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Original Research Article

Dipeptidyl peptidase-4 inhibitor (teneligliptin) significantly reduces liver fat content and delays progression of non-alcoholic steatohepatitis in type 2 diabetes mellitus patients

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ABSTRACT

Background: Dipeptidyl peptidase (DPP)-4 inhibitors, anti-diabetic agents, are expected to be effective for treatment of non-alcoholic fatty liver disease (NAFLD). Several studies have shown that some DPP-4 inhibitors alleviate hepatic steatosis or steatohepatitis in type 2 diabetic mice or rats. Teneligliptin is DPP4 inhibitor whose efficacy to control blood sugar is well established but its effect on liver is not studied well. In present study we investigated effect of teneligliptin, a DPP-4 inhibitor on patients of type 2 diabetes with non-alcoholic steatohepatitis (NASH).
Methods: This was a randomized, double-blind study in which 64 patients between ages of 18 to 80 years were selected for study. Participants were identified as type 2 diabetes with biopsy confirmed NASH. We excluded the patients with glucocorticoid use, hepatitis B or C, and other diseases that might affect liver function.
Results: The mean HbA1c change after 48 weeks of therapy in group A was-1.06 % and in group B was-0.77% and this was statistically insignificant ($p>0.06$). The mean AST change after 48 weeks of therapy in group A was-45.4% and in group B was-33.3% and this was statistically significant ($p<0.001$). The mean ALT change after 48 weeks of therapy in group A was-41.6% and in group B was-22.7% and this was statistically significant ($p<0.001$). The change in liver fat content (LFC) after 48 weeks of therapy in group A was-15.4% and group B was-7.14% and this was also statistically significant ($p<0.001$).
Conclusions: Result of our study revealed that teneligliptin significantly reduce serum transaminases in patients of NASH with type 2 DM. Teneligliptin significantly reduce LFC and delay progression of NASH independent of diabetes control in type 2 diabetes mellitus (DM) patients. These data show significant antisteatotic and anti-inflammatory effect of teneligliptin in type 2 diabetes patients.

Keywords: Teneligliptin, NASH, DPP4 inhibitors

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in Western countries that is predicted to become also the most frequent indication for liver transplantation by 2030. Over the last decade, it has been shown that the clinical burden of NAFLD is not only confined to liver-related morbidity and mortality, but there is now growing evidence that NAFLD is a multisystem disease, affecting extra-hepatic organs and regulatory pathways.[1] For example, NAFLD increases risk of type 2 DM (T2DM), cardiovascular (CVD) and cardiac diseases, and chronic kidney disease (CKD). Although the primary liver pathology in NAFLD affects hepatic structure and function to cause morbidity and mortality from cirrhosis, liver failure and hepatocellular carcinoma, the majority of deaths among NAFLD patients are attributable to CVD. DPP-4 inhibitors, anti-diabetic agents, are expected to be effective for the treatment of NAFLD. Several studies have shown that some DPP-4

inhibitors alleviate hepatic steatosis or steatohepatitis in type 2 diabetic mice or rats.[2] Teneligliptin is a DPP4 inhibitor whose efficacy to control blood sugar is well established but its effect on liver is not studied well. In present study we investigated effect of teneligliptin, a DPP-4 inhibitor on patients of type 2 diabetes with the NASH.

METHODS

The study was conducted in department of medicine GSVM medical college Kanpur between April 2017 to December 2018. We recruited 100 patient of type 2 DM with NASH from out-patient and indoor of our department. Out of 100 patients 36 patients were excluded from study due to positive HCV, HBsAg and history of glucocorticoids use in past. 64 patients were randomized for the study. This was a randomized, double-blind study in which 64 patients between ages of 18 to 80 years were selected for study. Participants were identified as type 2 diabetes with biopsy confirmed NASH. We excluded the patients with glucocorticoid use, hepatitis B or C, and other diseases that might affect liver function.

All enrolled patients randomized into 2 main groups, on the basis of drugs prescribed to them. Group A, (n=34): teneligliptin 20 mg-once a day. Group B, (n=30): metformin 1000 mg once a day. Patients were analyzed for their fasting, postprandial blood glucose level along with HbA1c value as baseline and followed up at regular interval of 12 weeks apart till 48 weeks. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level were measured at base line and 12-week interval till 48 weeks. Hepatic steatosis was measured by transient elastography (Fibroscan).

