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A PROSPECTIVE, FOLLOW UP STUDY TO ASSESS THE PLEIOTROPIC EFFECT OF TENELIGLIPTIN IN TYPE -2 DIABETES MELLITUS PATIENTS

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ABSTRACT

Aims: Recently, beneficial pleiotropic effects with dipeptidyl peptidase-4 (DPP-4) inhibitors have been demonstrated in some studies. So this study was planned to investigate pleiotropic effect with recently approved Teneliglipitin in Indian population. The objective of our study was to find out the effect of teneligliptin as add on therapy on body weight, blood pressure, lipid profile, liver function test and renal function test. **Methods:** The study was a prospective follow up study conducted on type 2 diabetes mellitus patients. Forty patients having insufficient glycemic control with metformin and started on teneligliptin as add on therapy were enrolled for the study. The body weight, blood pressure, serum HBA1c, lipid profile, liver function test (GOT/GPT) and renal function test (Urea, Creatinine) were done at the baseline and follow up. **Result:** A total of 40 patients were enrolled for the study. Only 21 patients were available for follow up after 4 weeks and only one patient could be followed up after 8 weeks, so only 21 patients were included in the analysis at 4 weeks. The result of our study showed that there is pleotropic effect of teneligliptin on BP, body weight, lipid profile, liver function and renal function as seen with sitagliptin, though the results could not be proven statistically. **Conclusion:** This study concluded that teneligliptin has favourable effect on blood pressure, body weight, and renal function although the results were not statistically significant due to small sample size and short duration of study.

KEYWORDS: Pleiotropic, Teneligliptin, Type II Diabetes mellitus.

INTRODUCTION

Diabetes has become a major concern for global public health. India is among the top three countries having largest number of diabetic population.[1] According to WHO, India had 69.2 million people living with diabetes accounting for 8.7% as per 2015 data. There are sufficient data to suggest that effective management of diabetes can decrease the risk for both the microvascular as well as macrovascular complications of diabetes.[2,3] During the last decade, many new glucose-lowering drugs acting on novel pathways have been developed. These drugs include the glucagon-like peptide agonists such as exenatide and liraglutide, dipeptidyl peptidase-4 (DPP-4) inhibitors such as sitagliptin and vildagliptin and sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitor) like dapagliflozin and empagliflozin. DPP -4 inhibitors act by inhibiting the degradation of incretins like GLP-1 and GIP, which inhibit glucagon release, which in turn increases insulin secretion, decreases gastric emptying and decreases blood glucose levels. Owing to the unique mechanism of DPP-4 inhibitors it is postulated that administration of these agents from the early stage may have protective effect on pancreatic ß cells along with reliable hypoglycemic action. In 2016, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) position statement, DPP-4 inhibitor is recommended as an option for first add on or second add on pharmacological agent. Studies conducted in other countries like Japan have demonstrated some pleiotropic effects like decrease in blood pressure and serum cholesterol levels with DPP-4 inhibitor like sitagliptin.[4] These additional effects could be beneficial in patients with diabetes as they are individual risk factors for cardiovascular morbidity. Teneligliptin, a novel DPP-4 inhibitor, has efficacy and safety profiles similar other DPP-4 inhibitors.[5] It has a long half-life (approximately 24 h), allowing once a day dosing and better stabilization of the blood glucose fluctuations throughout the day.[5] Various studies were conducted in the past especially retrospective studies with DPP-4 inhibitor sitagliptin. It was demonstrated that Sitagliptin was not only lowering blood glucose but also had effect on lowering blood pressure, lipid, and ALP levels.[4] Some interventional studies have also demonstrated statistically significant reductions in blood pressure measurements with sitagliptin.[6,7] Similary another open label observational study demonstrated that Sitagliptin improves body weight, blood pressure and lipid profile in type 2 diabetic hyperlipidaemia patients.[8] A recent meta- analysis suggested that sitagliptin has beneficial effect on lipid profile.[9] An interventional study carried out on drug naïve patients with tenegliptin 20 mg/day demonstrated no effect on lipid parameters .[10] DPP-4 inhibitors have distinct chemical structures and pharmacokinetic properties although the antidiabetic mechanism of

action is similar. These differences may have impact on lipids or other non-glycemic profiles. The studies done in other countries have demonstrated beneficial pleiotropic effects with Sitagliptin. It is still not proved whether this effect is a class effect or restricted to individual agent. Moreover there is lack of this kind of study in Indian population. So this study was planned to investigate whether the similar profile of pleiotropic effect is also seen with other DPP-4 inhibitor (Teneliglipitin) in our population.

