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Effect of dapagliflozin on metabolic dysfunction-associated steatohepatitis: multicentre, double blind, randomised, placebo controlled trial

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ABSTRACT

OBJECTIVE

To assess the efficacy and safety of the sodium-glucose cotransporter 2 inhibitor dapagliflozin in participants with metabolic dysfunction-associated steatohepatitis (MASH).

DESIGN

Multicentre, double blind, randomised, placebo controlled trial.

SETTING

Six tertiary hospitals in China from 23 November 2018 to 28 March 2023.

PARTICIPANTS

154 adults with biopsy diagnosed MASH, with or without type 2 diabetes.

INTERVENTIONS

All participants were randomly assigned to receive 10 mg orally of dapagliflozin or matching placebo once daily for 48 weeks.

MAIN OUTCOME MEASURES

The primary endpoint was MASH improvement (defined as a decrease of at least 2 points in non-alcoholic fatty liver disease activity score (NAS) or a NAS of ≤3 points) without worsening of liver fibrosis (defined as without increase of fibrosis stage) at 48 weeks. The secondary endpoints included the MASH resolution without worsening of fibrosis and fibrosis improvement without worsening of MASH. Analyses used the intention-to-treat dataset.

RESULTS

MASH improvement without worsening of fibrosis was reported in 53% (41/78) of participants in the dapagliflozin group and 30% (23/76) in the placebo group (risk ratio 1.73 (95% confidence interval (CI) 1.16 to 2.58); P=0.006). Mean difference of NAS was −1.39 (95% CI −1.99 to −0.79); P<0.001). MASH resolution without worsening of fibrosis occurred in 23% (18/78) of participants in the dapagliflozin group and 8% (6/76) in the placebo group (risk ratio 2.91 (95% CI 1.22 to 6.97); P=0.01). Fibrosis improvement without worsening of MASH was reported in 45% (35/78) of participants in the dapagliflozin group, as compared with 20% (15/76) in the placebo group (risk ratio 2.25 (95% CI 1.35 to 3.75); P=0.001). The percentage of individuals who discontinued treatment because of adverse events was 1% (1/78) in the dapagliflozin group and 3% (2/76) in the placebo group.

CONCLUSION

Treatment with dapagliflozin resulted in a higher proportion of participants with MASH improvement without worsening of fibrosis, as well as MASH resolution without worsening of fibrosis and fibrosis improvement without worsening of MASH, than with placebo.

TRIAL REGISTRATION

ClinicalTrials.gov NCT03723252.

WHAT IS ALREADY KNOWN ON THIS TOPIC

SGLT2 inhibitors improve non-invasive liver parameters (ie, liver fat content, liver enzymes, and liver stiffness) in patients with metabolic dysfunction-associated steatotic liver disease

The effect of SGLT2 inhibitors on liver histological outcomes in patients with metabolic dysfunction-associated steatohepatitis has not been investigated

WHAT THIS STUDY ADDS

Dapagliflozin for 48 weeks can lead to MASH improvement without worsening of fibrosis, MASH resolution without worsening of fibrosis, and fibrosis improvement without worsening of MASH, in patients with MASH

These results support the potential for dapagliflozin to provide benefit to patients with biopsy diagnosed MASH and liver fibrosis

Introduction

Metabolic dysfunction-associated steatohepatitis (MASH, formerly known as non-alcoholic steatohepatitis) is a progressive liver disease characterised by hepatic steatosis, lobular inflammation, and hepatocellular ballooning, with faster fibrosis progression than metabolic dysfunction-associated steatotic liver disease (MASLD, formerly known as non-alcoholic fatty liver disease).[1] The condition affects more than 5% of adults and more than 30% of individuals with diabetes or obesity.[2-4] MASH can progress to cirrhosis in up to 25% of individuals,[5] and is closely associated with obesity, insulin resistance, dyslipidaemia, type 2 diabetes, and cardiovascular disease.[1]

To date, therapeutic options for MASH are limited. Pioglitazone, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, and glucagon receptor agonist (ie, liraglutide, semaglutide, tirzepatide, and survodutide) may be considered as possible treatment options, with management focused on treatment of coexisting

conditions such as type 2 diabetes and obesity.[6-10] In 2024, the first therapeutic drug, resmetirom, a thyroid hormone receptor β-selective agonist, was approved for the treatment of MASH in the USA.[11] However, its long term safety for MASH remains uncertain.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are now widely used to treat type 2 diabetes, heart failure, and chronic kidney disease,[12-14] but their effects on MASH remain to be determined. SGLT2 inhibitors modulate energy homoeostasis, improve insulin resistance, and exhibit anti-inflammatory, anti-oxidant, and anti-fibrotic effects, which counteract the pathogenic characteristics of MASH.[15] Several clinical studies have reported that SGLT2 inhibitors can improve liver fat content, liver enzymes, and liver stiffness in participants with MASLD or MASH.[16-24] Two small clinical trials have reported inconsistent findings of SGLT2 inhibitors (ipragliflozin and tofogliflozin) on liver histological features among people with diabetes and MASLD,[25 26] but no trial has been conducted among participants with biopsy diagnosed MASH. Therefore, high quality evidence is required to develop clinical guidelines for SGLT2 inhibitors in MASH treatment. We conducted a randomised, placebo controlled trial to evaluate the efficacy and safety of the SGLT2 inhibitor dapagliflozin in participants with biopsy confirmed non-cirrhotic MASH.

