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Synergistic benefit of thiazolidinedione and sodium-glucose cotransporter 2 inhibitor for metabolic dysfunction-associated steatotic liver disease in type 2 diabetes: a 24-week, open-label, randomized controlled trial

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Abstract

Background The close interplay between metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes supports the need to identify beneficial combination therapies of antidiabetic medications targeted for the treatment of MASLD. This study aimed to investigate the complementary effects of combination therapy with pioglitazone (PIO) and empagliflozin (EMPA) on MASLD in individuals with type 2 diabetes.

Methods In a randomized, open-label trial, 50 participants with type 2 diabetes and MASLD were assigned 1:1:1 to receive PIO 15 mg, EMPA 10 mg, or a combination (PIO 15 mg plus EMPA 10 mg) daily for 24 weeks. Liver fat fraction and stiffness were evaluated using magnetic resonance imaging-proton density fat fraction (MRI-PDFF) and magnetic resonance elastography (MRE), respectively.

Results Combination therapy resulted in the largest reduction in liver fat and stiffness among treatment groups. Participants experiencing a relative reduction ≥ 30% or an absolute reduction ≥ 5% in liver fat were the most prevalent in the combination group (100.0% vs. 57.1% in PIO and 87.5% in EMPA, $p = 0.010$). In addition, the combination group showed the highest proportion of individuals with a relative reduction ≥ 30% in liver fat and ≥ 20% in liver stiffness than the monotherapy groups (50.0% vs. 21.4% in PIO and 6.3% in EMPA, $p = 0.029$). Combination therapy did not induce the changes in subcutaneous fat deposition observed in the monotherapy groups, but it did show the most substantial reduction in visceral fat, concurrently showing the largest increase in adiponectin level across the three groups ($p = 0.036$).

Conclusions Combination therapy of PIO with EMPA showed synergistic benefits for MASLD in individuals with type 2 diabetes, compensating for the inadequate or unfavorable effects of monotherapies; ClincialTrials.gov number, NCT03646292.

Trial registration The trial was registered at ClinicalTrials.gov (registration number: NCT03646292).

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Keywords Metabolic dysfunction-associated steatotic liver disease, Type 2 diabetes, Thiazolidinedione, Sodium-glucose cotransporter 2 inhibitor

Background

The prevalence of non-alcoholic fatty liver disease (NAFLD) has experienced a substantial rise, closely associated with the global obesity pandemic, making NAFLD the most common cause of chronic liver disease [1, 2]. However, the term "nonalcoholic" in NAFLD is based on the concept of diagnosing the disease by excluding cases with a significant alcohol consumption, which did not accurately reflect the underlying aetiology of the disease [2, 3]. Recently, a multi-society Delphi consensus statement proposed the term "steatotic liver disease (SLD)" to replace the traditional term "fatty" as an overarching term that encompasses the diverse etiologies of hepatic steatosis, including those related to metabolic disorders, alcohol consumption, and other causes [2, 3]. In the statement, the term "metabolic dysfunction-associated SLD (MASLD)" was chosen instead of NAFLD, with the aim of reflecting the central aspect of disease pathophysiology driven by metabolic disease or dysfunction that leads to steatosis [2–4]. Additionally, the term "metabolic dysfunction-associated steatohepatitis (MASH)" has been introduced to substitute non-alcoholic steatohepatitis (NASH) [2, 3], representing the advanced stage of NAFLD with inflammation and hepatocellular ballooning on histopathology [5]. MASLD is diagnosed based on SLD with the presence of at least one of five cardiometabolic risk factors, in the absence of significant alcohol consumption [3, 4]. The parameters for these cardiometabolic risk factors include body mass index (BMI), blood glucose, blood pressure, and lipid profile [3]. Therefore, according to the diagnostic criteria for MASLD, all individual with type 2 diabetes who present with SLD can be classified as having MASLD. Given the pathogenesis of MASLD, the effort to repurpose antidiabetic medications for the treatment of MASLD can be a logical and natural approach [1, 2, 6].

Pioglitazone (PIO), one of the thiazolidinediones (TZDs) and a drug for type 2 diabetes, is a peroxisome proliferator-activated receptor (PPAR)-γ agonist that ameliorates insulin resistance [6]. PIO could be a therapeutic option for patients with type 2 diabetes and MASH, as it has shown positive results regarding MASH [6, 7]. However, previous studies used PIO in high doses (30 mg/day and 45 mg/day) that may raise concerns about its unfavorable side effects of weight gain, edema, and heart failure [6–8]. Therefore, there is an unmet demand for strategies that can effectively treat MASH using low doses of PIO (≤ 15 mg/day) to minimize side effects.

Among antidiabetic drugs, sodium-glucose cotransporter 2 (SGLT2) inhibitors have also received attention for their favorable effects on MASLD [6, 9]. Evidence of the effect of SGLT2 inhibitors on MASLD has mainly been related to liver fat reduction, which could be attributed to weight reduction induced by urinary caloric loss [9]. However, in terms of improving hepatic fibrosis, the evidence supporting the efficacy of SGLT2 inhibitors has been insufficient [9].

