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Beyond Glucose: Empagliflozin's Impact on Fatty Liver in Patients with Type 2 Diabetes; A True Game Changer

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ABSTRACT

Background: Type 2 Diabetes develops in adulthood, and is caused due to failure of pancreatic B-cells to secrete insulin, gradually causing desensitization of B-cells to glucose, leading to insulin resistance1-5. According to American Diabetes Association, due to the chronicity of this disease, long-term complications arise which mostly occur due to hyperglycemia causing microvascular and macrovascular damage6. This brings about significant damage to the heart, eyes(retinopathy), kidneys (chronic kidney disease) and nerves(neuropathy).5 Metabolic dysfunction-associated fatty liver disease (MAFLD) previously known as non-alcoholic fatty liver disease (NAFLD), is defined inclusively as presence of fatty liver disease associated with presence of obesity or Type 2 Diabetes mellitus (T2DM). **Objectives:** To determine the efficacy of Empagliflozin on liver fat content in type 2 diabetics and metabolic dysfunction associated fatty liver disease. **Methodology:** In this Observational study, 200 patients were enrolled via Non-Probability Convenient sampling. It was conducted at Department of Endocrinology Fatima Memorial Hospital, Lahore from 12th October 2024 to 11 January 2025. **Results:** There were total of 200 patients who were enrolled and 114(57%) were males and 86(43%) patients were female. The mean age of the participant was 44.6±6 years. Empagliflozin led to a significant 12.07%± 2.86% reduction on USG. Empagliflozin after three months showed a significant ALT reduction to 28 IU/L from 38 IU/L, showing remarkable results. (p-value <0.0001) whereas looking at HbA1c, Empagliflozin significantly reduced HbA1c by 1.6% ±0.38. (p-value <0.0001) Empagliflozin showed significant improvement in MALD reduction, ALT levels, and HbA1c as compared to the findings noted on first visit and when they were being enrolled for the study. **Conclusion:** Empagliflozin drastically reduced the alanine transaminase (ALT) levels along with and liver fat and reduction in glycosylated Hemoglobin (HbA1c), all are beneficial for the patients having diabetes, which can in turn prevent the further complications related to diabetes.

INTRODUCTION

Diabetes mellitus is a 'disease of pancreas', it is a chronic disease characterized by a group of metabolic dysfunctions inevitably leading to hyperglycemia [(1)]. According to World health organization (WHO) about 422 million people are diagnosed with diabetes, most of them living in low-middle income countries and estimated death per year directly due to diabetes is 1.5 million [(2)]. Both the number of cases and prevalence of diabetes is increasing over time [(2)]. A report done in 2021 by International Diabetes Federation (IDF) estimated that there are 537 million people living with diabetes which accounts for 10.5% of the global population [(3)]. And yet another report by IDF stated that in 2022, almost 26.7% of adults in Pakistan were affected by diabetes, this number is extremely high and is increasing with the passage of time, in addition to this many cases goes undiagnosed, making the actual prevalence and the complication much higher [(4)]. Pakistan is amongst the top ten countries with the highest prevalence rate of diabetes in the world [(3)]. This increase in prevalence is due to westernization of lifestyles, being overweight or obese, as well as with growing age, ethnicity and family history [(3)].

Type 2 Diabetes develops in adulthood, and is caused due to failure of pancreatic B-cells to secrete insulin, gradually causing desensitization of B-cells to glucose, leading to insulin resistance [1][5]. According to American Diabetes Association, due to the chronicity of this disease, long-term complications arise which mostly occur due to hyperglycemia causing microvascular and macrovascular damage [6]. This brings about significant damage to the heart, eyes(retinopathy), kidneys (chronic kidney disease) and nerves(neuropathy) [5].