Methods

Study design

This multicentre, double blind, randomised, placebo controlled trial was conducted at six sites in China. The DEAN trial protocol was approved by the review board at each participating centre. The trial was conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonization, Good Clinical Practice guidelines, and all relevant regulations. The trial was overseen by a steering committee at Nanfang Hospital of Southern Medical University. The protocol is available in the appendix.

Participants

Participants were eligible if they were 18 years or older and had MASH as determined by liver biopsies, with or without type 2 diabetes. Histological evidence of MASH was defined as a non-alcoholic fatty liver disease activity score (NAS) of 4 or higher, with a subscore of 1 or higher for each subcomponent (steatosis, hepatocyte ballooning, and lobular inflammation). All participants had a liver biopsy within six months before randomisation.

Key exclusion criteria were liver diseases other than MASH, cirrhosis, excessive alcohol consumption (>20 g per day for women; >30 g per day for men), a glycated haemoglobin level (HbA_{1c}) of more than 9.5% at screening, and concomitant drug use that might affect MASH (eg, thiazolidinedione, glucagon-like peptide-1 receptor agonist, vitamin E, and cortisol). Full eligibility criteria are available in the appendix. Participants provided written informed consent. Individuals with a weight change of more than 5% between screen and randomisation were also excluded.

Randomisation and masking

Participants were randomly assigned to receive 10 mg dapagliflozin (AstraZeneca; IN, USA) or matching placebo once daily in a 1:1 ratio. The randomisation schedules were generated using a computer program centrally and stratified by the presence of type 2 diabetes. Dapagliflozin and placebo were supplied as identical tablets in coded containers. Participants, investigators, site personnel, and pathologists were masked to treatment assignments.

Procedure

Participants received placebo or dapagliflozin 10 mg orally once daily for 48 weeks. All participants attended health education sessions semi-annually, in accordance with current recommendations.[27] Screening biopsy results were used as baseline histological variables, and a follow-up biopsy was done at week 48. All biopsy findings were read centrally by two independent liver pathologists to determine the steatosis, ballooning, lobular inflammation, and fibrosis stage, according to the NASH Clinical Research Network criteria.[28] The NAS is assessed on a scale of 0 to 8, with higher scores indicating more severe disease; the components of NAS are steatosis (scale 0-3), hepatocellular ballooning (scale 0-2), and lobular inflammation (scale of 0-3); the fibrosis stage is assessed on a four point scale: F1 is mild fibrosis, F2 is significant fibrosis, F3 is advanced fibrosis, and F4 is cirrhosis. Pathologists were unaware of the treatment assignments, participant characteristics, and each other's assessments. Both baseline and follow-up biopsies were reread in batches by the panel to minimise the variability of the individual reader over the study period. A consensus score was derived from the two individual reader scores. In cases of discordant assessment on any variable, the third pathologist would make the final decision (appendix).

Assessment of body weight, waist circumference, blood pressure, glucose, and liver enzymes were conducted at baseline, and at weeks 4, 12, 24, 36, and 48. Physical activity, dietary intake, health related quality of life, glycated haemoglobin, insulin, and lipids were assessed at baseline, and at weeks 24 and 48. Liver steatosis and stiffness (as assessed by FibroScan (Echosens)) and visceral fat area (as assessed by abdominal CT) were measured every 24 weeks.

Outcomes

The primary endpoint was MASH improvement (defined as a decrease of at least 2 points in NAS or a NAS of ≤3 points) without worsening of liver fibrosis (defined as without increase of fibrosis stage) at week 48. The confirmatory secondary endpoints included MASH resolution (defined as a hepatocellular ballooning score of 0 and lobular inflammation score of 0 or 1) without worsening of fibrosis, and fibrosis

improvement (defined as reduction in fibrosis of at least 1 stage) without worsening of MASH (defined as without an increase in steatosis, ballooning, or inflammation score) at week 48.[29] Other secondary endpoints included changes from baseline to week 48 in each subcomponent score in the NAS, fibrosis stage, liver enzymes, liver steatosis and stiffness, visceral fat area, metabolic variables (body weight, waist circumference, body mass index, blood pressure, glucose, glycated haemoglobin, insulin resistance, lipids), and health related quality of life.

Statistical analysis

We estimated that a sample size of 148 participants (74 per group) would provide the trial with greater than 90% power to detect a difference of 27% between dapagliflozin and placebo for the primary endpoint at a two sided significance level of 0.05, assuming that 20% of the participants in the placebo group would reach the primary endpoint and 47% of the participants in the dapagliflozin group would meet the primary endpoint, as well as an anticipated dropout rate of 20%.[6 24 30]

