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Enavogliflozin Improves Non-invasive Hepatic Steatosis Indices in Patients With Type 2 Diabetes: A Pooled Analysis of Three Randomised Trials

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1 | Introduction

Type 2 diabetes mellitus (T2DM) is increasingly prevalent and is frequently accompanied by metabolic dysfunction-associated steatotic liver disease (MASLD) [1], which can progress to advanced liver disease [2].

Metabolic benefits of sodium-glucose cotransporter 2 (SGLT2) inhibitors extend beyond glucose lowering [3], and improve biochemical markers of liver injury in patients with T2DM [4].

Enavogliflozin is a novel, potent SGLT2 inhibitor that lowers glucose levels [5–7]. However, its hepatic effects have not yet been evaluated in individuals with T2DM. Therefore, this study aims to assess the effects of enavogliflozin 0.3 mg on hepatic steatosis and fibrosis in patients with T2DM using data from three randomised, double-blind, phase III clinical trials.

2 | Methods

2.1 | Study Design and Population

This study is a post hoc pooled analysis of three multicentre, randomised, 24-week clinical trials conducted in South Korea, including a placebo-controlled trial (ENHANCE-A) [5] and two active comparator-controlled trials (ENHANCE-M and ENHANCE-D) [6, 7].

Among 223 patients screened for the ENHANCE-A trial, 167 were randomised, of whom, 82 in the enavogliflozin group and 79 in the placebo group were included in the final analysis (Figure S1). Patient disposition in the ENHANCE-M and ENHANCE-D trials was comparable to that of the ENHANCE-A trial (Figure S2). Following screening and randomisation, 214 patients in the enavogliflozin group and 213 patients in the dapagliflozin group were included in the final analysis.

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Analyses were conducted separately for the placebo-controlled trial and the active-controlled trials. Hepatic steatosis- and fibrosis-related outcomes were evaluated within each trial framework (Figure S3).

2.2 | Clinical and Laboratory Assessments

Baseline demographic and clinical variables were collected at the screening visit and included anthropometric measurements, vital signs and routine laboratory tests.

Hepatic steatosis was assessed using the Hepatic Steatosis Index (HSI) and the Framingham Steatosis Index (FSI), calculated as follows:

HSI = 8 × (alanine aminotransferase [ALT]/aspartate aminotransferase [AST] ratio) + body mass index (BMI) (+2 for diabetes; +2 for female sex) [8].

FSI = −7.981 + 0.011 × age (years) − 0.146 × sex (female = 1, male = 0) + 0.173 × BMI (kg/m^2) + 0.007 × triglycerides (mg/dL) + 0.593 × hypertension (yes = 1, no = 0) + 0.789 × diabetes (yes = 1, no = 0) + 1.1 × ALT:AST ratio ≥ 1.33 (yes = 1, no = 0) [9].

Patients meeting predefined steatosis threshold (HSI > 36[8] or FSI ≥ −1.2) [9] constituted the hepatic steatosis subgroup for subsequent fibrosis analyses. Hepatic fibrosis was assessed using validated non-invasive indices, calculated as follows:

Fibrosis-4 index (FIB-4) = age (years) × AST [U/L]/[platelets ($\times 10^9$/L) × $ALT^{1/2}$ (U/L)]; cut-off ≥ 1.3 [10].

NAFLD fibrosis score (NFS) = −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × Impaired fasting glucose or T2D (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet count ($\times 10^9$/L) − 0.66 × albumin (g/dL); cut-off > 0.676 [11].

2.3 | Outcomes

The primary outcome was the improvement in hepatic steatosis at week 24, defined as falling below established steatosis cut-off values (HSI > 36 or FSI ≥ −1.2). The proportion of patients with improvement from baseline was compared across treatment groups. Supportive analyses evaluated continuous changes in HSI and FSI from baseline to week 24 among patients with baseline hepatic steatosis.