MATERIAL AND METHODS

This prospective follow up study was conducted from May 2017 to July 2017 in a tertiary care hospital of Uttarakhand, as a project under short-term studentship (STS) from the Indian Council of Medical Research (ICMR), after approval from the institutional ethics committee. Inclusion criteria was type 2 diabetes mellitus patients with insufficient glycemic control despite the use of metformin and being started on teneligliptin as add on therapy. Exclusion criteria was patients with clinically significant renal creatinine (CRE) > 1.5 mg/dL, liver glutamic oxaloacetic transaminases/glutamic pyruvic transaminases (GOT/GPT) > 70/70 IU/L), hypertensive (blood pressure above 160/100 mm Hg) disorders, type 1 diabetes (T1DM) pregnancy, patients whose antihypertensive and lipid medications had been started or changed during the study period and patients receiving any other drugs which can affect the outcome measures directly. After taking written informed consent, 40 diabetes mellitus patients with insufficient glycemic control despite the use of metformin and being started on teneligliptin as add on therapy were enrolled for the study. At the baseline the body weight ,blood pressure, serum HBA1c, lipid profile, liver function test (GOT/GPT) and renal function test (Urea, Creatinine) was done. Patients were started on add on therapy of teneligliptin 20 mg OD along with metformin. The patients were followed up and again reevaluated at 4 weeks and 8 weeks for all the parameters. The patients were actively monitored for any adverse effect throughout study period. Data was presented as means ± SD. GraphPad InStat 3 was used for statistical analysis. Data of pre and post treatment were analyzed by paired t test. A P value < 0.05 is considered significant

RESULT

A total of 40 patients were enrolled for the study. Only 21 patients were available for follow up after 4 weeks and only one patient could be followed up after 8 weeks, so only 21 patients were included in the analysis at 4 weeks. The demographic and baseline clinical characteristic of the participants were as follows: The male: female ratio in the patients included in the

study was 2:1. The patients had a mean age of 56.8±10.4 years, duration of diabetes was 8.5 ± 7.4 years and the mean HbA1c was 8.1 ± 0.9.

Figure 1 shows the change in the body weight at 0 and 4 weeks. The body weight was slightly reduced from 63.12 ± 7.59 to 62.24 ± 6.88 (P value = 0.87). Similarly, as demonstrated in Fig.2 there was slight reduction in systolic BP from 124.76 ± 16.28 to 123.2381 ± 17.78 (P value = 0.49) as well as in diastolic BP from 78.86 ± 15.86 to 76.48 ± 7.92 (P value = 0.87). Changes in the lipid profile are shown in Fig.3, a decreasing trend was observed in triglyceride levels from 81.24 ± 20.89 to 77.61905 ± 9.95 (P value = 0.44) and HDL levels 46.28 ± 17.35 from 41.10 ± 10.53 (P value = 0.91) whereas LDL cholesterol increased from 98.81 ± 38.67 to 108.71 ± 48.81 (P value = 0.85). There was slight increase in SGPT from 33.86 ± 16.25 to 37.30 ± 18.46 (P value = 0.99) and SGOT from 38.58 ± 22.61 to 35.19 ± 21.63 (P value = 0.99) as shown in Fig.4. In the renal function test there was decrease in levels of urea from 24.49 ± 9.20 to 23.96 ± 9.13 (P value = 0.62) and creatinine from 1.13 ± 0.84 to 0.77 ± 0.25 (P value = 0.92) as shown in Fig.5.

Only two patient reported adverse drug event. One patient experienced hypoglycemia and another patient reported rash over the body.

