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# Role of SGLT-2 Inhibitors in Treatment of Patients with Type 2 Diabetes and NAFLD

Research Article

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## Abstract

**Background:** The role of sodium-glucose cotransporters-2 (SGLT-2) inhibitors in treatment of non-alcoholic fatty liver disease (NAFLD) is unclear.
Objective: To examine the possible therapeutic role of SGLT-2 inhibitors in patients with type 2 diabetes and NAFLD.
**Methods:** Pubmed search of English literature up to February 17, 2022. Search terms are fatty liver, SGLT-2, sodium-glucose cotransporter-2 inhibitors, diabetes, weight loss, liver biopsy. Randomized studies are reviewed with focus placed on double-blind, placebo-controlled trials. Meta-analyses and pertinent reviews are also included.
**Results:** Six randomized double-blind placebo-controlled trials examined the effects of SGLT-2 inhibitors on intra-hepatic fat content (IHFC) over 8-24 weeks mostly by magnetic resonance imaging (MRI) techniques. Two trials reported significant reduction in IHFC with SGLT-2 inhibitors, one reported borderline statistically significant reduction, and the remaining 3 trials showed a trend towards amelioration of IHFC that did not reach statistical significance. One placebo-controlled study showed that empagliflozin (10 mg/d) may decrease IHFC in patients with NAFLD without diabetes. Weight loss induced by SGLT-2 inhibitors appears to be a major factor in decreasing IHFC. Two small non-randomized biopsy studies showed that canagliflozin could improve histopathologic disease severity in patients with confirmed NAFLD and type 2 diabetes.
**Conclusions:** SGLT-2 inhibitors are promising agents for treatment of NAFLD. Long-term randomized studies using paired hepatic biopsies as endpoints are urgently needed to establish the therapeutic role of SGLT-2 inhibitors in NAFLD in patients with and without diabetes.

**Keywords:** Fatty Liver; Sodium-Glucose Cotransporter-2 Inhibitors; Diabetes; Liver Biopsy.

**Abbreviations:** HA1c: Hemoglobin A1c, MRI: Magnetic Resonance Imaging, GGT; Gamma-Glutamyl Transferase, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase.

## Introduction

There are multiple reasons to evaluate SGLT-2 inhibitors for treatment of NAFLD. First, the prevalence of NAFLD in patients with type 2 diabetes is very common ranging from 29.6% to 87.1%, with an estimated pooled prevalence of 59.6% (95% CI; 54.3–64.9%) [1]. Second, NAFLD is associated with increased incidence of cardiovascular and chronic kidney disease [2, 3]. In the meantime, there is strong evidence from randomized trials that SGLT-2 inhibitors may reduce cardiorenal events in patients with type 2 diabetes [4, 5]. Third, uncontrolled glycemic control may be linked to increased severity of histological changes of NAFLD [6]. Thus, every 1% increase in mean hemoglobin A1c (HbA1c) levels was associated with 15% higher odds of increased fibrosis stage (odds ratio 1.15; 95% CI, 1.01-3.01) [6]. Therefore, it is possible that improving glycemic status by SGLT-2 inhibitors could decrease severity and progression of NAFLD. Fourth, while weight loss is the cornerstone therapy for NAFLD, the use of SGLT-2 inhibitors results in mild weight loss of approximately 2-3 kg [4, 5]. This magnitude of weight loss, although modest, could contribute to amelioration of NAFLD [7]. Finally, there is currently no medications approved by the Federal Drug Administration (FDA) for treatment of NAFLD. Hence, it is necessary to pursue research efforts to find effective and safe drugs to fill this large gap. The main purpose of this article is to summarize human data regarding the potential therapeutic benefits of SGLT-

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2 inhibitors in NAFLD. Special emphasis will be placed on the strongest evidence derived from randomized, double-blind-placebo controlled trials.

