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Systematic review

# Effect of empagliflozin on liver function in type 2 diabetes: A systematic review and meta-analysis of randomized trials

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## Abstract

Many reports are indicating the blood sugar-lowering potential of empagliflozin in type 2 diabetes mellitus and its anti-lipogenesis effects in the liver, as studied in mice models; while few clinical trials have evaluated its effect on liver fat content and liver function. This study aimed to evaluate the effect of empagliflozin on the treatment of non-alcoholic fatty liver disease in type 2 diabetes mellitus patients. Scopus, Cochran Library, PubMed, and Web of Science databases were searched from 1990 to 2022 with reference checking and citation searching to identify additional studies. The inclusion criteria for studies included were the evaluation of patients with non-alcoholic fatty liver disease and type 2 diabetes being treated with empagliflozin for 24 weeks. Our interest outcomes were Liver fat, Alanine transaminase (ALT), and Aspartate transaminase (AST). Data analysis random effect size model was used for pooling data to calculate mean differences in RevMan Version 5.3. $I^2$ was used to evaluate heterogeneity. Three clinical trial studies were included with 2344 patients. In pooled ALT mean difference evaluation within 24 weeks of studies, there was a significant difference between subjects receiving empagliflozin versus controls (MD = -6.6 CI95% (-10.27 to -3.73; P = 0.06; $I^2$ = 99%). In the case of AST (MD = -9.06 CI95% (-20.45 to 2.34; P = 0.12; $I^2$ = 98%) and Liver fat (MD = -4.46 CI95% (-10.06 to 0.77; P = 0.09; $I^2$ = 98%), there was not any significant difference between subjects receiving empagliflozin versus controls. While empagliflozin seems to be effective in lowering ALT levels; further studies are needed to confirm its efficacy in lowering liver fat.

**Keywords:** Non-alcoholic fatty liver disease, Empagliflozin, Type 2 diabetes mellitus

## 1. Introduction

Non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) have many semblances in underlying risk factors, pathogenicity, and epidemiology [1]. NAFLD includes a histological range from simple steatosis (SS) to steatosis with necrotic empagliflozin (nonalcoholic steatohepatitis, NASH) with or without fibrosis that can only be detected by liver biopsy [2]. Today, NAFLD is known to be highly associated with liver transplantation in the United States and is reported annually as the leading cause of a significant percentage of hepatocellular carcinoma (HCC) [3]. NAFLD affects 30% of the adult population and 60-80% of diabetic and obese patients [4]. NAFLD directly increases the risk of cardiovascular disease (CVD) and diabetes through its association with other cardiovascular disorders, including obesity and metabolic syndrome [5]. Sodium-glucose-2 (SGLT2) inhibitors increase renal glucose excretion and decrease HbA1c by reducing renal glucose reabsorption, which in turn lowers blood sugar in people with type 2 diabetes [6]. Empagliflozin,

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a highly selective SGLT2 inhibitor, was the first glucose-lowering agent to reduce cardiovascular outcomes in people with type 2 diabetes and cardiovascular disease [7]. Empagliflozin is probably associated with weight loss due to reducing caloric intake [8]. Approximately 90% of weight loss with empagliflozin is due to the reduction of adipose mass in the visceral adipose tissue of the abdomen and subcutaneous tissue, which results in a very high probability of recovery of liver fat with empagliflozin [9]. Empagliflozin inhibits the progression of NAFLD by reducing the expression of genes involved in hepatic lipogenesis [10]. While many reports are suggesting the beneficial effects of empagliflozin in non-alcoholic fatty liver disease and type 2 diabetes in mice models [10, 11]; only a few research studies are conducted as clinical trials to investigate its effect on NAFLD. So, we aimed to provide a meta-analysis to combine these studies' results. Also, the present study aims to answer the following questions: Is there a significant difference between subjects receiving empagliflozin versus controls in pooled Alanine transaminase (ALT) mean difference evaluation within 24 weeks of studies? Is there any significant difference between subjects receiving empagliflozin versus controls in the case of Aspartate transaminase (AST) and liver fat?

## 2. Materials and Methods

### *2.1 Research strategy*

This is a systematic review and meta-analysis study based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. This study was performed based on Helsinki's research ethics. To identify studies related to the topic, Scopus, Cochran Library, PubMed, and Web of Science were investigated from 1990 to 2020. There was also a manual search of randomized clinical trial studies registration sites such as the Trial Register, Clinical Trial, International Diabetes Congresses, and the Food and Drug Administration US (FDA). Conferences related to diabetes and the list of sources of identified articles were also reviewed for further study.

