# EFFECT OF EMPAGLIFLOZIN ON LIVER ENZYMES OF PATIENTS IN NON-ALCOHOLIC STEATOHEPATITIS IN TYPE 2 DIABETES MELLITUS

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***ABSTRACT***

***OBJECTIVES***

*To assess the effect of 10 mg and 25 mg once daily Empagliflozin on liver enzymes of patients of non-alcoholic steatohepatitis in patients of type 2 diabetes mellitus (T2DM).*

***METHODOLOGY***

*The study design was open labelled, Quasi Experimental Design Thirty three adult patients of Type 2 diabetes mellitus (T2DM) who were already on 2000 mg of metformin and 100 mg of Sitagliptin and were having suboptimal glycemic control (HBA1C > 7% <12%), had elevated Alanine Transaminase (ALT) levels and had ultrasonographic features consistent with non-alcoholic fatty liver disease (NAFLD) were randomized to three groups. One group received 10 mg Empagliglozin as add-on treatment (Group A), the second group received 25 mg of Empagliflozin (Group B) as an additional treatment, and the third group continued with the previous medications without any additional treatment (Group C). HbA1C levels and ALT levels of all the three groups were taken at baseline and at 12 weeks.*

***RESULTS***

*Total patients and their mean ages in group A, B and C were 10, 12 and 11, and 52.40 ±4.24 years, 52.42 ± 5.27 years and 52.34 ± 4.37 years, respectively. There was a statistically significant (p > 0.00) decrease mean ALT levels in Group A and B both 12 weeks post treatment as compared to pre-treatment levels. In group C, however, there was no statistically significant decrease in ALT levels after 12 weeks of follow up.*

***CONCLUSION***

*Empagliflozin in both 10mg and 25 mg once daily doses cause statistically significant reduction in ALT levels in patients with NASH associated with T2DM.*

***KEYWORDS:*** *Empagliflozin, Type 2 Diabetes Mellitus, Alanine Transaminase, Non-Alcoholic Fatty Liver Disease, Non-Alcoholic Steatohepatitis.*

## INTRODUCTION

It is estimated that Non-alcoholic fatty liver disease (NAFLD) affects approximately more than half of those with T2DM.[1,3] Hepatic steatosis is the first stage of NAFLD when the fat content is more than 5% of the liver volume.[4] It is postulated that ectopic liver fat plays an important part in the pathogenic process of diabetes, causing the addition of hepatic insulin resistance, enhanced gluconeogenesis, and greater levels of fasting glucose levels.[5] Along with that, hepatic steatosis caused by NAFLD leads to increased levels of hepatic aminotransferases such that alanine aminotransferase (ALT) levels are more than those of aspartate aminotransferase (AST).[6] In clinical practice, non-alcoholic steatohepatitis (NASH) is suspected by higher ALT levels.[7] Elevated ALT levels (typically more than 40–50 U/l) are common in patients with T2DM and for a given serum ALT, those with T2DM have more liver fat compared with age, sex and BMI-matched individuals without diabetes .[8,9,10] In NAFLD, a minority of individuals with hepatic steatosis progress to non-alcoholic steatohepatitis (NASH). This is the point at which monitoring and treatment become crucial to prevent progression to cirrhosis as well as other life-threatening sequelae.[7] In patients with T2DM and elevated liver enzymes, improved glycemic control is important to delay hepatic complications.[11,12] The preferred therapeutic approach is to encourage lifestyle changes to reduce a patient's weight by ≥7% through changes in diet and lifestyle habits, including regular exercise.[13] However, a pharmacologic approach is often

necessary to treat NASH because most patients fail to reduce their weight sufficiently. Pharmacologic options include pioglitazone and metformin, both of which are insulin-sensitizing agents that are used to treat T2DM.[14,15,16] Studies of these drugs have reported their effectiveness in the treatment of NASH and its comorbidities.[15,16] However, pioglitazone may promote weight gain and should not be used in patients with heart failure. Liraglutide, a Glucagon-like peptide 1 (GLP1) agonist, is effective in treating NASH.[17] Cost, however, is the main issue with GLP1 agonists, especially in low-resource countries like Pakistan. Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce hyperglycemia in individuals with type 2 diabetes by decreasing renal glucose reabsorption, thereby increasing urinary glucose excretion, and lowering HbA1c.[19] Nearly 90% of the weight loss with SGLT2 inhibitors is due to a reduction in fat mass, with reductions in subcutaneous adipose tissue and abdominal visceral fat mass.[19] Studies in the western world have shown improvement of liver fat mass and liver enzymes with SGLT2 inhibitors in patients with type 2 diabetes mellitus and elevated liver enzymes or NASH.[19,20] To our knowledge no study on SGLT2 inhibitors has been carried out in Pakistan to see its effect on patients with T2DM and NASH in terms of improvement of liver enzymes. We, therefore, studied the impact of two doses of empagliflozin on ALT levels of T2DM patients who still had more than Upper Limit Normal (ULN) ALT and suboptimal glycemic control despite being on maximum doses of Metformin and Sitagliptin and having ultrasonography evidence of NAFLD.