Secondary outcomes included changes in non-invasive fibrosis scores (NFS and FIB-4) from baseline to week 24 among patients with baseline hepatic steatosis.

2.4 | Statistical Analysis

Continuous and categorical variables were compared using appropriate statistical tests. Within-group changes and between-group differences were assessed using Chi-square or Fisher's exact test, as appropriate. Between-group differences were assessed using an analysis of covariance (ANCOVA) adjusted for baseline values, and results were reported as least squares (LS) means with 95% confidence intervals (CIs). Exploratory analyses of factors associated with HSI improvement were performed using a multivariable ANCOVA model including treatment group, changes in AST/ALT, BMI and sex as independent variables, with treatment regimen and baseline HbA1c included as covariates. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value < 0.05 was considered statistically significant.

2.5 | Ethics Statement

All parent trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice, approved by the institutional review boards at participating sites and written informed consent was obtained from all participants before study procedures.

3 | Results

3.1 | Baseline Characteristics of the Study Population

At baseline, demographic and clinical characteristics were generally similar between treatment groups (Table S1). In the active comparator-controlled trial, systolic and diastolic blood pressure differed modestly between groups (SBP, $p = 0.016$; DBP, $p = 0.026$).

3.2 | Effects of Enavogliflozin on Hepatic Steatosis

At week 24, the proportion of patients with hepatic steatosis was significantly lower in the enavogliflozin group than in the placebo group (Figure 1). In the placebo-controlled trial, steatosis prevalence in the enavogliflozin group decreased from 48.0% to 16.0% based on HSI criteria and from 41.3% to 16.0% according to FSI criteria (both $p < 0.001$), with no meaningful change in the placebo group (Figure 1A,B).

In the active comparator-controlled trial, enavogliflozin and dapagliflozin significantly reduced the prevalence of hepatic steatosis based on non-invasive indices, with no significant difference in magnitude between both treatments (HSI: $p = 0.7235$; FSI: $p = 0.5497$, Figure 1C,D).

3.3 | Changes in Steatosis Indices Among Participants With Baseline Hepatic Steatosis

For secondary analyses, we evaluated a predefined subgroup of patients with baseline hepatic steatosis, defined based on established cut-off values (HSI > 36 or FSI ≥ −1.2). Among them, enavogliflozin significantly reduced HSI and FSI over 24 weeks. In the placebo-controlled trial, HSI decreased by an LS mean