Articles written in English were searched. To choose proper keywords, Structured Question Components or PICO methodology was considered: Population (P): patients with type 2 diabetes and NAFLD, Intervention (I): Empagliflozin, Comparison (C): with control or placebo; Outcome (O): Decreased liver fat, Design (D): clinical trials. Then, keywords were selected based on the Mesh dataset for the search. The search strategy was as follows: "(Empagliflozin OR SGLT-2 OR Sitagliptin Phosphate) AND (type 2 diabetes OR TDM2 OR diabetes) AND (non-alcoholic fatty liver disease OR fatty liver)".

### *2.2 Inclusion and exclusion criteria*

Also, inclusion and exclusion criteria of the study were determined based on the PICO: Population: The inclusion criteria for the study population was the non-alcoholic fatty liver disease in type 2 diabetes patients. Studies examining other unrelated disorders were excluded. Intervention: Studies that do not have the intended intervention of Empagliflozin treatment were excluded. Comparison: Studies that did not examine our comparison groups, which were mainly retrospective studies, were excluded. Outcome: Studies that have examined outcomes unrelated to our study were excluded from the study. Our interest outcomes were Liver fat, ALT, and AST. Design: Studies that have inappropriate validity or have used inappropriate methods to design the study and have obvious biases are excluded from the study. Finally, studies using empagliflozin as one of the arms of the clinical trial were included in the meta-analysis.

Based on the inclusion and exclusion criteria of the study, two researchers independently reviewed the title and abstracts. After removing duplicated cases and irrelevant articles, the full text of selected studies was evaluated for inclusion and exclusion criteria. Final articles were selected and the list of references of the main articles that were finally included in the study was also reviewed. Wherever there was a dispute between the two investigators, the third person judged. Variables including first author name, year of study publication, age of individuals, sample size, ALT levels, AST levels, and liver fat percentage were extracted from the studies.

### *2.3 Data extraction and quality assessment*

All search results were managed with EndNote X7.1 (Clarivate Analytics, Philadelphia, PA, USA). Duplicates were deleted and the title and abstract of remaining citations were reviewed to exclude irrelevant articles. For the remaining citations, full texts were downloaded and evaluated. To evaluate the Risk of bias, RoB 2 Cochrane risk-of-bias tool was

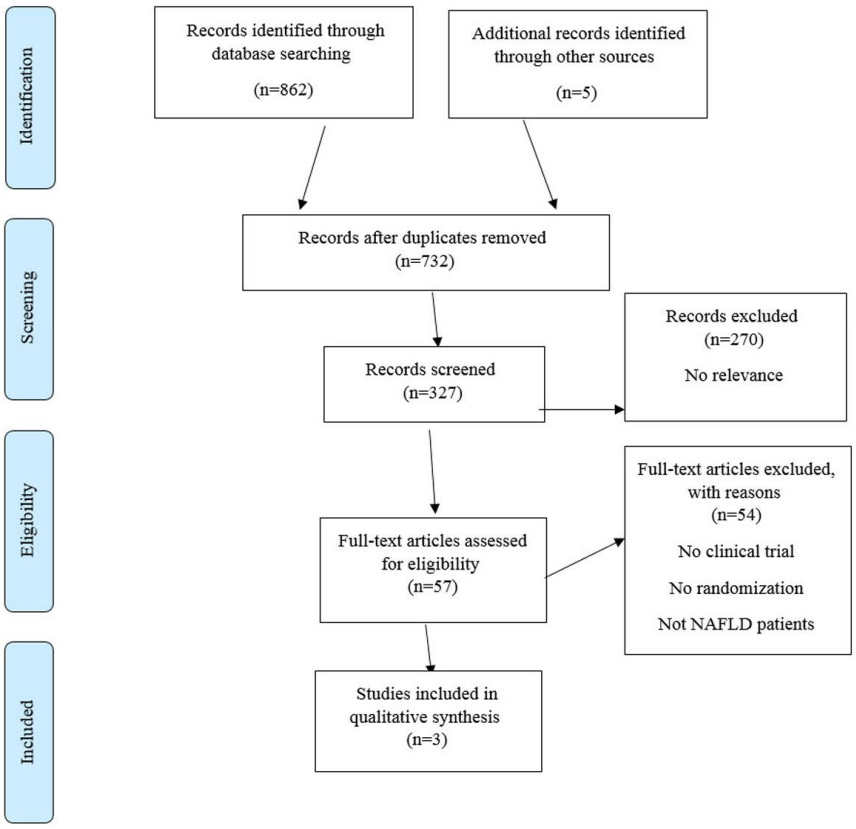


Figure 1. PRISMA flowchart showing the search and study selection strategy

used. Considering that to evaluate the bias in the publication of studies should not be less than ten studies, we were not able to evaluate the publication bias [12]. To calculate the effectiveness, the standardized effect difference index of the means (MD) was used. Results were based on a random model effect size with a 95% confidence interval. A value of p less than 0.05 was considered a statistically significant value. $I^2$ was used to evaluate the heterogeneity between the studies. Study data was entered in RevMan Version 5.3 software and analyzed.

