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EDITORIAL

# Fat and Fibrosis: Does Empagliflozin Impair the Progression of Nonalcoholic Steatohepatitis in Patients with Type 2 Diabetes Mellitus?

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Nonalcoholic fatty liver disease (NAFLD), that has an estimated prevalence of 25% in the population with cirrhosis secondary to nonalcoholic steatohepatitis (NASH), is currently the second leading cause of liver disease treated with liver transplantation in the USA. Despite this considerable disease burden, there is a lack of effective licensed treatments available.

NAFLD is closely associated with diabetes mellitus and obesity and also appears linked with the metabolic syndrome [1] with its prevalence being fivefold higher in patients with type II diabetes mellitus (T2DM) [2]. Furthermore, insulin resistance is implicated in the pathogenesis of NAFLD and also in disease progression from steatosis to NASH [3], leading to significant interest in the use of insulin sensitizers in patients with NAFLD. Such treatments could potentially improve NASH histologically as well as improve glycemic control, thus reducing cardiovascular risk. In patients with NASH, there is evidence that glucagon-like peptide-1 (GLP-1) agonists, such as liraglutide, can improve glycemic control and histological outcomes [4], and in patients with diabetes, they have been associated with reduced cardiovascular risk [5]. Similarly, the thiazolidinedione pioglitazone is associated with improved histological outcomes in NASH [6], as well as a reduction in cardiovascular risk [7], although weight gain and edema have limited its use.

Sodium glucose co-transporter 2 (SGLT2) inhibitors, such as canagliflozin, empagliflozin, ipragliflozin, and dapagliflozin, are oral formulations that exert their effects through inhibition of SGLT2, which accounts for approximately 90% of glucose re-absorption by the kidney. In patients with T2DM, SGLT2 inhibitors are reported to have reno-protective and cardio-protective effects [8], yet there is relatively little research on their contributions toward NAFLD therapy, with the vast majority of studies small and uncontrolled, usually consisting of post hoc analysis of retrospective data [9]. Nevertheless, most studies suggest that SGLT2 inhibitors are associated with improvements in serum alanine aminotransferase (ALT) and hepatic steatosis as assessed with imaging [9], with only one, single-arm, open-label study evaluating the effects of an SGLT-2 inhibitor (canagliflozin) on histological outcomes [10]. In all five patients in this small study, 24 weeks of treatment with canagliflozin was associated with histological improvement, defined as a decrease in NAFLD activity score (NAS) by at least one point, without a worsening of fibrosis. In this issue of *Digestive Diseases and Sciences*, Lai et al. report the results of a single-arm, open-label pilot study in which nine patients were treated with empagliflozin 25 mg daily for 24 weeks in comparison with a 48-week placebo arm [11]. They report improvements in histological outcomes (steatosis, fibrosis, and hepatocyte ballooning) as measured by paired biopsy samples, with secondary outcomes including improvements in body mass index, waist circumference, blood pressure, and biochemical parameters (fasting blood glucose, total cholesterol, and gamma glutamyl peptidase). Of note, there was no change in serum aminotransferase values.

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A key strength of this study is in its use of sequential liver biopsies to evaluate the effects of empagliflozin treatment, which is important given the poor correlation between serum aminotransferase values and histological parameters in NASH. While MRI-estimated proton density fat fraction is highly accurate for assessment of steatosis, there are no readily available imaging techniques or biomarkers that can effectively replace the use of biopsy in the assessment of the hallmarks of NASH, hepatocyte ballooning, and fibrosis. Another strength of this study is the use of MRI evaluation of steatosis in order to corroborate the histological findings. The authors also took care to avoid inclusion of patients that were receiving drugs that could have confounded the study results, including thiazolidinediones, GLP-1 agonists, and other SGLT-2 inhibitors. The biopsy specimens were evaluated by a single pathologist, and a standardized NASH scoring system was used, although it is unclear whether the pathologist was blinded as to whether patients were taking empagliflozin.

A limitation of this study is the lack of a true placebo arm and the use of a historical placebo for the control biopsy for comparison along with its open-label design. It is also unclear from the reported study methodology whether the same pathologist was used for histological assessment in the placebo and empagliflozin groups, as this is a potential source of inter-observer variability. The data from the placebo group were based on paired biopsies after a 48-week rather than a 24-week interval, which makes it possible that there was naturally more disease progression in the placebo group. Further, Lai et al. report that in this study there were baseline differences in the historical placebo control group and the experimental group, with the key difference being that only 60% of participants in the placebo group had T2DM, whereas all of the patients receiving empagliflozin had T2DM. It is possible that if empagliflozin's primary action were via changes in insulin resistance, that greater improvements in histological parameters would be seen in patients with more severe insulin resistance at baseline. Indeed, when subgroup analysis was performed to include only patients with T2DM, significant differences in hepatocyte ballooning and waist circumference were no longer seen.

Another drawback of this study was its small sample size ($n = 9$), as although the results are promising, the study lacks the statistical power to make meaningful conclusions about the effects of empagliflozin. Further, the study does not provide insight into the likely underlying mechanism of empagliflozin action. The sample size is insufficient to study whether the positive histological effects are due to a direct effect of empagliflozin on the liver, or whether they are mediated by weight loss. While a number of metabolic parameters were measured in this study, the authors did not measure insulin resistance, which could have provided useful mechanistic insights.

In summary, Lai et al. report the results of the first study testing the effects of empagliflozin on NASH histology (based on paired liver biopsy specimens) and metabolic parameters. The results of these data are promising, with 44% of patients with evidence of NASH resolution, although results require verification through the conduct of larger, double-blinded randomized controlled clinical trials designed to investigate the utility of empagliflozin as a treatment for NASH. It would also be valuable to compare the effectiveness of different doses of empagliflozin and to compare results from other types of SGLT-2 inhibitors. Since in this study empagliflozin was continued for an arbitrary duration of 24 weeks, it would be helpful to conduct further work aimed at determining optimal treatment duration. It would be interesting to know whether empagliflozin may also be useful in patients with NASH without diabetes. A longer follow-up period is necessary to assess the impact of empagliflozin on additional outcomes such as development of liver cirrhosis, incidence of hepatocellular carcinoma, and effect on the need for transplantation.

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## Compliance with ethical standards

**Conflict of interest** Dr Newsome reports consultancy/speaker fees on behalf of the University of Birmingham from Boehringer Ingelheim, Dignity Sciences, Intercept, Johnson and Johnson, Novo Nordisk, and Shire. His institution receives grant funding from Pharmaxis and Boehringer Ingelheim. Dr Khan has nothing to disclose.

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