Data were analysed in the intention-to-treat population. We used the Cochran-Mantel-Haenszel method, controlling for the randomisation stratification factor (baseline diabetes status), for analysis of the primary and secondary endpoints. The estimate was derived by weighting the diabetes specific risk ratios, with greater weight assigned to strata with larger sample sizes. Participants with missing biopsies were considered as non-responder.[6 8 11] We report the risk ratios that were estimated with Cochran-Mantel-Haenszel method and corresponding 95% confidence intervals (CIs). A hierarchical testing procedure that included the primary endpoint and secondary endpoints were conducted to control the family-wise type 1 error rate at 0.05. We sequentially tested three clinically relevant endpoints of MASH improvement without worsening of fibrosis, MASH resolution without worsening of fibrosis, and fibrosis improvement without worsening of MASH, in a fixed sequence, at the significance level of 0.05, and proceeded to the next endpoint only after a successful rejection of non-difference on the previous endpoint. All tests for other secondary endpoints and the associated P values were not controlled for multiple comparison and were considered nominal and descriptive. Sensitivity analyses were also conducted to assess the robustness of the results of the primary analysis using multiple imputation methods. Multiple imputation was based on the missing at random assumption that a participant with a missing end-of-study biopsy would have a similar histological response as a participant with an end-of-study biopsy and comparable baseline characteristics. Variables used for the imputation included treatment group, age, sex, baseline diabetes status, BMI, liver fat and stiffness assessed by FibroScan, and histological characteristics (ie, NAS, steatosis, ballooning, inflammation, and fibrosis score). One hundred imputations were generated and the results were pooled using Rubin's rule.[31] Subgroup analyses were conducted according to metabolic risk factors, diabetic status, and histological scores. A mixed-effects model with compound symmetry structure was used to assess the difference between treatment groups on changes of continuous endpoints over the study period. In this model, the individuals were considered as random effects, whereas the diabetes status, baseline value, intervention group, follow-up time, and group-time interaction were considered as fixed effects. An exploratory mediation analysis was conducted to address the impact of weight loss in the efficacy of dapagliflozin. We considered a two sided P<0.05 as statistically significant. Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute). More information can be found in the appendix (statistical analysis plan).

Patient and public involvement

Patients and the public were not involved in the design, conduct, or reporting of our research because no funding was allocated for such involvement.

Results

Participants

From 23 November 2018 to 28 March 2023, 154 eligible participants were randomly assigned to receive dapagliflozin (n=78) or placebo (n=76) orally once daily for 48 weeks. In total, 90% (139/154) of the participants completed the final visit and 81% (125/154) completed the end-of-study biopsy (fig 1). The mean age of the participants was 35.1 (standard deviation (SD) 10.2) years, mean body mass index was 29.2 (SD 4.3), and mean NAS was 6.0 (SD 1.1). A total of 33% participants (51/154) had stage F1 fibrosis, 45% (70/154) had stage F2, and 19% (29/154) had stage F3. Of them, 85% (131/154) were male, 85% (131/154) had dyslipidaemia, and 45% (69/154) had type 2 diabetes. The characteristics of the participants at baseline were similar between groups (table 1). Participants received anti-diabetic, anti-hypertensive, and anti-dyslipidaemia drugs according to the study protocol, if necessary. During the 48 week intervention, the proportion of participants who received concomitant medication were similar between groups. At week 24, the placebo group had a modestly higher proportion of participants who received α-glucosidase inhibitor and fibrate (supplementary table 1); meanwhile, other concomitant medications were similar during the intervention. Dietary and physical activity were similar during the intervention (supplementary table 2).

Primary and secondary endpoints

The proportion of participants in whom MASH improvement was reached with no worsening of fibrosis at week 48 was 53% (41/78) in the dapagliflozin group, and 30% (23/76) in the placebo group (risk ratio 1.73 (95% CI 1.16 to 2.58); P=0.006) (fig 2). The mean difference of NAS between groups was −1.39 ((−1.99