## 3. Results

In the current meta-analysis study, three clinical trial studies were included [13-15]. A PRISMA flowchart showing the search and study selection strategy is presented in Figure 1. Also, the detailed information presented in the three included studies are summarized in Table 1.

A total number of 2344 patients were evaluated in this meta-analysis study. In pooled ALT mean difference evaluation within 24 weeks of studies, there was a significant difference between subjects receiving empagliflozin versus controls (MD =-6.6 CI95% (-10.27 to -3.73; P = 0.06; $I^2$ = 99%) (Figure 2).

In pooled AST mean difference evaluation in 24 weeks empagliflozin treatment, there was not any significant difference between subjects receiving empagliflozin versus controls (MD =-9.06 CI95% (-20.45 to 2.34; P = 0.12; $I^2$ = 98%) (Figure 3).

In the pooled Liver fat percentage mean difference following the 24 weeks of treatment with empagliflozin, there was not any significant difference between subjects receiving empagliflozin versus controls (MD =-4.46 CI95% (-10.06 to 0.77; P = 0.09; $I^2$ = 98%) (Figure 4).

## 4. Discussion

Empagliflozin is a new drug that has been introduced for the treatment of type 2 diabetes. Despite its importance, until now there is no comprehensive study regarding the effect of this drug in the treatment of patients with non-alcoholic fatty liver disease and type 2 diabetes.

Table 1. The detailed information presented in the three included studies

| Study ID | Treatment protocol | Study population | Outcome measurements | Bias | | | |
|---|---|---|---|---|---|---|---|
| | | | | Randomization process | Missing outcome data | Measurement of the outcome | Selection of the reported result |
| Sattar, 2018 | Empagliflozin 10 mg, empagliflozin 25 mg or placebo once daily for 24 weeks. | 2477 T2D patients | ALT and AST change | + | ? | + | + |
| Kahl, 2020 | 24 weeks of treatment with 25 mg daily | 84 patients with T2D | Liver fat content by magnetic resonance methods and Tissue-specific insulin sensivity | + | + | + | ? |
| Kuchay, 2018 | Standard treatment for T2D plus empagliflozin 10 mg daily vs. control standard. | 50 patients with NAFLD | MRI-PDFF, ALT, AST | + | ? | + | + |

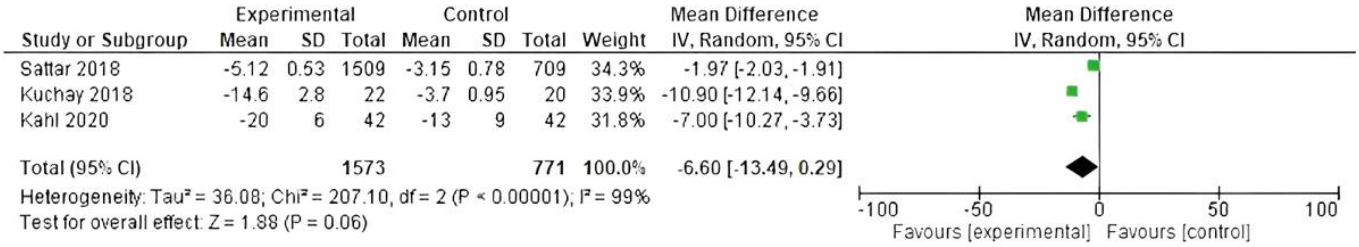


Figure 2. The pooled ALT mean difference evaluation within 24 weeks of studies

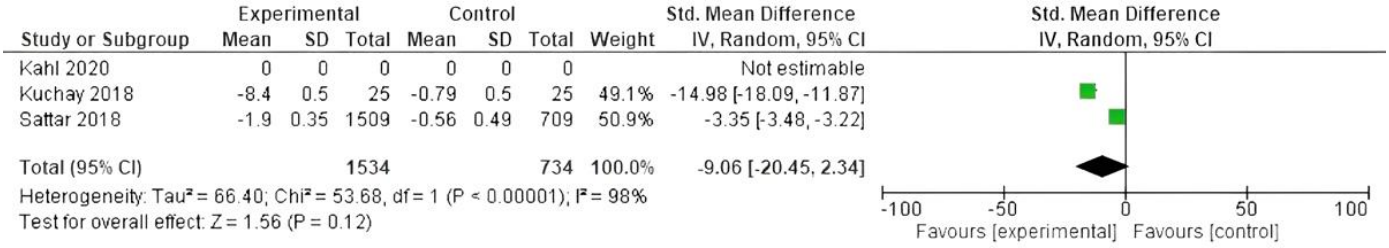


Figure 3. The pooled AST mean difference evaluation in 24 weeks Empagliflozin treatment