Metabolic dysfunction-associated fatty liver disease (MAFLD) previously known as non-alcoholic fatty liver disease (NAFLD), is defined inclusively as presence of fatty liver disease associated with presence of obesity or Type 2 Diabetes mellitus (T2DM) [7]. NAFLD and MAFLD are not interchangeable as their definition are quite different. MAFLD diagnostic criteria is presence of metabolic dysfunction and hepatic steatosis [8][9], while in NAFLD patients have hepatic steatosis with no other liver disease or secondary cause of hepatic steatosis (7). A longitudinal cohort analysis was done which reported that the prevalence of T2DM was 24.6% in MAFLD [10]. In other study conducted in tertiary care hospital in Gujranwala, Pakistan reported significant association of MAFLD with type 2 diabetes, with 47.9% diabetic patient having MAFLD [11].

Among many treatment options of NAFLD in type 2 diabetics, weight loss is the first mainstay. But sometimes it becomes very difficult to achieve desired results of weight loss in some patients. Although, many antidiabetic drugs play a vital role in weight loss e.g. thiazolidinedione and glucagon like peptide 1 receptor agonists. But there is no accepted pharmacological treatment for NAFLD and TD2 patients [12]. The mechanism of Sodium glucose cotransporters 2 inhibitors (SGLT2) to reduce glycaemia is to excrete glucose in urine, it also decreases weight and blood pressure [13]. Latva et al. (2019), described in a placebo-based study that SGL2 like dapagliflozin may also improves NAFLD. Cusi et al. (2019), noted that SGL2 like canagliflozin and dapagliflozin trended towards decrease liver fat as compared to placebo [14,15]. Body weight loss and Glycosylated Haemoglobin (HbA1C) are mainly responsible for the decrease liver fat content [15]. Kuthey and Sattar et al. (2018) concluded that Empagliflozin could improve LFC independent of bodyweight and glycaemia [16,17]. According to a study by Kahl et al, Empagliflozin can effectively reduce liver fat in T2DM with NAFLD [18]. A study by Sattar et al, showed that Empagliflozin reduces aminotransferase in TD2, which is effective in those patients with NAFLD along with high ALTs [17]. According to a study by Bodis et al, Empagliflozin effectively controls HCL in T2D and increase serum adiponectin with beneficial effects on hepatocyte integrity which may improve NAFLD [19]. Totally, Empagliflozin can improve NAFLD by composition, insulin resistance, liver fibrosis, and decrease the hepatic enzymes. However, the beneficial effects of Empagliflozin didn't achieve statistical value in terms of AST and liver fat content in previous studies so the more randomized controlled studies and larger sample was required to prove the roles of Empagliflozin in T2DM with NAFLD to establish adequate guidelines for clinical practice.

Rationale of the Study

To the best of our knowledge according to various studies available in Pakistan addressing this problem, this study was among few studies done to assess the efficacy of Empagliflozin on liver fat content in type 2 diabetics and MAFLD. This study was carried out in the endocrinology department of Fatima memorial Hospital Lahore.

OBJECTIVE

To determine the efficacy of Empagliflozin on liver fat content in type 2 diabetics and metabolic dysfunction associated fatty liver disease.

MATERIALS & METHODS

Study design: Observational

Study Duration: Three months after approval from IRB and patients were followed up at 03 months after starting the treatment with Empagliflozin on their first visit who met the inclusion criteria

Study Settings: This study was conducted at Department of endocrinology Fatima memorial Hospital, Lahore.

Ethical Approval

This study was conducted after approval from Institutional review board, IRB approval letter# FMH-0312//2024-IRB-1574

Sample size

A sample size of 200 patients was calculated with 95% confidence interval and 5% margin of error taking prevalence as 24.6%[11] using software (openepi)n= Z^2/d^2 P(1-P)

Sampling Technique

Non-Probability Convenient**.** Patients included, both male and female of age ≥20 year and ≤60 year presenting in endocrinology department of Fatima memorial Hospital, Lahore and Patient with type 2 diabetes mellitus**,** Metabolic dysfunction-associated fatty liver disease**(**MAFLD) as per operational definition (evidence of MAFLD on ultrasonography USG) and these patients were excluded from the study**;** patient consuming alcohol, Type 1 diabetes mellitus, Severe renal impairment, Patients with chronic liver diseases, Patients with Metabolic dysfunction-associated steatohepatitis (MASH)**,** Patients with Hepatitis B, C as

per history and laboratory investigations to avoid any bias.