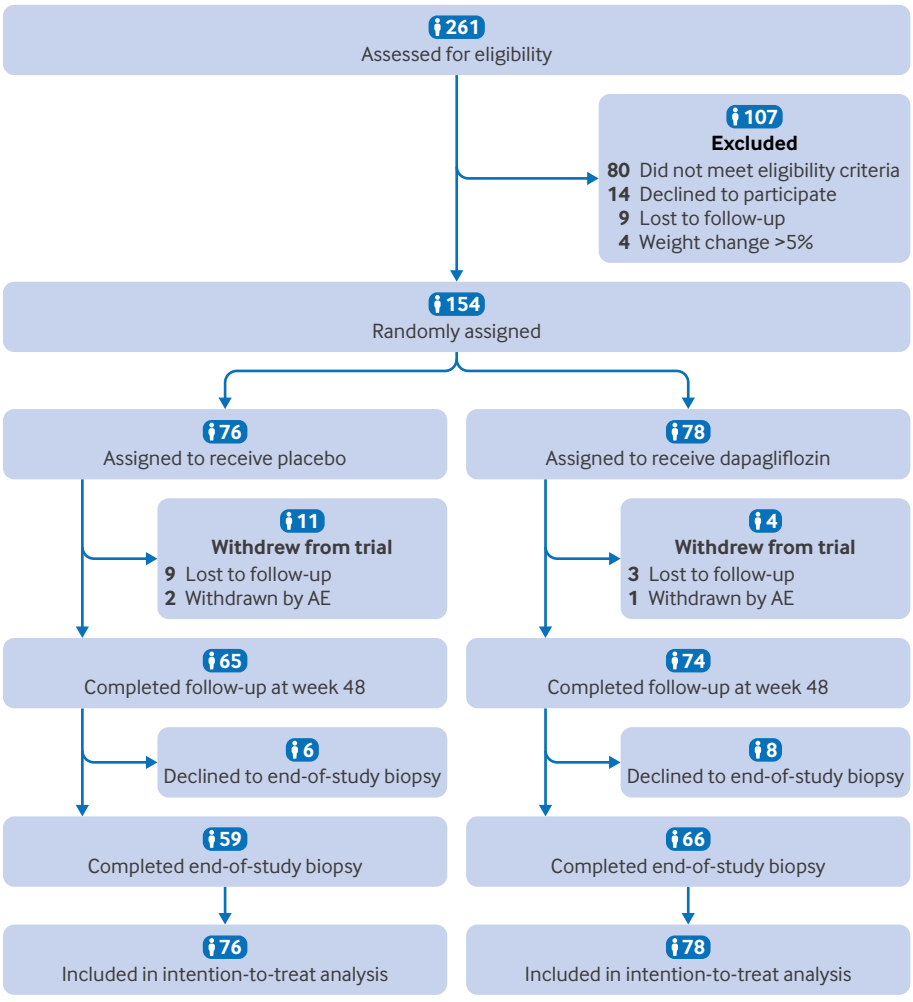

Fig 1 | Flowchart of trial participants

to −0.79); P<0.001), after adjusting for the diabetes status, baseline value, the intervention group, follow-up time, and the group-time interaction. In addition, the proportion of participants with MASH resolution without worsening of fibrosis at week 48 was 23% (18/78) in the dapagliflozin group and 8% (6/76) in the placebo group (2.91 (1.22 to 6.97); P=0.01) (fig 2). The proportion of participants with improvement in fibrosis stage without worsening of MASH at week 48 was 45% (35/78) in the dapagliflozin group and 20% (15/76) in the placebo group (2.25 (1.35 to 3.75); P=0.001) (fig 2). Similar results of the primary endpoint were noted in the sensitivity analysis using multiple imputed data (1.50 (1.05 to 2.14) or per protocol data 1.59 (1.10 to 2.30) (supplementary table 3). The results of primary analysis were also consistent with various definitions of MASH improvement (supplementary table 4).

In addition, the results of the analyses among the participants with F2-F3 fibrosis were also consistent with those of the main analysis for primary and confirmatory secondary endpoints (supplementary figure 1). Similar results of the primary and the confirmatory endpoints were also reported when stratified by metabolic factors and NAS (supplementary figure 2-4). Conversely, participants with diabetes seemed to have higher proportions of fibrosis improvement with no worsening of MASH at week 48 than participants with no diabetes (supplementary figure 4). A sensitivity analysis with adjustment of sites showed similar results and no interaction across sites were found (supplementary table 5, supplementary figure 5).

Other secondary endpoints

Treatment with dapagliflozin was associated with reductions in each subcomponent of histological features, including steatosis, ballooning, lobular inflammation, and fibrosis (table 2). Among all trial participants, worsening of fibrosis occurred in 5% (4/76) in the dapagliflozin group, and 22% (17/78) in the placebo group at week 48 (supplementary figure 6). The proportion of participants who had both MASH resolution and an improvement in fibrosis stage at week 48 was 21% (16/78) in the dapagliflozin group and 1% (1/76) in the placebo group (supplementary figure 7).

Treatment with dapagliflozin was associated with reductions in liver steatosis and stiffness assessed

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Table 1 | Characteristics of the participants at baseline

Characteristics	Placebo (n=76)	Dapagliflozin (n=78)
Age, mean (SD), years	35.4 (10.9)	34.7 (9.5)
Sex, No. (%):		
Male	64 (84%)	67 (86%)
Female	12 (16%)	11 (14%)
Type 2 diabetes, No. (%)	35 (46%)	34 (44%)
Dyslipidaemia, No. (%)	66 (87%)	65 (83%)
Hypertension, No. (%)	19 (25%)	13 (17%)
SF-36 quality of life, median (IQR)*:		
Physical component summary	52.6 (49.5-55.6)	52.9 (49.9-55.9)
Mental component summary	51.0 (42.7-56.7)	54.7 (45.7-58.3)
Body weight, mean (SD), kg	82.8 (16.1)	84.1 (15.6)
Body mass index, mean (SD)	28.8 (4.4)	29.5 (4.3)
Waist circumference, mean (SD), cm	97.8 (11.1)	98.2 (10.1)
Systolic blood pressure, mean (SD), mm/Hg	125.6 (12.1)	125.8 (12.1)
Diastolic blood pressure, mean (SD)mm/Hg	77.7 (8.9)	78.9 (8.6)
Fasting plasma glucose, mean (SD), mmol/L:		
Participants with type 2 diabetes	7.1 (2.6)	6.6 (1.7)
Participants with no type 2 diabetes	5.0 (0.5)	5.1 (0.5)
Glycated haemoglobin, mean (SD), %:		
Participants with type 2 diabetes	7.1 (1.1)	7.2 (1.2)
Participants with no type 2 diabetes	5.4 (0.4)	5.4 (0.5)
HOMA-IR index value, median (IQR)†	3.5 (2.6-4.9)	3.9 (2.5-5.1)
Lipids:		
Triglycerides, median (IQR), mg/dL	181.1 (121.3-259.0)	168.2 (140.8-247.9)
Total cholesterol, mean (SD), mg/dL	183.8 (36.0)	192.9 (36.8)
High density lipoprotein cholesterol, mean (SD), mg/dL	37.3 (7.0)	38.3 (6.7)
Low density lipoprotein cholesterol, mean (SD), mg/dL	117.7 (30.0)	125.1 (33.2)
Liver enzyme levels:		
Alanine aminotransferase, mean (SD), U/L	65.0 (34.6)	69.4 (38.4)
Aspartate aminotransferase, mean (SD), U/L	36.3 (15.7)	39.7 (20.5)
γ-glutamyltransferase, mean (SD), U/L	55.8 (36.9)	65.4 (45.1)
Non-invasive measures as assessed by FibroScan:		
Liver steatosis, mean (SD), dB/m	325.2 (34.1)	321.9 (32.2)
Liver stiffness, mean (SD), kPa	8.9 (3.6)	9.3 (3.0)
Abdominal visceral fat area, median (IQR), cm^2	137.5 (110.4-164.8)	137.0 (116.3-169.1)
Liver biopsy findings:		
NAFLD activity score, mean (SD)‡	5.9 (1.1)	6.1 (1.1)
Steatosis, mean (SD)	2.4 (0.7)	2.4 (0.7)
Ballooning, mean (SD)	1.6 (0.5)	1.7 (0.4)
Lobular inflammation, mean (SD)	1.9 (0.7)	1.9 (0.6)
NASH-CRN fibrosis stage, mean (SD)	1.8 (0.8)	1.9 (0.8)
F0, no fibrosis, No. (%)	2 (3)	1 (1)
F1, mild fibrosis, No. (%)	26 (34)	25 (32)
F2, significant fibrosis, No. (%)	35 (46)	35 (45)
F3, advanced fibrosis No. (%)	12 (16)	17 (22)
F4, cirrhosis, No. (%)§	1 (1)	0 (0)