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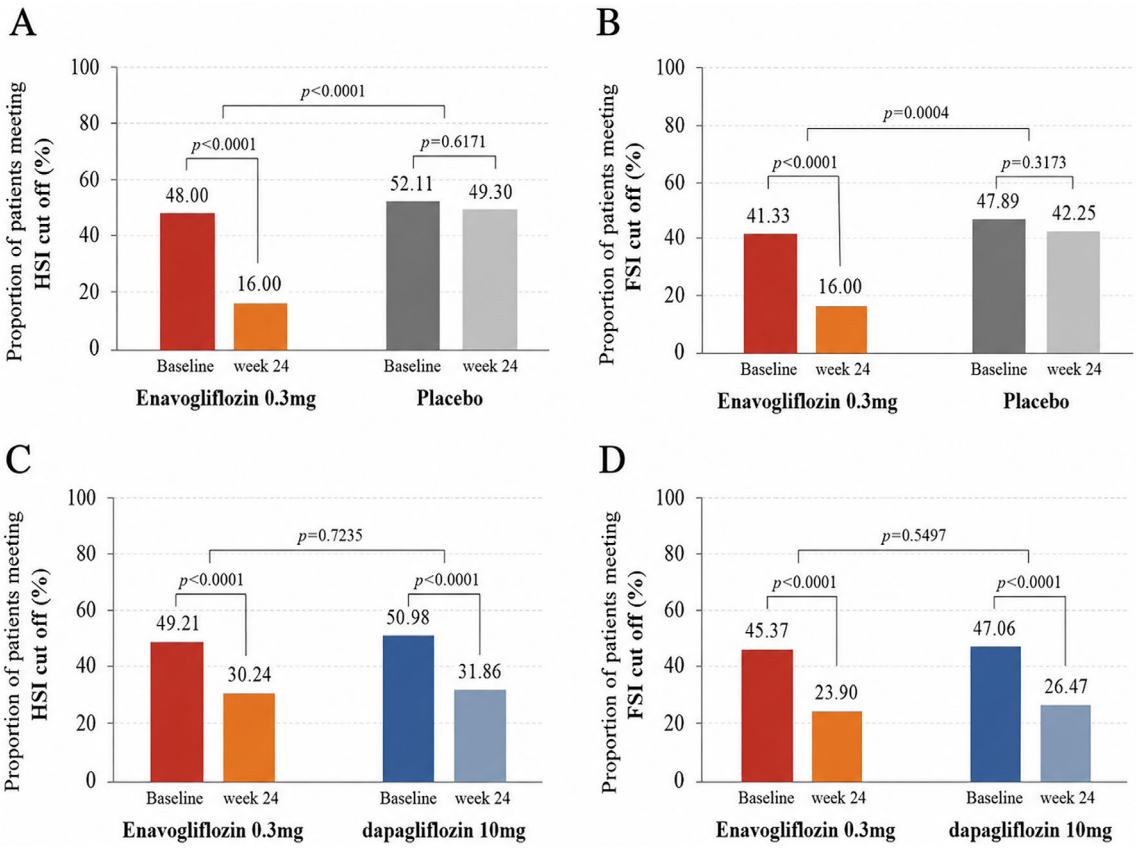

FIGURE 1 | Changes in hepatic steatosis prevalence according to HSI and FSI criteria over week 24. (A) and (B) depict the results from the placebo-controlled study, and (C) and (D) illustrate the results from the active-controlled study with dapagliflozin. HSI, hepatic steatosis index; FSI, Framingham steatosis index. Figures display the proportion of patients with HSI > 36 and FSI ≥ −1.2. Statistical analyses were performed using the Chi-square or Fisher's exact tests for between-group differences and McNemar's or exact McNemar's test for within-group changes.

difference of −3.66 (95% CI, −5.08 to −2.25; $p < 0.0001$) and FSI by −1.12 (95% CI, −1.75 to −0.50; $p = 0.0006$) compared with placebo (Figure 2A,B).

In the active comparator-controlled trial, enavogliflozin had a significantly greater reduction in HSI than dapagliflozin (LS mean difference −1.02; 95% CI, −1.91 to −0.12; $p = 0.0257$), whereas no significant between-treatment difference was observed for FSI (LS mean difference −0.07; 95% CI, −0.32 to 0.19; $p = 0.6195$; Figure 2C,D).

3.4 | Changes in Non-Invasive Fibrosis Scores

As shown in Table S2, among patients with baseline hepatic steatosis (HSI > 36), enavogliflozin was associated with a statistically significant improvement in NFS compared with placebo, with an adjusted LS mean difference of −0.19 (95% CI, −0.36 to −0.01; $p = 0.0361$). In contrast, no significant difference was observed in FIB-4 between enavogliflozin and placebo (LS mean difference 0.07; 95% CI, −0.14 to 0.27; $p = 0.5066$).

In the active comparator-controlled trial, changes in fibrosis scores did not differ significantly between enavogliflozin and dapagliflozin. LS mean differences were 0.09 (95% CI, −0.02 to 0.21; $p = 0.1206$) for NFS and 0.02 (95% CI, −0.19 to 0.23; $p = 0.8818$) for FIB-4 (Table S2).

Similar to the HSI-based subgroup, fibrosis outcomes in the FSI ≥ −1.2 subgroup showed no meaningful treatment effect (Table S3).