Data Collection Technique

Evaluation of each of the patients was done by the principal investigator of the study according to the inclusion and exclusion criteria of the study. Demographic, personal and social history regarding factors mentioned in Performa was taken from the patients. The principal investigator and the team collected the data on their follow up visit with the same parameters as they were assessed on their first visit.

Data Collection Tool

Every patient meeting the inclusion criteria was enrolled after a written and informed consent and was evaluated by detailed history taking, followed by general physical examination and few mandatory investigations. These included liver function tests and liver ultrasonography (USG) and HbA1c and all the findings were noted on specially designed proforma and same findings were reassessed after three months and noted on the same proforma.

Statistical Analysis

SPSS 25.0 was used to analyze the data. The outcome variable, incidence of diabetes mellitus type 2 with MALD were presented as percentage of whole population that was included in the study. Quantitative variables like age, and HbA1c were presented as mean and standard deviation. Data was stratified for age and gender. Post-stratification chi-square and t-test were used. P-value of ≤0.05 was considered as significant.

RESULTS

There were total of 200 patients who were enrolled and 114(57%) were males and 86(43%) patients were female. The mean age of the participant was 44.6±6 years. Empagliflozin led to a significant 12.07%± 2.86% reduction on USG. Empagliflozin after three months showed a significant ALT reduction to 28 IU/L from 38 IU/L, showing remarkable results. (p-value <0.0001) whereas looking at HbA1c, Empagliflozin significantly reduced HbA1c by 1.6% ±0.38. (p-value <0.0001) Table-1, Regarding gender and HbA1c there were almost similar drop with a slightly more drop in females were noted. Table-1. Empagliflozin showed significant improvement in MALD reduction, ALT levels, and HbA1c as compared to the findings noted on first visit and when they were being enrolled for the study, these findings suggest Empagliflozin can be game changer in Pakistani patients too with type-2 diabetes mellitus.

Table 1

Parameters assessed	Age mean± SD[!]	MALD[#] reduction after Empagliflozin assessed by USG (%)- {p-value}	ALT[@] Before (U/L) Mean±SD	ALT After (U/L) Mean±SD - {p-value}	HbA1c[$] Change (%) Mean±SD - {p-value}
	44.6(6)	12.07 ± 2.86 (<0.0031)	38 ± 7.84	28±3.2 (<0.0041)	-1.6± 0.38 (<0.0001)
Males	42.3(5)	12.1±2.4	36± 4.1	31±5.2	-1.14±0.46
Females	47.2(6)	11.94±2.1	39± 3.7	28±4.9	-1.43±0.41

!SD standard deviation, #MALD- metabolic dysfunction associated liver disease, @ALT-Alanine transaminase,$HbA1c Glycosylated Haemoglobin further visualizations of the results can be interpreted in pie charts and histograms.