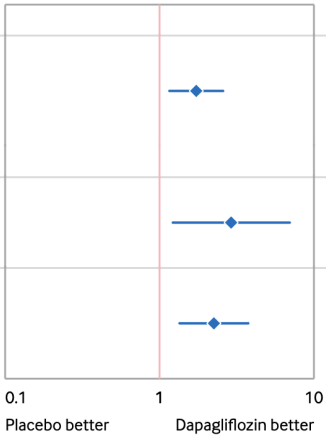
HOMA-IR=homeostatic model assessment for insulin resistance; IQR=interquartile range; NAFLD=non-alcoholic fatty liver disease; NASH=non-alcoholic steatohepatitis; SD=standard deviation.
*Component summary scores from the 36-Item Short-Form Health Survey (SF-36) are interpreted as standardized T-scores, with a mean of 50 and SD of 10 in the American general population, higher scores indicate better physical or mental health.
†HOMA-IR denotes homoeostatic model assessment of insulin resistance. Participants with insulin treatment were excluded.
‡The NAFLD activity score is assessed on a scale of 0 to 8, with higher scores indicating more severe disease.
§One participant was initially assessed as having F3 fibrosis but determined as having F4 fibrosis by the central reading.

by FibroScan over 48 weeks (table 2; supplementary figure 8). Likewise, Liver enzymes such as γ-glutamyl transferase were significantly improved in the dapagliflozin group as compared with the placebo group (table 2; supplementary figure 9). Furthermore, treatment with dapagliflozin was also associated with a reduction in body weight, waist circumference, and abdominal visceral fat (table 3; supplementary figure 10). Concentrations of glycated haemoglobin were reduced in the dapagliflozin group in participants with type 2 diabetes, and improvements in Homeostatic Model Assessment for Insulin Resistance were observed in the dapagliflozin group in participants with no type 2 diabetes, as compared with the placebo group (table 3; supplementary figure 11-12). Improvement in lipids were also observed in the dapagliflozin group (table 3; supplementary figure 13). Changes in quality of life are summarised in table 3. In addition, weight loss was found to largely mediate the total effect of dapagliflozin on the higher proportion of MASH improvement and MASH resolution, but not fibrosis improvement in the mediation analysis (supplementary table 6).

Primary and confirmatory secondary endpoints at week 48

Percentages of participants with MASH improvement without worsening of fibrosis, MASH resolution without worsening of fibrosis, and fibrosis improvement without worsening of MASH at week 48

Endpoint	Responses in placebo group (%)	Responses in dapagliflozin group (%)	Risk ratio (95% CI)	P value
Primary endpoint				
MASH improvement without worsening of fibrosis	23 (30)	41 (53)	1.73 (1.16 to 2.58)	0.006
Comfirmatory secondary endpoints				
MASH resolution without worsening of fibrosis	6 (8)	18 (23)	2.91 (1.22 to 6.97)	0.01
Fibrosis improvement without worsening of MASH	15 (20)	35 (45)	2.25 (1.35 to 3.75)	0.001



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MASH denotes metabolic dysfunction-associated steatohepatitis
The risk ratios (RRs), 95% confidence intervals (CIs), and P values were calculated using the Cochran-Mantel-Haenszel (CMH) test, controlling for baseline diabetes status. MASH improvement was defined as a decrease in non-alcoholic fatty liver disease activity score (NAS) of at least 2 points or a NAS score of less than or equal to 3 points after treatment) without worsening of fibrosis (defined as with increase of fibrosis stage) at week 48; MASH resolution was defined as a hepatocellular ballooning score of 0, and lobular inflammation score of 0 or 1, without worsening of fibrosis at week 48; fibrosis improvement was defined as reduction in fibrosis of at least 1 stage without worsening of MASH (defined as without an increase in steatosis, ballooning, or inflammation of at least 1 stage) at week 48. Participants with missing biopsies were considered as not responding