## METHODOLOGY

This study was conducted between January 2020 and December 2020 at the department of Medicine, Naseer Teaching Hospital, Peshawar and the Center of Gastroenterology and Hepatology, Hayatabad, Peshawar. Consecutive patients who were previously diagnosed to have T2DM having sub-optimal glycaemic control (HbA1C of > 7% and < 12%) with Metformin 2000 mg daily and Sitagliptin 100 mg daily and elevated ALT (>40 IU/L) along with ultrasonographic evidence of NAFLD were included. Other inclusion criteria were age of more than 18 years and both genders. Exclusion criteria were patients with impaired renal function (estimated Glomerular Filtration rate of < 45ml/min/1.73m$^2$), pregnancy, chronic liver disease, positive viral serology for hepatitis B and C, history of alcohol consumption, having clinical features of hyperthyroidism, recent infections, history of cancer, evidence of gall-stones/cholecystitis on ultrasound, recent (within six months) acute coronary syndrome and age more than 75 years. A total of 43 patients met the inclusion criteria, of which six were excluded as per the exclusion criteria, and the rest (thirty-seven) were included in the study. These were allocated in 1:1:1 to Groups A, B and C by consecutive sampling. Group A received Empagliflozin 10 mg on top of the previous treatment, group B received Empagliflozin 25 mg in addition to the previous treatment, and Group C continued with the same medications without any addition. All three groups were counselled about lifestyle changes, including compliance with a diabetic diet and daily exercise/physical activity. These three groups were followed up for 12 weeks during the study duration of 1 year. Two patients from group A, one from group B and one from Group C were lost to follow-up. Therefore at the end of the study duration, we had the follow-up data of a total of 33 patients (10 in group A and 12 in group B and 11 in Group C). HbA1C levels and ALT levels were obtained 12 weeks after intervention with Empagliflozin addition in Groups A and B and 12 weeks after continuation of Sitagliptin and Metformin in Group C. The SPSS 23.0 version was used to analyze the data. Mean ± SD were calculated for quantitative variables like age, HBA1C and ALT levels. Percentages and frequency were calculated for qualitative variables like gender. Analysis was done by doing paired sample t-test to determine group mean differences between descriptive variables of the three groups at 12 weeks and baseline. To see the outcome difference between Group A and Group B, an independent sample t-test was used. A value of p-value < 0.05 was considered statistically significant.

## RESULT

A total of 33 patients (14 males and 19 females) were included in the study. In Group A, there were 10 patients, four male and six female, and the mean age was 52.40 ±4.24 years. In Group B, there were 12 patients, out of which five patients were male and seven were female, and the mean age was 52.42 ± 5.27 years. In group C, there were 11 patients, of which 5 were males and six were female, and the mean age was 52.34 ± 4.37 years. The clinical and demographic variables of Group A, Group B and Group C are depicted in Tables 1, 2, and 3, respectively. The between-group difference is shown in table 4.

**Table 1: Clinical and Demographic Data in Patients Receiving Empagliflozin Treatment in Group**

| Parameter | Baseline (Mean ± SD) | After 12 weeks (Mean ± SD) | P-Value |
|---|---|---|---|
| HbA1C | 9.99 ± 1.73 | 8.37 ± 0.80 | 0.000 |
| ALT,IU/L | 67.00 ± 7.98 | 61.00±4.76 | 0.001 |

HbA1C= HeamoglobinA1C, ALT=Alanine Transaminase

**Table 2: Clinical and Demographic Data in Patients Receiving Empagliflozin Treatment in Group B**

| Parameter | Baseline (Mean ± SD) | After 12 weeks (Mean ± SD) | P-Value |
|---|---|---|---|
| HbA1C | 9.47±1.41 | 8.37±1.05 | 0.000 |
| ALT,IU/L | 65.25± 10.01 | 59.83±8.26 | 0.000 |