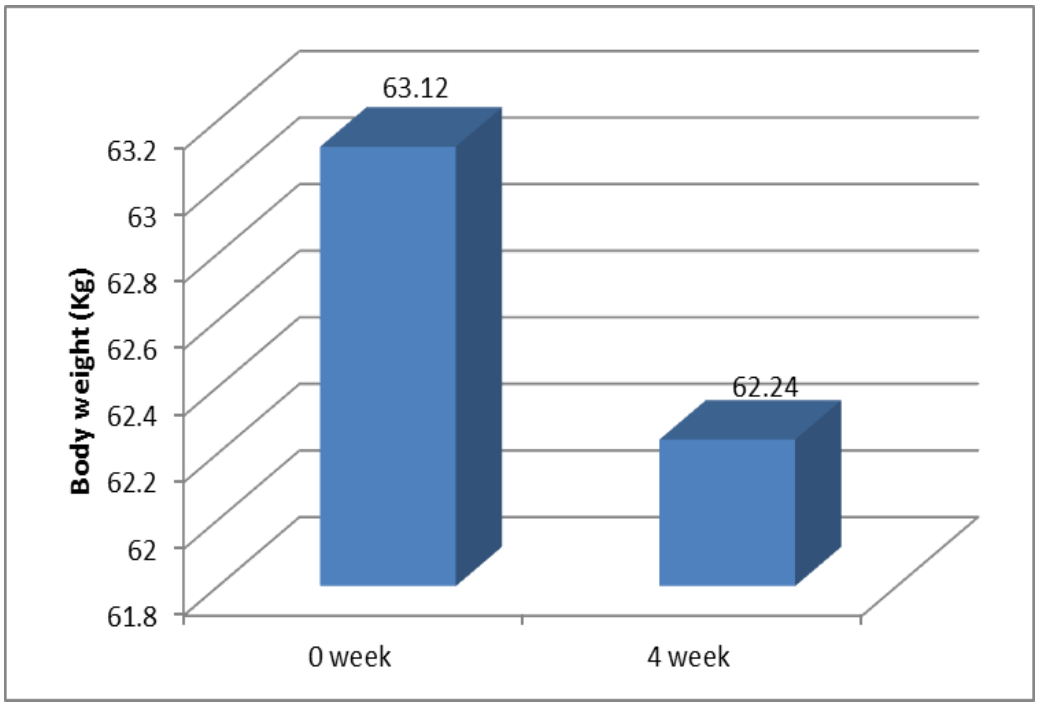

Figure 1: Change in body weight from baseline to 4 week.

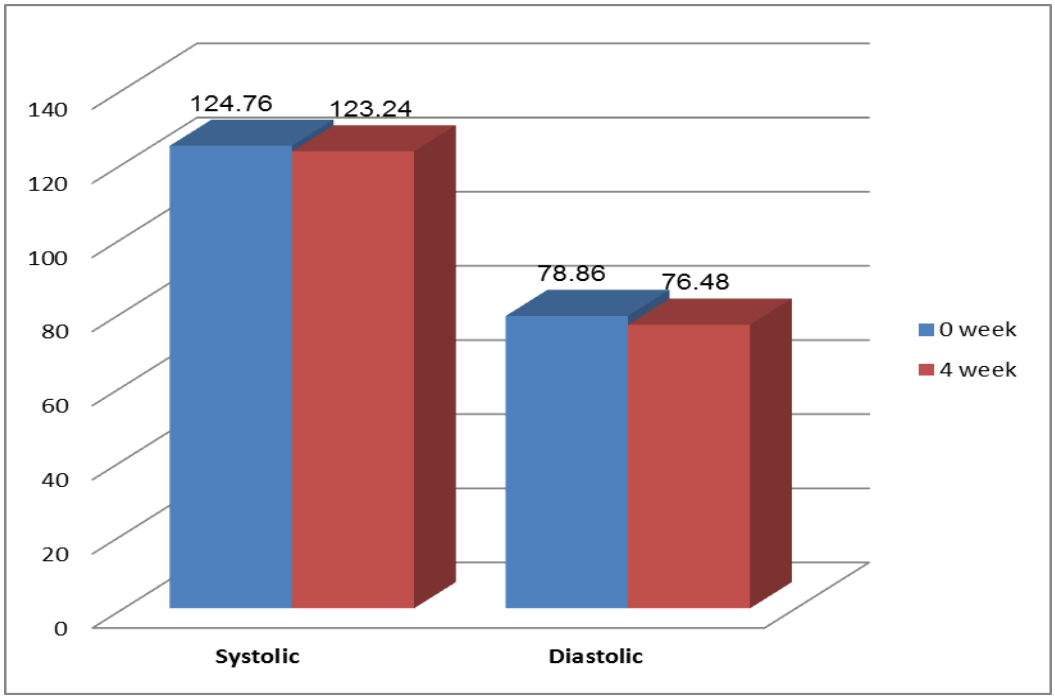

Figure 2: Changes in BP at 0 week and 4 week during study period.