## Randomized, Double-Blind, Placebo-Controlled Studies

Six randomized double-blind, placebo-controlled trials (summarized in table 1) are available for evaluation of effects of various SGLT-2 inhibitors on IHFC [8-13]. Intrahepatic fat was measured by MRI in 5 studies, and by transient hepatic elastography (liver FibroScan) in one study [8] (table 1). The studies were generally small (32-106 patients) and of short duration (8-24 weeks). In 5 studies, majority of patients (56-70%) were men (table 1). NAFLD was not a prerequisite inclusion criterion, except in the trial conducted by Eriksson et al [12] in which all patients had NAFLD at baseline (defined as proton density fat fraction of ≥5.5% by MRI) and in the trial by Chehrehgosha et al [8] (defined as controlled attenuation parameter ≥238 dB/m in transient hepatic elastography by FibroScan). In 2 of the 6 studies, dapagliflozin and empagliflozin were associated with significant decrease in IHFC after 8 weeks and 24 weeks, respectively compared with placebo (table 1) [9, 10]. In one trial [8], empagliflozin 10 mg/d was associated with borderline significant reduction in IHFC versus placebo (P=0.05). In the remaining 3 studies using canagliflozin and dapagliflozin, there was a trend toward reduction in IHFC versus placebo that did not attain statistical significance [11-13] (table 1). Overall, the magnitude of reduction in IHFC was modest [9, 10] (table 1). For instance, placebo-corrected relative reduction in IHFC of 22% was demonstrated with empagliflozin [9]. Meanwhile, emerging data suggests that a relative reduction of at least 30% of IHFC may be clinically meaningful [14]. Of note, all 6 studies included overweight and obese patients with fairly controlled type 2 diabetes (mean baseline HbA1c 6.8-7.7%). However, in one open-label, and non-placebo-controlled trial, Kuchay et al [15] included patients with poorly controlled type 2 diabetes (mean HbA1c 9.0%) and all subjects had documented hepatic steatosis at baseline (defined as liver fat > 6% as measured by MRI-proton density fraction). After 20 weeks, small dose of empagliflozin (10 mg/d) was associated with significantly greater relative reduction of IHFC of 4% than the control group receiving standard diabetes care (P<0.0001) [15].

## Comparison Head To Head Trials

Few randomized trials compared the effect of SGLT-2 inhibitors with other agents on fatty liver in patients with type 2 diabetes. The placebo-controlled trial of Chehrehgosha et al [8] mentioned above included a third group of patients randomized to pioglitazone (30 mg/d), another anti-diabetic agent that showed previous efficacy in decreasing IHFC in patients with and without diabetes [16, 17]. After 24 weeks, the decrease in liver fibrosis (evaluated by liver stiffness measurement) was significantly greater with empagliflozin compared with pioglitazone [8]. In one open-label Japanese study, Kinoshita et al [18] compared effects of dapagliflozin (5 mg/d), pioglitazone (mean daily dose 17.3 mg), and glimepiride (mean daily dose 0.9 mg) on NAFLD assessed by change in liver-to-spleen (L/S) ratio on abdominal computed tomography. All included patients (n=98) had NAFLD at baseline defined as L/S ratio <1.0, After 28 weeks, all 3 groups of patients had similar glycemic control. Yet, glimepiride had no impact on L/S ratio, whereas dapagliflozin and pioglitazone had similar effects on de-

**Table 1. Randomized, double-blind, placebo-controlled trials to evaluate effects of SGLT-2 inhibitors in NAFLD liver in patients with type 2 diabetes.**

| Reference (from most recent to older references) | Type and dose of SGLT-2 inhibitor | Follow-up, patients' number, mean baseline HbA1c | Placebo-corrected difference in liver fat content* | Effect on liver enzymes vs placebo |
|---|---|---|---|---|
| Chehrehgosha et al [8] | Empagliflozin 10 mg/d vs pioglitazone 30 mg/d vs placebo | 24 weeks, n= 106 (43% men), HbA1c 8.0% | Borderline significant decrease with empagliflozin vs placebo (P=0.05). | Significant decrease in ALT with empagliflozin and in ALT and AST with pioglitazone vs baseline but not vs placebo). |
| Kahl et al [9] | Empagliflozin 25 mg/d | 24 weeks, n=84 (69% men), HbA1c 6.8% | Absolute difference: -1.8% (95% CI, -3.4 to -0.2, P=0.02). Relative difference: -22% (95% CI, -36 to -7, P=0.009). | No significant difference in GGT, AST and ALT. |
| Latva-Rasku et al [10] | Dapagliflozin 10 mg/d | 8 weeks, n=32 (80% men), Hb A1c 6.9% | Absolute difference -3.7% (95% CI, -6.1 to -1.3, P <0.01). | No significant difference. |
| Cusi et al [11] | Canagliflozin 300 mg/d | 24 weeks, n=56 (66% men), HbA1c 7.7% | Absolute difference -2.2% (P =0.09). Relative difference -18% (P=0.09). | Not reported. |
| Eriksson et al [12] | Dapagliflozin 10 mg/d vs omega carboxylic acid vs their combination vs placebo | 12 weeks, n=84 (70% men), HbA1c 7.4% | No significant difference between dapagliflozin and placebo in relative reduction of liver fat (-13% and -3%, respectively) | Significant decrease in ALT, AST and GGT. |
| Bolinder et al [13] | Dapagliflozin 10 mg/d | 24 weeks, hepatic fat was measured in a subgroup of 80 patients, HbA1c 7.1% | No significant difference between dapagliflozin and placebo in absolute reduction of liver fat -2.3% and -1.5%, respectively, P=0.044. | Not reported. |