**Table 3: Clinical and Demographic Data in Patients in Group C**

| Parameter | Baseline (Mean ± SD) | After 12 weeks (Mean ± SD) | P-Value |
|---|---|---|---|
| HbA1C | 9.13±1.60 | 9.04±1.62 | 0.033 |
| ALT,IU/L | 63.63± 10.46 | 63.27±10.55 | 0.267 |

**Table 4: Comparison of Pre-and Post-Added Empagliflozin Therapy differences in Parameters between Group A and Group B**

| Parameter | Change from Baseline Treatment (Mean ± SD) | | P-Value |
|---|---|---|---|
| | Group A | Group B | |
| Δ HbA1C %(SD) | 1.62 ± 0.94 | 1.10 ± 0.74 | 0.165 |
| Δ ALT IU/L (SD) | 6.0 ± 3.97 | 5.41 ± 2.46 | 0.678 |

## DISCUSSION

Our study showed that both doses of Empagliflozin caused statistically significant reductions in ALT levels of patients with type 2 diabetes mellitus have elevated ALT levels along with sonographic features of NAFLD. This is in line with numerous international studies.[21-25] The mean change in ALT levels after 12 weeks in patients to whom empagliflozin 10 mg and 25 mg were added on top of Sitagliptin and metformin was 6.0 ± 3.97 IU/L and 5.41 ± 2.46 IU/L respectively. Other studies have documented reductions of ALT in the Empagliflozin treatment group to be less (4.88 U/l (95% CI −6.68, −3.09) than shown in our study.[21] The reason could be the higher baseline ALT levels in our study (63.63± 10.46 in Group A and 65.25± 10.01 in Group B) compared to those in the above-cited study (28.2 ± 15.7 U/l). The same study showed that higher reductions of ALT were observed in the highest ALT tertile.[21] Along with that, there was a statically significant reduction of HbA1C in both the groups treated with empagliflozin. The increased decrease of HbA1C in the 10 mg Empagliflozin add-on group than that of the 25 mg add-on group in our study could be explained by higher pre-treatment HbA1C levels in the former than the latter group (9.99 ± 1.73 % vs 9.47±1.41 %). All the patients, including those treated with the addition of 10 mg or 25 mg of Empagliflozin to Sitagliptin and Metformin, along with those treated with Sitagliptin and Metformin alone, were advised about lifestyle change and dietary compliance, there was a reduction of HbA1C in all the groups which was statistically significant, more so with empagliflozin addition (p=0.00, 0.00 and 0.03 in groups A, B and C respectively). Therefore, ALT reduction seemed to be independent of HbA1C improvement. Indeed, this fact is best demonstrated in the study by Sattar et al, who showed that the ALT reductions observed with Empagliflozin are largely independent of changes in HbA1c.[21] The difference between the reduction in ALT and HbA1C in the two groups treated with 10 mg and 25 mg of empagliflozin was minimal and not statistically significant. This means that both doses of empagliflozin are equally effective in reducing the inflammatory process in non-alcoholic steatohepatitis. Indeed, most studies reporting a significant reduction in ALT levels in NAFLD patients with T2DM used empagliflozin in a 10 mg dose.[21-28] Transaminases, in particular ALT, correlate with liver fat. The change in ALT observed with empagliflozin is broadly consistent with a reduction in liver fat.[4] According to the twin-cycle hypothesis of diabetes, excess pancreatic and liver fat are major contributors to the pathogenesis of type 2 diabetes.[26] The E-LIFT Trial reported an absolute reduction in liver fat content in patients with NAFLD who were treated with empagliflozin.[24] This study reported that a 4% reduction in total liver fat was associated with improving steatosis. It has also been shown that individuals with type 2 diabetes with a history of NAFLD have an increased risk of death from cardiovascular disease, all-cause mortality, and incident or recurrent cardiovascular events than those without such history.[27] Therefore, any intervention that lowers liver fat could have particularly important benefits for patients with type 2 diabetes.

## LIMITATIONS

Our study's limitations were the shorter study duration and the fact that ALT levels were taken at one point only before intervention. Of course, diagnosis of NASH on histological grounds and seeing the improvement in histological terms would provide stronger evidence, and more studies are required at the national level.

## CONCLUSION

It is therefore concluded that empagliflozin in both 10 mg and 25 mg doses decreases the ALT levels in T2DM patients, having raised baseline ALT levels and ultrasonographic features of NAFLD.

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