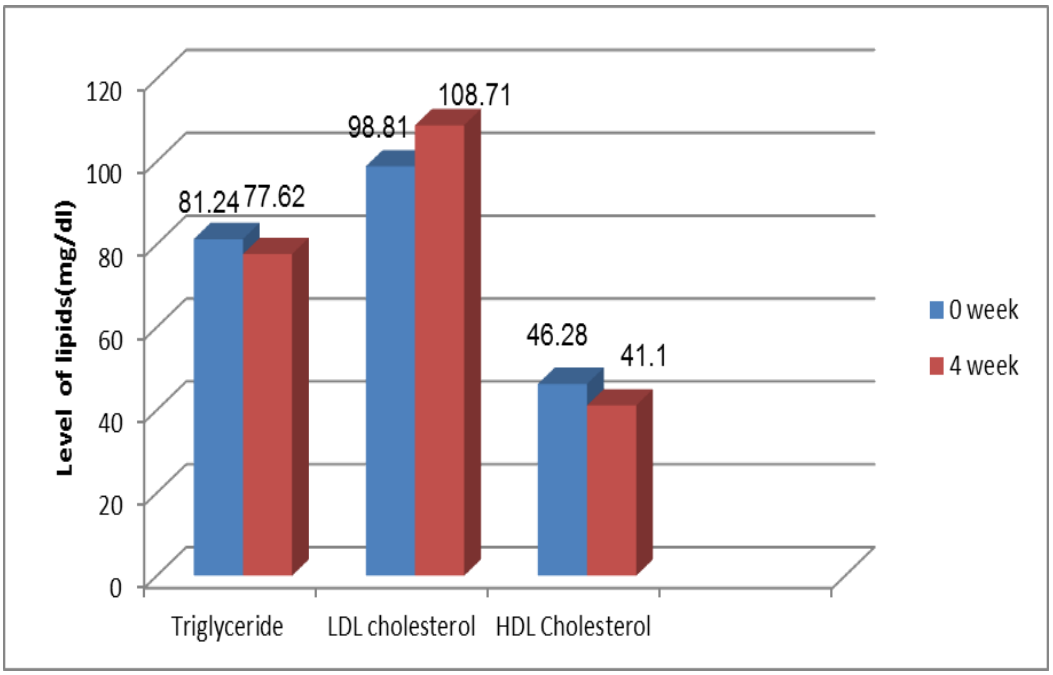

Figure 3: Changes in lipid levels at 0 week and 4 week during study period.

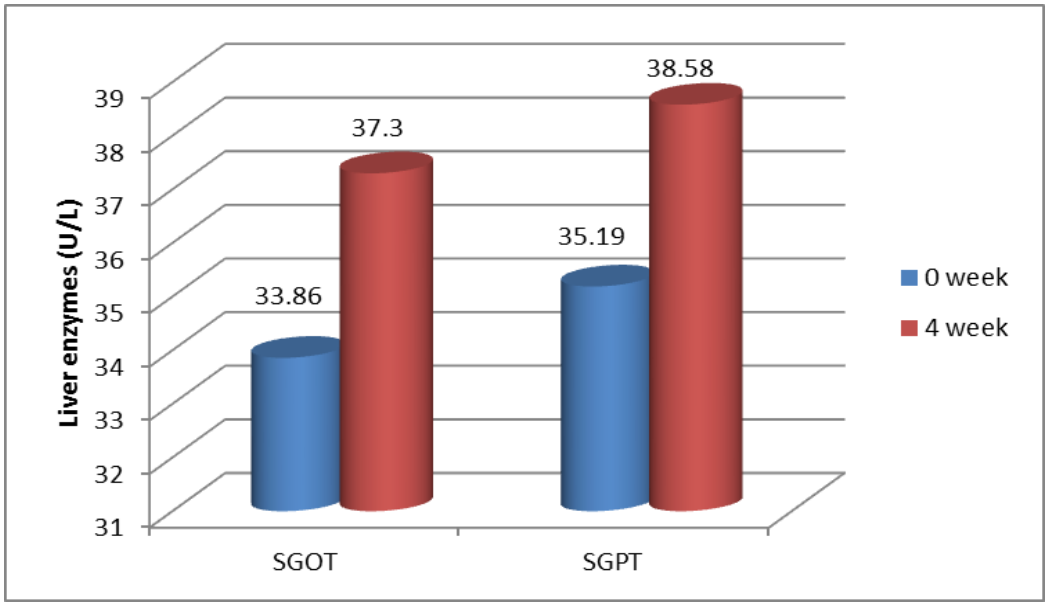

Figure 4: Changes in liver function test at 0 week and 4 week during study period.