Statistical analysis

The data was compiled and analysed using SPSS 23.0. Continuous variables were analysed using mean and standard deviation, comparison of means in different groups was done using unpaired t test. P<0.05 was considered significant.

RESULTS

Out of 64 patients, 36 pts were male and 28 were female. Most of the patients included in the study were more than 30 years of the age (Table 1).

The mean HbA1c change after 48 weeks of therapy in group A was-1.06% and in group B was-0.77% and this was statistically insignificant (p>0.06) (Figure 1). The mean AST change after 48 weeks of therapy in group A was-45.4% and in group B was-33.3% and this was statistically significant (p<0.001). The mean ALT change after 48 weeks of therapy in group A was-41.6% and in group B was-22.7% and this was statistically significant (p<0.001) (Table 1). The change in LFC after 48 weeks of therapy group A was-15.4% and group B was-7.14% and this was also statistically significant (p<0.001) (Table 2).

Table 1: Age and sex distribution of patients in study.

Age (Years)	Males	Females	Total (%)
18-30	00	00	00
31-40	6	8	14 (22.96)
41-50	12	10	22 (24.88)
51-60	12	6	18 (30.62)
>60	6	4	10 (21.53)
Total (%)	36 (56.25)	28 (43.75)	64 (100)

Table 2: Comparison of group A, (n=34) and group B, (n=30) parameters.

Parameters	Group-A, baseline teneligliptin	Group-A, at 48 weeks	Change group-A (%)	Group-B, baseline	Group-B, at 48 weeks	Change group-B (%)	P (changes between groups)
HbA1c	8.75±0.4	7.69±0.3	-1.06	8.12±0.5	7.35±0.4	-0.77	0.06
AST, (IU/L)	88±6	48±2	-45.4	84±4	56±3	-33.3	<0.001
ALT, (IU/L)	96±3	56±4	-41.6	88±4	68±4	-22.7	<0.001
LFC (Db./m)	298.3±31.4	252.330±0.5	-15.4	309.4±32.1	287.6±26.3	-7.14	<0.001

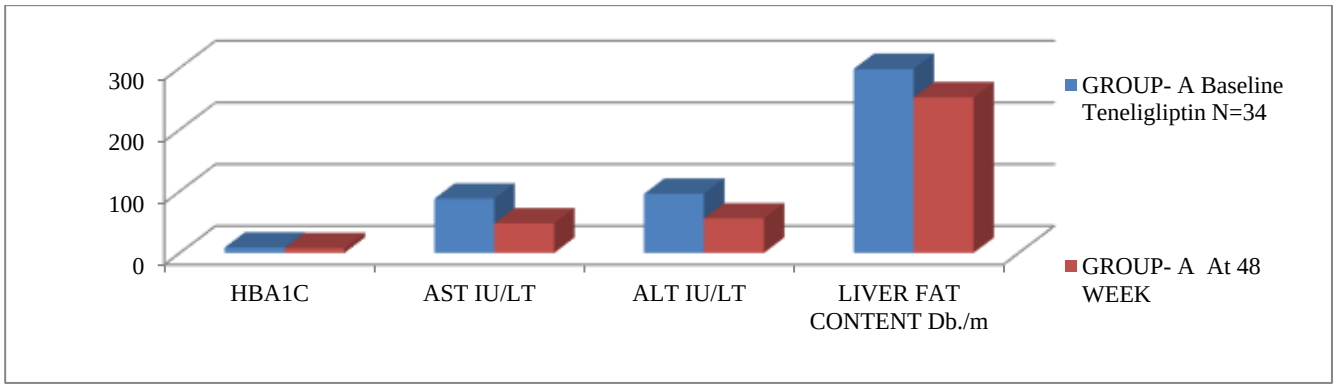

Figure 1: Group-A parameters at baseline and after 48 weeks.