Figure 1

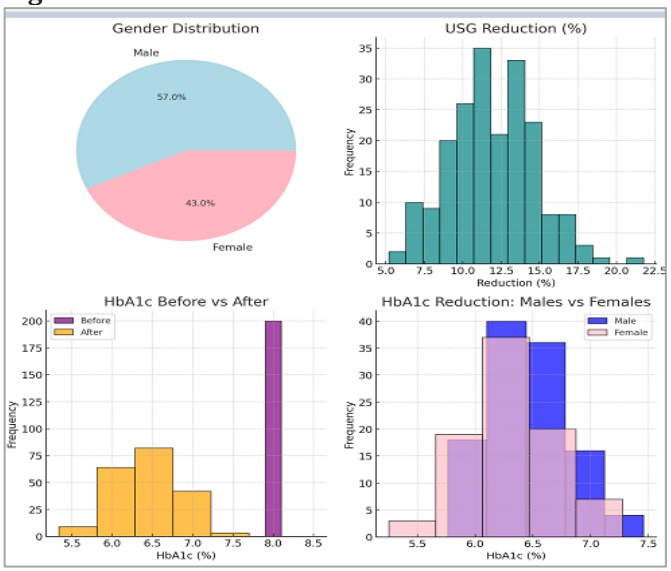


Figure 2

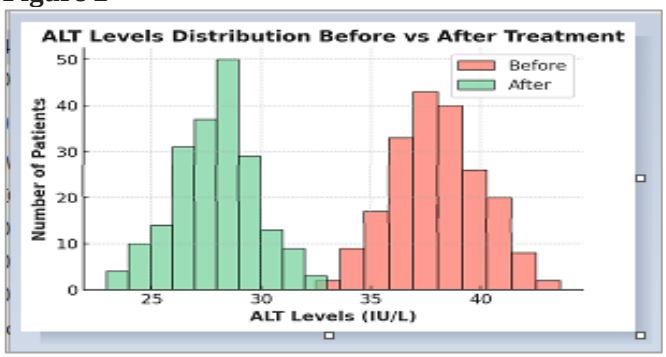


Figure 3

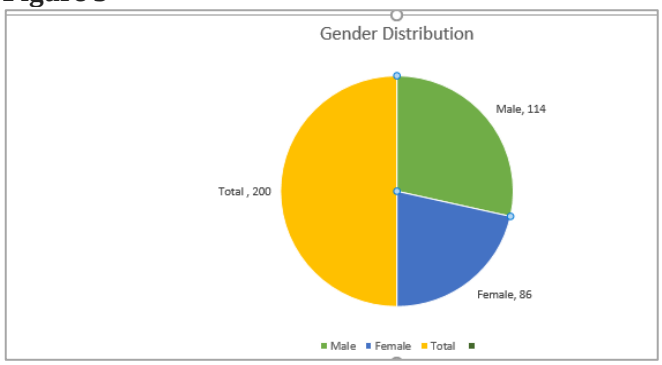
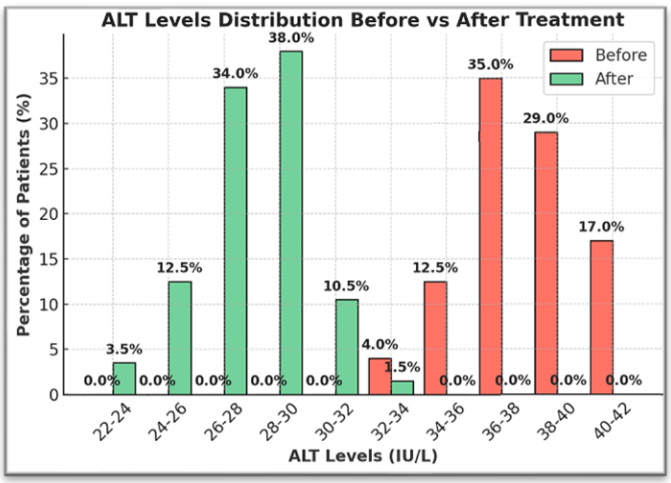


Figure 4



DISCUSSION

To the best of our knowledge, this study was first of its kind from Pakistan assessing the impact of Empagliflozin over fatty liver disease.