3.5 | Exploratory Analysis of Factors Associated With Steatosis Improvement

In an exploratory analysis of factors associated with significant HSI improvement compared with dapagliflozin at week 24, a multivariable ANCOVA model revealed a significant association with the change in the ALT/AST ratio ($\beta = -0.09$; 95% CI −0.17 to 0.00; $p = 0.0497$). In contrast, the change in BMI was not significantly associated with HSI improvement ($\beta = -0.06$; 95% CI −0.37 to 0.24; $p = 0.6765$; Table S4).

4 | Discussion

In this pooled analysis of three randomised, double-blind phase III trials, enavogliflozin significantly improved non-invasive hepatic steatosis indices over 24 weeks in patients with T2DM, with an effect comparable to dapagliflozin. Reduction were

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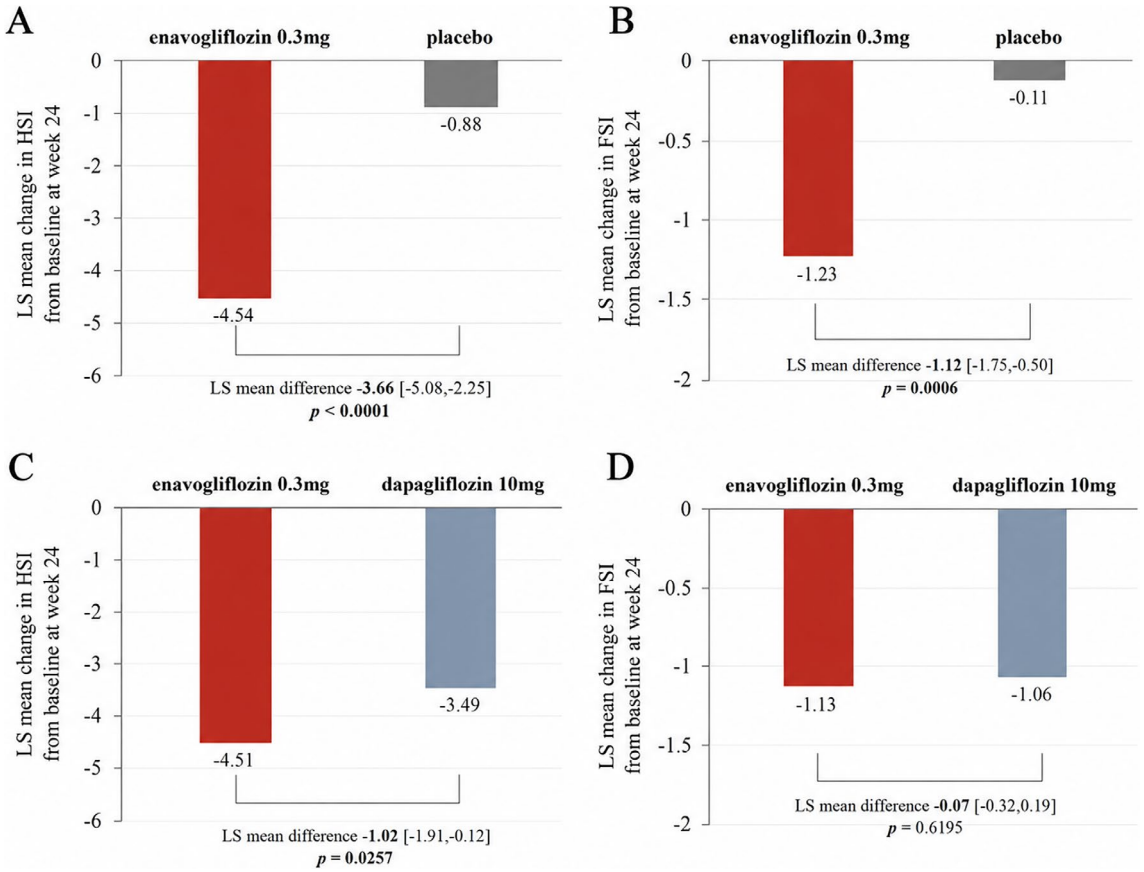