Fig 2 | Primary and confirmatory secondary endpoints at week 48. An interactive version of this graphic is available at https://public.flourish.studio/visualisation/23047808/

Safety

Adverse events were reported in 56% (44/78) of the participants in the dapagliflozin group, compared with 64% (49/76) of those in the placebo group (supplementary table 7). The common adverse events were covid-19, insomnia, and gout. Admission to hospital due to diabetic ketoacidosis was reported in one participant in the placebo group and no serious adverse event occurred in the dapagliflozin group. The proportion of participants who discontinued treatment because of adverse events was 1% (1/78) with dapagliflozin and 3% (2/76) with placebo. Urinary tract infection and diabetic ketoacidosis were the most common reasons for discontinuation. No cases of cardiovascular disease events, cancer, or deaths were observed. Furthermore, no cases of severe hypoglycaemia were reported. Occurrences of mild adverse events, such as insomnia, gout, nasopharyngitis, hypoglycaemia, urinary tract infection, gastrointestinal polyp, fatigue, dizziness, gastroenteritis, rash, bone fracture, alopecia, circumcision, dermatitis, face oedema, genital pruritus, headache, and upper abdominal pain, were similar between the two groups (supplementary table 7).

Discussion

Principal findings

In this trial, we found that 48 weeks of treatment with dapagliflozin led to a significant MASH improvement without worsening of fibrosis, as compared with placebo. In addition, the results also supported that treatment with dapagliflozin had a benefit with regard to MASH resolution without worsening of fibrosis, and fibrosis improvement without worsening of MASH among participants with MASH, as well as participants with stage 2 or 3 fibrosis that is of concern. Our findings indicate that dapagliflozin may affect key aspects of MASH by improving both steatohepatitis and fibrosis.

Comparison with other studies

Several clinical studies have shown that SGLT2 inhibitors can improve non-invasive liver parameters (ie, liver fat content, liver enzymes, and liver stiffness) in participants with MASLD or MASH.[16-24] Takahashi and colleagues showed that the SGLT2 inhibitor ipragliflozin improved hepatocyte ballooning and fibrosis compared with regular anti-diabetic drugs in 50 participants with diabetes and MASLD over a 72 week intervention period.[26] However, Takeshita and colleagues reported that the SGLT2 inhibitor

Table 2 | Changes in secondary liver endpoints from baseline to week 48

Endpoints	Changes from baseline (95% CIs)		Difference between groups (95% CIs)*	P value
	Placebo	Dapagliflozin		
Histological features				
Steatosis	−0.37 (−0.56 to −0.18)	−0.82 (−1.00 to −0.64)	−0.45 (−0.71 to −0.19)	<0.001
Ballooning	−0.17 (−0.31 to −0.03)	−0.60 (−0.74 to −0.47)	−0.43 (−0.63 to −0.24)	<0.001
Lobular inflammation	−0.07 (−0.26 to 0.11)	−0.56 (−0.73 to −0.38)	−0.49 (−0.74 to −0.23)	<0.001
NAFLD activity score	−0.60 (−1.03 to −0.17)	−1.99 (−2.40 to −1.58)	−1.39 (−1.99 to −0.79)	<0.001
Fibrosis stage	−0.22 (−0.39 to −0.06)	−0.77 (−0.92 to −0.61)	−0.54 (−0.77 to −0.31)	<0.001
Non-invasive measures assessed by FibroScan				
Liver steatosis, dB/m	−18.58 (−27.02 to −10.14)	−34.29 (−42.52 to −26.07)	−15.71 (−27.49 to −3.94)	0.009
Liver stiffness, kPa	−1.72 (−2.17 to −1.26)	−3.23 (−3.68 to −2.79)	−1.51 (−2.15 to −0.88)	<0.001
Liver enzymes				
Alanine aminotransferase, U/L	−12.99 (−19.62 to −6.36)	−17.80 (−24.23 to −11.37)	−4.80 (−14.03 to 4.42)	0.31
Aspartate aminotransferase, U/L	−4.44 (−7.61 to −1.27)	−8.35 (−11.41 to −5.28)	−3.90 (−8.31 to 0.50)	0.08
γ-glutamyltransferase, U/L	0.57 (−6.76 to 7.91)	−16.96 (−24.06 to −9.86)	−17.53 (−27.75 to −7.32)	<0.001

Data are presented as least-square mean changes (95% confidence interval (CI)) in each group, and mean difference (95% CI) between the two groups.
NAFLD=non-alcoholic fatty liver disease
*Analyses are conducted using mixed models for repeated measures, the individuals were considered as random effects, whereas the diabetes status, baseline value, the intervention group, follow-up time, and the group-time interaction were considered as fixed effects.

tofogliflozin did not result in a significant benefit in histological features compared with glimepiride for 48 weeks among 40 diabetic participants with MASLD.[25] These studies did not provide adequate information needed to formulate evidence based clinical guidance for MASH management because of the limited sample sizes and the possible absence of ballooning, lobular inflammation or fibrosis in the MASLD population. Therefore, the effect of SGLT2 inhibitors on MASH remains uncertain. In the current trial involving participants with biopsy diagnosed MASH, 48 week treatment with dapagliflozin led to 53% of participants with MASH improve without worsening of fibrosis, as compared with 30% in the placebo group. Of note, the treatment yielded a placebo subtracted effect of 15% on MASH resolution without worsening of fibrosis and 25% on fibrosis improvement without worsening of MASH. These confirmatory secondary endpoints are consistent with the endpoints that the US Food and Drug Administration (FDA) proposed as reasonably likely to predict long term clinical benefit for MASH.[29] The results also suggested that dapagliflozin provides similar benefits on MASH improvement without worsening of fibrosis and MASH resolution without worsening of fibrosis, regardless of whether the participants were living with obesity or not, diabetes or not, or with different severity of MASH.

