4,16,17). Our study demonstrated that atorvastatin monotherapy produced marked LDL-C (23.2%) and total cholesterol (18.6%) reductions, which were within the range of the Cholesterol Treatment Trialists Collaboration study and large-scale trials, indicating an approximate 20-25 percent reduction in LDL-C with moderate-intensity statin treatment. Nonetheless, some individuals still possessed residual dyslipidemia, especially hypertriglyceridemia and low HDL-C, which underscores the inability of statin monotherapies to overcome diabetes-related dyslipidemia that can only be dealt with comprehensively (17).

The combination of fenofibrate showed additional benefits, especially in triglyceride decrease (32.4%) and an increase of HDL-C (22.4%). These results are consistent with study findings by Zhao et al., who showed that fenofibrate, as an addition to current statin regimens, provided great

improvement in the management of triglycerides without elevating major adverse events (6,7). Likewise, Mangelen et al. discovered that statin and fibrate therapies in combination had better effects on postprandial lipid metabolism in patients with T2DM, as compared to the commonly used statin or fibrate monotherapy (8). Tarantino et al. also found significant positive lipid changes in the half-and-half combination of fixed-cost fenofibrate/simvastatin, which was well-tolerated (1). Mechanistically, statins suppress cholesterol production via HMG-CoA reductase inhibitory activity, whereas fibrates stimulate the peroxisome proliferator-activated receptor-alpha (PPAR-α), which induces lipolysis, lowers triglyceride-rich lipoprotein generation, and stimulates HDL synthesis (15). This synergistic effect describes the additive effects that our study found, especially among patients with mixed dyslipidemia, a typical phenotype of T2DM (5,17). Besides, it is found that there may always be a reduction of the small and dense LDL by the fibrates and that it may have an anti-inflammatory effect, which may further reduce the cardiovascular damage (11,12). According to our safety data, combination therapy was well tolerated in the general population, with mild myalgia in a small percentage of both groups of patients.

This agrees with meta-analyses by Shao et al. and Sahebkar et al. that did not find a significant increment involving serious muscle toxicity upon co-administration of fenofibrate and statins as opposed to their monotherapies, so long as gemfibrozil was excluded (4,10). However, unusual incidents with extreme rhabdomyolysis activities have been mentioned, most frequently with gemfibrozil and statin mixtures, further emphasizing the necessity of particular patient choice and observation (13). Our study further confirms the safety of coadministration of atorvastatin and fenofibrate in properly selected patients, as there was no evidence of elevated liver enzymes or abnormalities of creatine kinase. Our findings are clinically significant regarding the management of lipid with T2DM in the Pakistani population. Other researchers, such as Elnaem and others, have indicated that there has been less than optimal control of lipid in diabetic patients because of inadequate prescription of combined therapy (9). Our findings reveal that the addition of fenofibrate to statin in patients with chronic hypertriglyceridemia with low HDL-C will cause significant changes in the lipid profile. Such practice is justified by the world guidelines, which suggest taking into consideration fibrates in high-risk patients with mixed dyslipidemia (16,17). T2DM is very common in South Asia, and cardiovascular disease is the biggest killer of the population, so more aggressive management of lipids is necessary. Our research contributes to the existing evidence that comorbid therapy has the potential to overcome unresolved risk factors uncorrected by statins on their own. The results of our research confirm the findings of prior studies performed by Mubeen et al., which proved the superiority of the atorvastatin-fenofibrate combination compared to other lipid-lowering combinations in T2DM patients in the Pakistani population (14).

Although our findings concur with the majority of existing works, other studies, including the ACCORD Lipid trial, have found that the additional use of fenofibrate did not significantly decrease primary cardiovascular outcomes in adults, except for high triglycerides and low HDL-C. This is a strong point of attention regarding the role of targeted therapy, where the combination treatment must not be a universal one and should be tailored to patients with the typical atherogenic dyslipidemia shape of the profile, but not in all T2DM patients (3,6). Another factor to be considered is the version of the fenofibrate used. According to studies by Patel and Barkate and by Oikawa and others, newer preparations like choline fenofibrate have a possibility of better bioavailability and tolerability (18, 19). Our study employed micronized fenofibrate, but alternative studies should determine whether the newer formulations offer more superiority among the Pakistani population.

In our study, there are some limitations. Although 12 weeks may be considered adequate to assess the efficacy in terms of the biochemical effect, this length of follow-up may not reflect overall long-term cardiovascular consequences and rare adverse outcomes. Other limitations to the study are that this tertiary care center was only used in the study, leaving the generalizability to primary care or a rural population. However, due to a randomized study, standardized doses, and high compliance rates, our results may prove more valid. The findings are good evidence that the combination treatment of atorvastatin-fenofibrate improves the levels of total, LDL-C, triglyceride, and HDL-C more than monotherapy with atorvastatin in T2DM patients with dyslipidemia, with a good level of safety. The

study results justify the targeted application of combination therapy to mixed dyslipidemia patients, particularly those whose triglycerides do not normalize and whose HDL-C levels are not raised even after treatment with statins. Having considered that cardiovascular risk is high in the Pakistani diabetic population, such an intervention may lead to positive long-term outcomes when used judiciously in clinical practice.

Conclusion

The research carried out at the Ayub Teaching Hospital, Abbottabad, Pakistan, proved that statin monotherapy and the statin and fibrate combination therapy have significant effects on enhancing lipid profiles of persons with type 2 diabetes and dyslipidemia. Nonetheless, atorvastatin in combination with fenofibrate exerted better effects than atorvastatin given alone in the reduction in total cholesterol, LDL-C, and triglycerides, and increases in HDL-C. The combination therapy has been quite tolerable, as mild self-limiting adverse effects seemed to have been reported, and no serious biochemical toxicities were experienced. The results imply that concomitant use of fenofibrate in patients who already have low HDL-C and persistent hypertriglyceridemia despite statin therapy can have a positive impact on these patients. The connection between combination therapy and the individualized treatment plans can assist in covering residual cardiovascular risks of high-risk diabetic populations. Additional long-term trials in new areas are justified to evaluate cardiovascular outcomes and safety in expanded clinical practice in Pakistan.

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