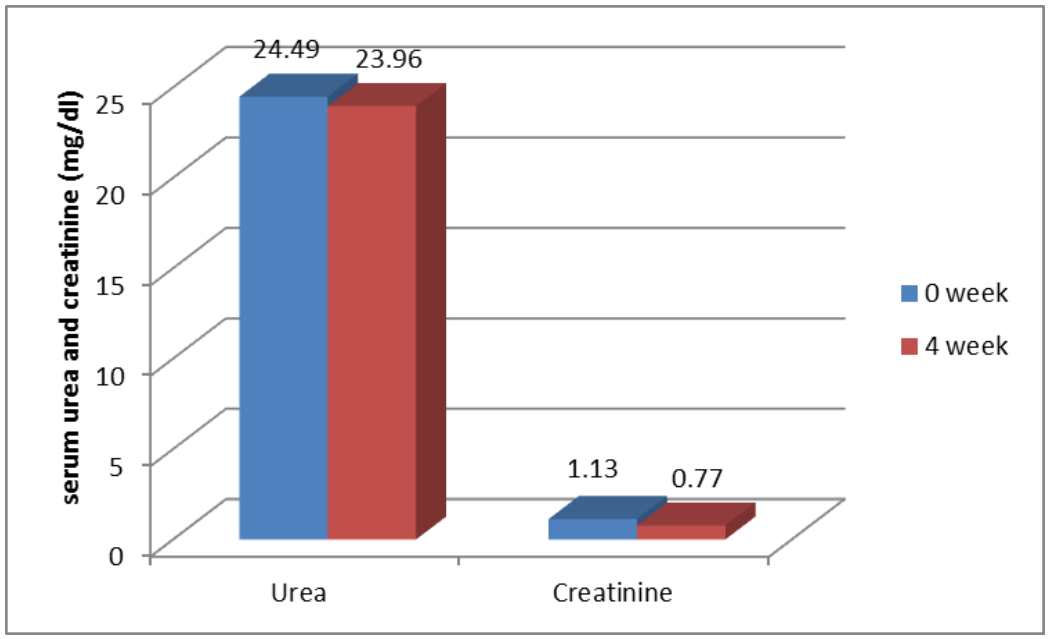

Figure 5: Changes in Renal function test at 0 week and 4 week during study period.

DISCUSSION

The results of our study on 21 patients of type 2 diabetes mellitus patients treated with tenegliptin as add on therapy with metformin showed that there was decrease of 0.88 kg of weight with tenegliptin therapy. Although the result was not significant due to less number of patients involved but the decrease in body weight was seen similar to as seen in other retrospective study with sitagliptin.[4]

Similarly, there was a decrease of 1.52 mmHg in systolic pressure and 2.38 mmHg in diastolic pressure after 4 weeks. This is in concurrence with some other studies which show similar trend with sitagliptin administration.[6,7] Various mechanisms proposed for blood pressure reduction by sitagliptin include GLP-1 receptor mediated endothelial vasodilatation by nitric oxide stimulatory effect.[6,7]

Interestingly, in the present study we found that although the triglyceride levels were decreased but there was increase in LDL and decrease in HDL levels. This was in contrast to other study where favorable effect on lipid profile was observed with sitagliptin therapy.[8,9] But a recent study with teneligliptin demonstrated non significant effect on lipid profile.[10] Multiple mechanisms are postulated for the triglyceride-lowering effect of sitagliptin, including inhibited TG absorption from the intestine. Teneligliptin may have similar effect though further studies are required to confirm the mechanism and effect on lipid profile.

There was slight increase in levels of SGPT and SGOT in our study with teneligliptin. This result was in contrast to the retrospective study conducted with sitagliptin.[4] Studies have also demostrated that sitagliptin improves fatty liver.[11] The reason for this variation can be ascribed to short duration of study. There was slight decrease in Serum urea and creatinine in our study. This was in contrast to a retrospective study where sitagliptin showed increased serum creatinine and uric acid levels significantly.[4]

Only two patients out of 21 experienced adverse effect namely hypoglycemia and rash. Similar profile of adverse drug effect was demonstrated in study with tenegliptin elsewhere.[4]

The result of our study showed that there is pleotropic effect of tenegliptin on BP, body weight, lipid profile, liver function and renal function as seen with sitagliptin, though the results could not be proven statistically. The major strength of this study was that it was a prospective study with tenegliptin. Majority of studies related to this topic are either retrospective studies or studies with sitagliptin. To our best knowledge it is the first study in India to study the effect of tenegliptin on pleotropic effects. The major limitation of this study was its short duration of study period and smaller number of patients, due to which none of the results were found to be statistically significant. Though we had planned to include 40 patients initially but since we could not get the follow up of all the patients we only included 21 patients. The future studies with longer follow up and more number of patients can be carried out to elucidate the effects of tenegliptin.

CONCLUSION

This study concluded that tenegliptin has favourable non glycemic effect also on blood pressure, body weight, and renal function although the results were not statistically significant due to small sample size and short duration of study. The effect on lipid profile and liver function was not favorable.

Conflicts of Interest: None.

Ethics statement: Approved from institutional ethics committee.

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