Fibrosis is the most important prognosis factor in people with MASH, so that fibrosis regression is considered to improve long term clinical

Table 3 | Changes in metabolic endpoints and quality of life from baseline to week 48

Endpoints	Changes from baseline (95% CIs)		Difference between groups (95% CIs)*	P value
	Placebo	Dapagliflozin		
Body weight, kg	−0.75 (−1.60 to 0.11)	−4.26 (−5.07 to −3.44)	−3.51 (−4.69 to −2.33)	<0.001
Body mass index	−0.31 (−0.61 to −0.01)	−1.53 (−1.82 to −1.25)	−1.22 (−1.64 to −0.81)	<0.001
Waist circumference, cm	−0.61 (−1.50 to 0.28)	−3.35 (−4.20 to −2.49)	−2.74 (−3.96 to −1.51)	<0.001
Abdominal visceral fat area, cm^2	−3.04 (−9.73 to 3.66)	−24.92 (−31.86 to −17.99)	−21.89 (−31.51 to −12.26)	<0.001
Systolic blood pressure, mm/Hg	−1.92 (−3.74 to −0.09)	−5.19 (−6.93 to −3.45)	−3.28 (−5.80 to −0.76)	0.01
Diastolic blood pressure, mm/Hg	0.38 (−0.96 to 1.72)	−1.94 (−3.22 to −0.66)	−2.32 (−4.17 to −0.47)	0.01
Fasting glucose, mmol/L	0.06 (−0.20 to 0.33)	−0.32 (−0.57 to −0.06)	−0.38 (−0.75 to −0.01)	0.04
Glycated haemoglobin, %	−0.08 (−0.25 to 0.08)	−0.37 (−0.52 to −0.21)	−0.29 (−0.51 to −0.06)	0.01
HOMA-IR index value†	1.53 (0.76 to 2.31)	0.28 (−0.45 to 1.01)	−1.26 (−2.30 to −0.21)	0.02
Lipids				
Triglycerides, mg/dL	−3.53 (−23.59 to 16.53)	13.53 (−5.85 to 32.90)	17.06 (−10.79 to 44.90)	0.23
Total cholesterol, mg/dL	10.86 (5.25 to 16.48)	1.43 (−3.98 to 6.85)	−9.42 (−17.23 to −1.63)	0.02
HDL-c, mg/dL	4.00 (2.80 to 5.20)	5.64 (4.48 to 6.80)	1.64 (−0.03 to 3.30)	0.06
LDL-c, mg/dL	6.44 (1.32 to 11.56)	−5.13 (−10.07 to −0.20)	−11.57 (−18.67 to −4.47)	0.001
SF-36 quality of life‡				
Physical component summary	1.74 (0.85 to 2.64)	2.12 (1.25 to 2.99)	0.38 (−0.87 to 1.63)	0.55
Mental component summary	2.21 (0.85 to 3.58)	2.31 (0.98 to 3.64)	0.10 (−1.81 to 2.00)	0.92

Data are presented as least-square mean changes (95% confidence interval (CI)) in each group, and mean difference (95% CI) between the two groups.
HOMA-IR=homeostatic model assessment for insulin resistance; HDL-c=high density lipoprotein cholesterol; LDL-c=low density lipoprotein cholesterol; SF-36=36-Item Short-Form Health Survey.
*Analyses are conducted using mixed models for repeated measures, individuals were considered as random effects, whereas diabetes status, baseline value, intervention group, follow-up time, and group-time interaction were considered as fixed effects.
†Participants with insulin treatment were excluded from this analysis.
‡Component summary scores from the SF-36 are interpreted as standardised T-scores, with a mean of 50 and SD of 10 in the American general population, higher scores indicate better physical or mental health.

benefit for MASH progression (ie, cirrhosis and hepatocellular carcinoma).[32] Although randomised placebo controlled trials have shown that several anti-diabetic drugs (eg, pioglitazone, liraglutide, semaglutide, tirzepatide, or survodutide) had a benefit on MASH, only semaglutide and tirzepatide resulted in a statistically significant improvement on liver fibrosis without worsening of MASH in participants with or without diabetes.[6-10] The proportion of participants who had improvement in fibrosis stage without worsening of MASH at week 48 was 45% in the dapagliflozin group, compared with 20% in the placebo group in the current study. In line with our findings, two pilot clinical studies of SGLT2 inhibitors (ipragliflozin and tofogliflozin) on MASLD histology also supported the effects of SGLT2 inhibitors on fibrosis improvement.[25 26] Moreover, the result indicated that fibrosis improvement without worsening of MASH was independent of weight loss. Furthermore, participants with diabetes seemed to have higher proportions of fibrosis improvement without worsening of MASH than participants with no diabetes, indicating the potential effect of dapagliflozin on preventing fibrosis progression in patients with type 2 diabetes and fatty liver. However, this observation should be interpreted with caution, as these analyses were not adjusted for multiple comparisons. Overall, our findings indicated that dapagliflozin may modulate key aspects of the pathophysiology of MASH, including steatohepatitis and fibrosis. Nevertheless, the mechanism of SGLT2 inhibitors on MASH is largely unknown and requires further research.