FIGURE 2 | LS mean changes in HSI and FSI in patients meeting the baseline diagnostic cut-offs (HSI > 36 or FSI ≥ −1.2) over 24 weeks. (A) and (B) illustrate the results from the placebo-controlled study, and (C) and (D) depict the results from the active-controlled study with dapagliflozin. Figures display the least squares mean changes from baseline to week 24 in each parameter. Within-treatment group *p*-values were calculated using paired *t*-test or Wilcoxon signed-rank tests, as appropriate. Between-treatment group *p*-values were calculated using ANCOVA, adjusting for baseline value and stratification factors (prior antidiabetic drug use and HbA1c).

consistently observed across two independent steatosis indices (HSI and FSI) and across both placebo- and active comparator-controlled trials, reinforcing the robustness and reproducibility of the observed hepatic effect, and supporting class-consistent effect of SGLT2 inhibitors on hepatic steatosis.

Notably, exploratory analyses showed that the difference in HSI improvements between the enavogliflozin and dapagliflozin groups was significantly associated with changes in the ALT/AST ratio but not with changes in BMI. This suggests that mechanisms beyond weight loss—such as—altered substrate flux, reduced hepatic *de novo* lipogenesis or reduced hepatic inflammation reflected by enzyme pattern changes [12]—may contribute to steatosis improvement, although causal inference is limited by the composite nature of these indices. Nonetheless, the observed association supports the hypothesis that improvements in liver-related biochemical markers may track steatosis improvement independent of absolute weight change.

Despite clear improvement in hepatic steatosis indices, fibrosis indices remained unchanged. This finding is consistent with a post hoc analysis of the EMPA-REG OUTCOME trial, in which empagliflozin improved steatosis-related markers, whereas fibrosis-related indices showed limited change over time [13]. A similar observation has also been reported in recent analyses of dapagliflozin [14]. Together, these findings suggest that improvements in hepatic steatosis may occur earlier during SGLT2 inhibitor treatment, whereas fibrosis-related changes may require a longer treatment duration and may not be readily captured in populations with a low baseline fibrosis burden using non-invasive fibrosis indices.

This study has limitations. Hepatic outcomes were assessed using surrogate indices rather than imaging or histology, and these indices may be influenced by changes in individual components. In addition, the relatively low baseline fibrosis burden may have limited the ability to detect treatment-related changes in fibrosis indices, and NFS and FIB-4 may lack sensitivity for detecting short-term fibrosis changes. The 24-week duration may be insufficient to detect fibrosis dynamics. Finally, although findings were generally consistent across placebo- and active comparator-controlled trials, residual confounding related to differences in background glucose-lowering therapies cannot be completely excluded.

In conclusion, enavogliflozin effectively improved hepatic steatosis indices in patients with T2DM, with efficacy similar to that of dapagliflozin. These findings support the role of SGLT2 inhibitors as part of a metabolic strategy for patients with T2DM and hepatic steatosis, while highlighting the need for longer-term studies using direct hepatic endpoints.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.71007.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Baseline demographic and laboratory characteristics. **Table S2:** Mean changes in fibrosis scores (NFS, FIB-4) from baseline to 24 weeks in patients meeting HSI cut-off (> 36) at baseline. **Table S3:** Mean changes in fibrosis scores (NFS, FIB-4) from baseline to 24 weeks in patients meeting the FSI cut-off (≥ −1.2) at baseline. **Table S4:** Multivariable ANCOVA of factors associated with HSI improvement at week 24. **Figure S1:** Study design of the placebo-controlled ENHANCE-A trial. **Figure S2:** Study design of the active-controlled ENHANCE-M and ENHANCE-D trial. **Figure S3:** Study design overview.

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