*Liver fat was measured by magnetic resonance imaging, except in the trial of Chehrehgosha et al [8], which was measured by liver FibroScan.

creasing IHFC as reflected by a significant increase in L/S ratio [18]. Using the same previous methodology to evaluate NAFLD, Ito et al [19] compared the effects of ipragliflozin (50 mg/d) and pioglitazone (15-30 mg/d) on NAFLD in an open-label study including 66 patients with poorly controlled type 2 diabetes (mean baseline HbA1c 8.3%). After 24 weeks, the effects of ipragliflozin and pioglitazone on L/S ratio was similar [19]. Taken together, the above head to head trials suggest that SGLT-2 inhibitors are at least equivalent to pioglitazone in reducing IHFC. Interestingly, in the 3 previous studies, pioglitazone therapy was associated with weight gain, whereas the SGLT2 inhibitors (empagliflozin, dapagliflozin and ipragliflozin) were associated with weight loss [8, 18, 19]. This finding suggests that different mechanisms of actions may be involved in the decrease of IHFC between SGLT-2 inhibitors and pioglitazone. In support of this notion, is the demonstration of an "additive effect" on reduction of IHFC when both agents are used concomitantly as outlined in the coming paragraph.

## Combination Therapy

In a small (n=44) randomized trial of 26 week-duration, Han et al [20] showed that addition of ipragliflozin (50 mg/d) to ongoing pioglitazone therapy further decreased IHFC assessed by transient liver elastography. In a post-hoc analysis of a randomized trial (DURATION-8), Gastaldelli et al [21] compared efficacy of dapagliflozin 10 mg/d, the GLP-1 agonist exenatide (2 mg once weekly by subcutaneous injection), or their combination in reducing severity of NAFLD. After 52 weeks, they found that combination therapy was superior to each treatment alone in ameliorating serum markers of hepatic steatosis and fibrosis [21].

### Histological studies

Unfortunately, data from histological studies are very limited. Akuta et al [22] examined the effects of canagliflozin 100 mg bid in 5 patients with type 2 diabetes and histological evidence of NAFLD (defined as steatosis in 5% or more of hepatocytes). After 24 weeks, repeated liver biopsies showed improvement in the NAFLD activity score, which represents the sum of steatosis, lobular inflammation, and hepatocyte ballooning scores in all 5 patients [22]. In another pilot study, Lai et al [23] evaluated empagliflozin 25 mg/d in 9 patients with type 2 diabetes and confirmed NAFLD. These authors used historical placebo group for comparison. After 24 weeks, all histological histologic outcomes (steatosis, fibrosis, ballooning), either remained unchanged or improved, except in one patient who had worsening ballooning [23]. Thus, compared with historical placebo, empagliflozin therapy was associated with significantly greater improvements in steatosis (67% vs 26%, P=0.025), ballooning (78% vs 34%, P =0.024), and fibrosis (44% vs 6%, P=0.008) [23]. These preliminary data are encouraging. Clearly, they require confirmation by randomized double-blind and placebo-controlled histological studies.

### Effects of SGLT-2 inhibitors on NAFLD in patients without diabetes

In one randomized double-blind and placebo controlled, Taheri et al [24] evaluated effects of small dose empagliflozin (10 mg/d) on the degree of steatosis in 90 patients without diabetes by liver FibroScan. After 24 weeks, the percentage of patients of patients with improved steatosis was significantly greater in the empagliflozin group than the placebo group, 37.2% and 17%, respectively (P=0.035) [24]. Of note, this significant difference was observed only in the subgroup of patients (n=44) with significant steatosis at baseline [24]. Furthermore, fibrosis score was significantly improved in the empagliflozin group vs placebo (P==0.039) [24].

### Effects of SGLT-2 inhibitors on transaminases

Elevation of serum aminotransaminases is considered a surrogate marker of NAFLD. However, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) can be normal in many cases of NAFLD including patients with advanced fibrosis [25]. As seen in table 1, effects of SGLT-2 inhibitors on transaminases are variable, with no significant effect in most studies. A meta-analysis of randomized trials showed that treatment with SGLT-2 inhibitors significantly decreased levels of ALT (9 trials), and gamma-glutamyl transferase (GGT) (6 trials), but not AST (9 trials) [3].