A Study conducted by Kuchay MS, et al.[17] comparing the two groups, one group was given Empagliflozin and other group was given conventional management, and this study Published in Diabetes care revealed that there was significant improvement in fatty liver in Empagliflozin group as evidenced by magnetic resonance imaging(MRI) with a p value of <0.0001 and marked reduction of ALT levels with p value of (0.0005), these results are comparable with our study too but assessment of liver fat content was assessed by MRI in the study by Kuchay MS et al. whereas we assessed on USG abdomen, as we are resource constraint country with limitations of availability of this modality(MRI) so we confirmed our findings of USG by a senior radiologist to avoid any bias.

A Multicenter cohort study Conducted by Shao SC et al.[22] revealed marked reduction of HbA1c and ALT levels (-4.1 with a p value of < 0.001), and it was observed in the same study that higher the ALT levels, marked reduction in ALT levels at follow up after one year, these results are consistent with our study results as well.

An open label randomized controlled trial was done by Shimizu M[23] and colleagues and liver fat content and serum ALT levels were reduced in SGLT-2 inhibitor group but no change in control group at follow up and these results are consistent with our study but Shimizu M and colleagues assessed liver stiffness by elastography whereas we used USG, this difference can be attributed to the fact that we are underdeveloped country with limited resources.

A double blind randomized control trial was done by Taheri H, et al[24] this study was done on patients with MALD and they were offered Empagliflozin for 24 weeks, and they found it that 9.3% patients in empagliflozin group had no MALD at follow up which was not found in placebo group at all and at follow up a marked improvement in the severity of fatty liver was observed based on the blinded visual analysis and on USG In the empagliflozin group, 44.2% of participants had grade II fatty liver at baseline, which decreased to 18.6% at follow up with statistically significant difference (P = 0.001), these results are comparable with our study as well.

A meta-analysis of the randomized controlled trials was published by Tang X, et al.[25] revealed that there was no difference on ALT levels and fat liver content, this could be due to the fact that they had reviewed few studies and most of those studies had smaller sample size.

A study Conducted by Cheung KS, et al.[26] concluded that out of 98 recruited patients with a median age: 55.7 years and the Empagliflozin group had a remarkable improvement in median fat liver content as compared to the control group (-2.49% vs. -1.43%; p- value of 0.025), as compared to our study, we had almost same group of patients with mean age of 42 years, with

reduction in fat liver content, HbA1c and ALT levels.

A Systemic review and Meta-analysis was Conducted by Zhang & Colleagues[27] concluded that Empagliflozin better liver stiffness measurement with mean difference of 0.49 with 95% CI: −0.93, −0.06], p = 0.03), the results are comparable with our study apart from the difference of assessment method as we used USG for MALD assessment.

Another meta-analysis of six trials conducted by Xing B,et al[28] revealed that Empagliflozin could reduce the ALT levels by mean difference of -11.05 IU/L, with 95% confidence interval and p value 0f 0.05, highly comparable with our study as we had mean difference of 10 IU/L in ALT levels, whereas Xing B,et al[28] also concluded that there was no difference in Aspartate transaminase levels, which was not statistically significant whereas we didn't follow the AST levels, however weight reduction in both studies was statistically significant $P < 0.00001$.

Xing B et, al concluded that Empagliflozin drastically reduced the ALT levels along with and liver fat, with an additional benefit of weight loss, which can be attributed to the fact that it must have helped in improvement of fatty liver in patients with type 2 diabetes mellitus.[27]

CONCLUSION

Empagliflozin drastically reduced the ALT levels along with and liver fat and reduction in HbA1c, all are beneficial for the patients having diabetes, which can in turn prevent the complications related to diabetes and lot has been talked about the fat liver content, related to the

ischemic heart disease, so by reducing the liver fat content, we can get multiple benefits from this true game changer Empagliflozin esp. in resource constraint country like Pakistan.

Limitations and Recommendations

It was a single center study with relatively smaller sample size as compared to the disease burden in Pakistan, so multicenter randomized controlled trials targeting the impact of Empagliflozin over MALD and weight loss and HbA1c reduction are required to reanalyze our results among various cities of Pakistan to see the regional variations if any among different cities, provinces and cultures.

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