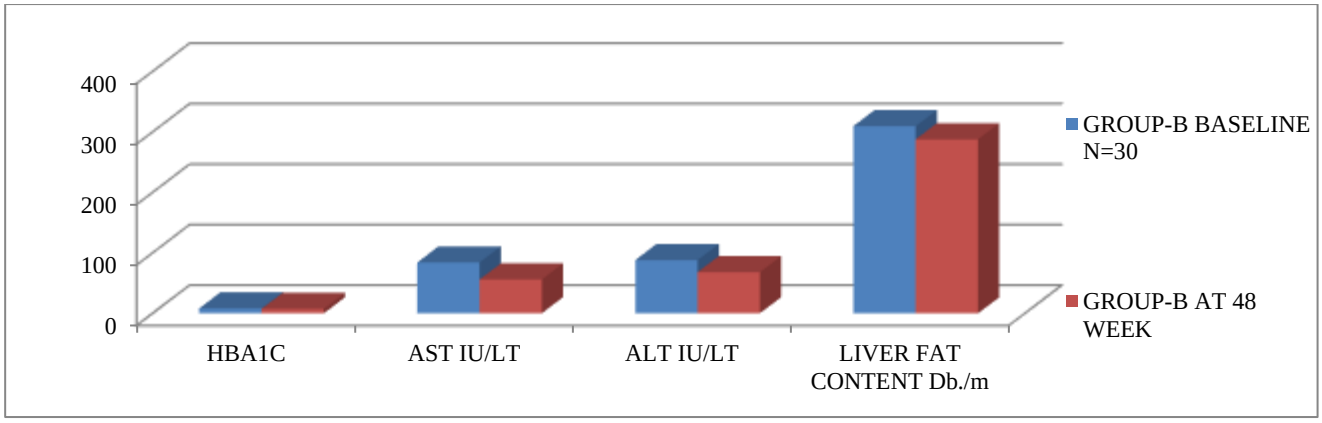

Figure 2: Group-B parameters at baseline and after 48 weeks.

DISCUSSION

In our study change in mean AST and ALT level were significantly improved in group A (teneligliptin) in compare to control group B (metformin) (Table 1). Similar result has seen in study conducted by Kanazawa et al which showed that DPP-4 inhibitors improve liver dysfunction in type 2 DM patients.[3] In our study teneligliptin significantly improves hepatic steatosis (measured by CAP score). Yilmaz et al examined paired liver biopsies in 15 diabetic patients with NASH and reported that a significant reduction of NASH scores was observed after 1-year treatment with sitagliptin, and that these effects were accompanied by significant decreases in body mass index, AST, and ALT levels.[4] Our present findings are consistent with these previous studies. Moreover, we found that the changes in AST and ALT by teneligliptin were independent of HbA1c level and body weight (Table 1). Thus, Teneligliptin has a desirable effect on liver function independent of diabetes status. Study conducted by Nakamura et al has revealed preventive effect of teneligliptin for development of hepatic steatosis in mice.[5] Gupta et al showed in their study that Glucagon-like peptide-1 receptor is present on human hepatocytes and has a direct role in decreasing hepatic steatosis *in vitro* by modulating elements of the insulin signalling pathway.[6,7] This could be a possible explanation for effect of DPP4 inhibitors to improve liver dysfunction in type 2 diabetes patients. In our study teneligliptin significantly decreased LFC (Table 2). Similar results have seen by study conducted by Bae et al their study revealed that DPP-4 inhibitors reduce hepatic steatosis.[8] These findings suggest that inhibition of local DPP-4 activity in the liver may be important for the treatment of NAFLD. Taken together, these findings suggest that DPP-4 inhibitors improve liver function via increasing GLP-1 activity, as well as directly inhibiting local DPP-4 activity in the liver. In previous studies different types of DPP4 inhibitors have been included like sitagliptin, vildagliptin and linagliptin but teneligliptin has not been studied in detail. In our study, the effects of teneligliptin (DPP-4 inhibitor) on the changes in AST and ALT were independent of HbA1c levels, suggesting that DPP-4 inhibitors have pleiotropic effects on liver function, not only in experimental studies, but also in clinical settings.

The limitation of our study is the small sample size, hence further studies with large sample size is needed to understand the mechanism for improving liver function of NAFLD by DPP-4 inhibitors.

CONCLUSION

Result of our study revealed that teneligliptin significantly reduce serum transaminases in patients of NASH with type 2 DM. Teneligliptin significantly reduce LFC and delay progression of NASH independent of diabetes control in type 2 DM patients. These data show significant anti-stenotic and anti-inflammatory effect of teneligliptin in type 2 diabetes patients.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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