### Predictors to favorable response to SGLT-2 inhibitors

Preliminary data from placebo-controlled trials suggest that the following 3 factors may predict a favorable response to SGLT-2 inhibitors in terms of reduction in IHFC. First, the magnitude of weight loss as shown in most studies [9, 11]. Second, the decrease in hepatic fat might be more pronounced in patients with baseline NAFLD [11, 24]. Third, response to SGLT-2 inhibitors with respect to gender was only analyzed in the study by Kahl et al [9]. In that study, there was only significant decrease in IHFC among males [-31% (95% -44 to -14; P=0.002)], but not females [-1% (95% CI -28 to +37); P=0.96] [9].

### Possible mechanisms of reduction of hepatic fat by SGLT-2 inhibitors

The exact mechanisms whereby SGLT-2 inhibitors may decrease IHFC are not fully elucidated. Possible mechanisms are discussed below.

**Weight loss:** While the use of SGLT-2 inhibitors is known to induce a weight low of approximately 2.5 kg [9, 11, 13], this minor degree of weight loss appears to be a major factor in decreasing liver fat. For example, in the study of Kahl et al [9], the difference in liver fat between the empagliflozin group and placebo group was no longer statistically significant after adjustment for change in body weight. Moreover, in the study of Cusi et al [11], significant correlation between weight loss and decrease in IHFC (correlation coefficient r =0.58, P<0.001) was observed in patients randomized to canagliflozin as well as those randomized to placebo. Conversely, Kuchay et al [15] did not find significant correlation between weight reduction and liver fat reduction (r=0.218, P=0.329). Thus, it is possible that factors other than weight loss could be also involved.

**Effect on insulin resistance:** Insulin resistance plays a major role in the pathogenesis of both type 2 diabetes and NAFLD [26]. Meanwhile, there is no evidence that SGLT-2 inhibitors improve insulin sensitivity either in the whole body [8] or in various tissues such as the liver, adipose tissue and muscle [9]. In addition, Cusi et al [11] did not find any effect of canagliflozin on insulin resistance in muscle and adipose tissue. Although these authors reported improvement of insulin sensitivity at the level of hepatic tissue

by canagliflozin, the drug had no significant effect on IHFC [11].

**Glycemic control:** The design of 2 trials allowed testing the hypothesis whether amelioration of glycemic status by SGLT-2 inhibitors may have a role in decreasing IHFC. Thus, in these 2 studies, the authors maintained similar HbA1c values throughout the trials both in patients with controlled type 2 diabetes in the study of Kahl et al [9], and patients with uncontrolled type 2 diabetes in the study of Kuchay et al [15]. In both studies, SGLT-2 inhibitors decreased IHFC despite similar glycemic control between patient groups. Another finding that supports the concept that reduction in IHFC by SGLT-2 inhibitors occurs independently of glycemic control is the observation showing that empagliflozin may decrease steatosis and fibrosis in patients without diabetes [24].

**Other mechanisms:** Other potential mechanisms include decrease in insulin levels by SGLT-2 inhibitors leading to reduction in hepatic de novo lipid synthesis and increase in glucagon levels. The latter leads to stimulation of hepatic β-oxidation of fatty acids [26, 27]. Further investigations are required to study the relative contribution of these mechanisms to the decrease in IHFC by SGLT-2 inhibitors.

## Conclusions And Future Needs

Preliminary data suggest that SGLT-2 inhibitors may have beneficial effects for treatment of NAFLD. Most placebo-controlled studies relied on MRI-imaging modalities to assess changes of IHFC after drug intervention. This methodology suffers from important limitations. Indeed, by analysis of data from 121 patients with paired liver biopsies and MRI, Bril et al [28] concluded that quantification of liver fat with MRI techniques may be misleading as a surrogate marker of treatment response and may not accurately predict histological improvement of steatohepatitis after treatment. In fact, liver biopsy remains the gold standard method to confirm diagnosis of NAFLD and evaluate its response to different therapeutic interventions. In that respect, the study of Dapagliflozin Efficacy and Action in NASH (DEAN) (NCT03723252) is an ongoing phase 3, randomized, placebo-controlled trial that will recruit 100 biopsy-proven NASH patients with type 2 diabetes. The primary outcome of the DEAN trial is to examine the effect of dapagliflozin (10 mg/d) on hepatic histological lesions after 12 months compared with placebo. Combat T2 NASH is another randomized 48 week-trial that compares empagliflozin with the once-weekly glucagon-like peptide-1 (GLP-1) agonist semaglutide and placebo on histological liver changes in patients with type 2 diabetes. Since SGLT-2 inhibitors were used with success in patients without diabetes for cardiac protection [4], it is worthwhile to extend biopsy studies to patients with NAFLD without diabetes. Results of these trials should determine with more certainty the role of SGLT-2 inhibitors for treatment of NAFLD in general.

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