In addition to consistent improvements in histological features, treatment with dapagliflozin also led to a reduction in liver steatosis and stiffness, assessed by FibroScan, and liver enzymes. In line with findings from previous studies, our results showed that the SGLT2 inhibitor dapagliflozin benefited the metabolic conditions (ie, body weight, waist circumference, visceral fat, glucose, insulin resistance, lipids, and blood pressure), which are strongly associated with MASH.[33] Moreover, our findings suggested that the effect of dapagliflozin on MASH improvement without worsening of fibrosis and MASH resolution without worsening of fibrosis might be largely mediated by weight loss. SGLT2 inhibitors have been proposed to modulate energy homoeostasis and exhibit anti-oxidative stress and anti-inflammatory effects, which counteract the pathogenic characteristics of MASH.[15] In 2024, Liu and colleagues reported that SGLT2 inhibitors promoted the synthesis of ketone bodies, leading to a reduction in the infiltration and effector functions of CD8+ T cells in the liver, thereby ameliorating the progression of MASH.[34] One possible explanation framework for these effects is the systemic metabolic reprogramming and negative energy balance induced by SGLT2 inhibitors,[35] accompanying potential direct effect on the pathogenesis of MASH.

SGLT2 inhibitors are well tolerated and widely used to treat type 2 diabetes, cardiovascular disease, and chronic kidney disease.[12-14] Although our trial involved participants with or with no type 2 diabetes, the safety profile of dapagliflozin was similar to what was observed in individuals with type 2 diabetes in other trials.[36] No serious adverse event was reported in participants with dapagliflozin use in this trial. Overall, the incidence of known potential side effects of SGLT2 inhibitors, such as hypoglycaemia, ketoacidosis, urinary tract infection, and genital pruritus, was mostly mild and did not differ from the placebo group. Discontinued treatment because of adverse events (ie, diabetic ketoacidosis and urinary tract infection) occurred in one participant who received dapagliflozin and in two participants who received placebo. In addition, the benefit-risk profiles of dapagliflozin on cardiovascular disease and chronic kidney disease may be instrumental in improving the risk of these comorbidities in MASH.

Strengths and limitations

To our knowledge, the DEAN trial is the first randomised controlled trial comparing the effects of SGLT2 inhibitor with placebo on biopsy confirmed improvement in participants with MASH. Moreover, findings from original analysis, multiple imputation analysis, and per protocol analysis agree. Our trial also has certain limitations. Firstly, our primary endpoint was MASH improvement without worsening of liver fibrosis instead of MASH resolution without worsening of fibrosis or fibrosis improvement without worsening of MASH according to the guidance of FDA,[29] because the trial was registered and initiated before publication of FDA guidance. However, the confirmatory secondary endpoints in this trial are consistent with the endpoints proposed by the FDA as reasonably likely to predict liver outcomes in adults with MASH and liver fibrosis. Secondly, the current trial was conducted in a Chinese population, which limits the broader generalisability of the conclusion. Thirdly, a high proportion of male and relatively younger participants were recruited in this trial because they may be more willing to accept liver biopsy at screening. Although the results showed no age and sex differences of dapagliflozin on MASH improvement, female and the older patients were underrepresented in the current study. Finally, because of the scarcity of major adverse liver outcomes (eg, cirrhosis and hepatocellular carcinoma), large scale and long term trials are needed to further confirm these effects.

Conclusion

In this randomised controlled trial, among participants with biopsy diagnosed MASH, 48 week treatment with dapagliflozin led to a higher proportion of participants, compared with placebo, who had MASH improvement without worsening of liver fibrosis, as well as MASH resolution without worsening of fibrosis and fibrosis improvement without worsening of MASH. These results support the potential for dapagliflozin to provide benefit to patients with MASH and liver fibrosis.

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Contributors: JL, YH, BX, XG, JH, JS, and HZ contributed equally to this study. HZ designed the trial. JL, BX, XG, JH, JS, LJ, CH, XW, JC, XC, JZ, LW, PZ, YZ, HX, GW, YL, SL, YZ, LZ, HJ, YX, FW, and HZ collected the data. JL, JH, YH, and HZ did the statistical analysis. JL, YH, and HZ wrote the first draft of the manuscript. All the authors participated in the revision of the manuscript and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. JL, YH, and HZ have accessed and verified the underlying data reported in the manuscript. HZ is the study guarantor. The corresponding author (HZ) had full access to the data and had primary responsibility for the final publication, and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: The study protocol and amendments were reviewed and approved by the Ethics Committees at each centre. All the participants provided written informed consent.

Data sharing: The codes used to analyse the data can be found in the supplemental files. The data underlying the findings of this paper are available in: https://github.com/Yurence/DEAN_trial.git. Usage of the data for publication purposes should require prior approval from the corresponding author. If you encounter problems accessing the data, please contact the corresponding author.

Transparency: The corresponding author (the manuscript's guarantor) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related participant and public communities: The findings of the study will be disseminated to the public through social media and write blogs. Once this study is published, we plan to present the study outcomes at meetings in China and worldwide.

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