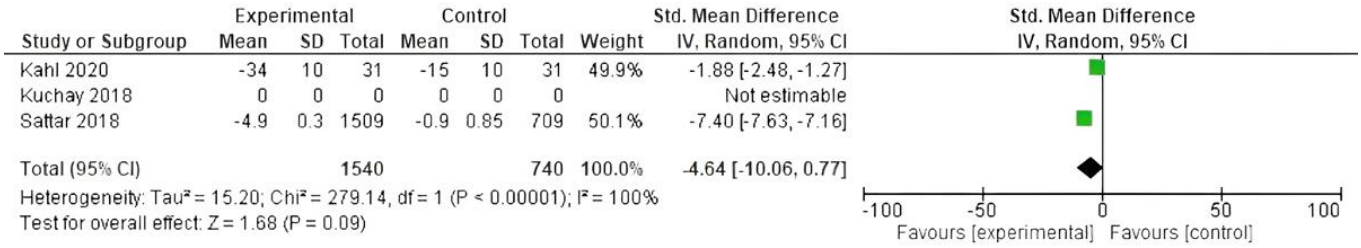


Figure 4. The pooled Liver fat percentage mean difference following the 24 weeks of treatment with Empagliflozin

In the present study we reviewed all documents published in English language on the topic across the world. The results of the present study demonstrated while empagliflozin seems to be effective in lowering ALT levels; in the case of AST and Liver there was not any significant difference between subjects receiving empagliflozin versus controls. Cherney et al. in a review of the empagliflozin efficiency in blood sugar control and tolerability in patients with type 2 diabetes have shown a moderate decrease in HbA1c [16]. As stated in Goldman's review [17], the combination therapy (metformin and empagliflozin was well tolerated in patients with type 2 diabetes, and blood glucose control improved significantly compared to monotherapy, but they stated that this combination was not suitable for every patient. Our results indicated a significant difference between subjects receiving empagliflozin versus controls in ALT levels; while no significant difference in the case of liver fat and AST. According to a study by Kahl et al., empagliflozin effectively reduces liver fat in patients with T2D with excellent glycemic control [13]. Interestingly, empagliflozin also reduces circulating uric acid and increases adiponectin levels despite not changing insulin sensitivity. Thus, empagliflozin can help in the early treatment of non-alcoholic fatty liver disease in T2D [14]. A study by Sattar et al. showed that empagliflozin reduces aminotransferases in people with type 2 diabetes, which is potentially compatible with reduced liver fat, especially when ALT aminotransferase levels are high [10]. According to a study by Bodis et al., empagliflozin effectively controls HCL in T2D patients and increases serum adiponectin with beneficial effects on hepatocyte integrity [18]. As a result, empagliflozin may improve NAFLD through various mechanisms [13]. According to a study by Kuchay et al. [15], Empagliflozin in the standard treatment of type 2 diabetes significantly reduces liver fat and improves serum ALT levels, and also shows that SGLT-2 inhibitors are beneficial agents for improving NAFLD, which is often present with type 2 diabetes [19]. According to a study by Lee et al., the use of empagliflozin is a new approach to glycemic control and is associated with several proven cardio-metabolic and renal benefits beyond the glucose-lowering effect [19]. Evidence from that study shows that among Chinese people with T2DM, with or without background insulin therapy, empagliflozin not only improves metabolic parameters but also improves liver function as a class [19].

Totally, empagliflozin can improve body composition, insulin resistance, liver fibrosis, and decrease the hepatic enzyme (ALT) in patients with T2DM. However, the beneficial effects of empagliflozin did not achieve statistical significance in terms of AST and liver fat in the present study. Thus, more RCTs with longer duration and larger sample sizes are required to decide the roles of empagliflozin in patients with NAFLD and T2DM to establish adequate guidelines for clinical practice.

The first limitation of this review is the very low number of studies in this field. One other limitation of this study that could be a huge trigger of high heterogenicity was the issue of other prescribed medications, as not all participants of the studies were receiving monotherapy of empagliflozin Also, one study used a control group; while the other 2 studies were using a placebo to make a comparison.

In summary, empagliflozin seems to be effective in lowering ALT levels; while further studies are needed to confirm its efficacy in lowering liver fat.

## Authors' contributions

ZR, DR: Investigation, Data curation. DR: Conceptualization, Methodology, Project administration. ZR, DR: Methodology, Project

administration, Writing - original draft, Resources, Visualization. ZR, KD, DR: Writing - review & editing. All authors contributed to the article and approved the final version.

## Conflict of interests

The authors have no conflict of interest to declare.

## Ethical declarations

Not applicable.

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