From these various backgrounds, we hypothesized that the unwanted weight gain and suboptimal effect of PIO in low doses could be compensated by adding SGLT2 inhibitors, which may enhance PIO's effect on MASH through their weight loss properties and associated therapeutic benefits. To the best of our knowledge, this is the first randomized active-controlled trial to investigate the complementary effects of combination therapy with PIO (15 mg/d) and an SGLT2 inhibitor, empagliflozin (EMPA, 10 mg/d), on MASLD in individuals with type 2 diabetes.

Methods

Study participants

This investigator-initiated, randomized, 24-week, open-label, active-controlled trial was conducted to investigate the efficacy of PIO 15 mg/day plus EMPA 10 mg/day compared with PIO 15 mg/day alone or EMPA 10 mg/day alone for 24 weeks to improve hepatic steatosis and fibrosis as measured by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) and magnetic resonance elastography (MRE), respectively, in participants with type 2 diabetes and confirmed MASLD. Participants of the study were recruited from Severance Hospital, Seoul, Korea, from Dec 2018 to Dec 2021, with the final follow-up visit in June 2022.

The trial was registered at ClinicalTrials.gov (registration number: NCT03646292). All participants provided written informed consent and the Ethics Committee of the Yonsei University College of Medicine approved this study (4-2018-0655), which conforms to the ethical principles of the 1975 Declaration of Helsinki. This study was conducted in adherence to the CONSORT guidelines.

Physicians prescreened the enrolment availability of candidates according to medical history and laboratory results. Participants were required to meet all the following criteria to be included: 19–75 years of age, diagnosed with type 2 diabetes (HbA1c ≥ 7.5% and < 11.0%)

and treated with antidiabetic drugs excluding TZD and SGLT2 inhibitor over the previous 12 weeks, and SLD as documented by abdominal ultrasonography (US) within the previous year. If participants had received abdominal US in the previous year, their results were checked for hepatic steatosis. If not, they underwent an abdominal US for screening purposes. Exclusion criteria are detailed in Additional file 1: Table S1.

Study design

Participants were randomly assigned on a 1:1:1 ratio to receive once-daily PIO 15 mg plus EMPA 10 mg, PIO 15 mg alone, or EMPA 10 mg alone for 24 weeks. The study consisted of four visits: an initial screening visit (visit 1) 4 weeks before the second visit, a randomization visit (visit 2), and follow-up visits (visits 3 and 4) at 12 and 24 weeks. MRI and fat computed tomography (CT) scans were performed on visits 2 and 4. All participants were instructed to fast for at least 8 h prior to each visit. The study design is graphically summarized in Additional file 1: Fig. S1. Clinical research timeline and the variables measured at each time point are presented in Additional file 1: Table S2.

Sample size and randomization

The sample size of this clinical trial was determined using the G*Power 3.1.9.7 program to achieve 80% power (one-sided, $\alpha = 0.05$) for testing the efficacy of antidiabetic drugs on hepatic steatosis compared to baseline. The calculated minimal sample size for the study was 15 participants in each treatment group, based on the mean difference and standard deviation (SD) observed in a previous study using pioglitazone [10]. The final sample size was set at 20 participants in each group, assuming a 25% dropout rate.

Before randomization, all participants received a baseline evaluation that included their medical history and a physical examination. Simple randomization was executed by a clinical research nurse using a computer-based random number generator. Participants were enrolled and assigned in consecutive order by a clinical research nurse, each receiving the next available allocation from the list. Treatment allocation was conducted in an open-label manner.

Primary and secondary outcomes

The primary outcome was change in liver fat fraction after 24 weeks of treatment as measured using MRI-PDFF in the largest possible polygonal region of interest (ROI) encompassing both lobes of the liver. Secondary outcome measures were change in liver stiffness measured using MRE and changes in lipid profile (total cholesterol, triglycerides, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and free fatty acid [FFA]), liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], and gamma-glutamyl transferase [GGT]), glycemic parameters (fasting glucose, glycated hemoglobin A1c [HbA1c], fasting insulin, homeostatic model assessment for insulin resistance [HOMA-IR] [11], and homeostasis model assessment of β-cell function [HOMA-β] [11]), and cytokines (high sensitivity C-reactive protein [hsCRP], adiponectin, and leptin). Alterations in other biochemical parameters (complete blood count, platelet count, total protein, albumin, total bilirubin, blood urea nitrogen, creatinine, and uric acid) were also evaluated before and after study participation. Blood pressure, body weight, BMI, waist circumference, and body composition determined by abdominal fat CT scan were assessed before and after drug administration. MASLD-related indices (hepatic steatosis index and fibrosis index based on 4 factors [FIB-4] index) [12, 13] were calculated using variables measured as secondary outcomes and compared between baseline and 24 weeks. After the study began, calculation of MASLD-related indices was decided to achieve additional information about hepatic steatosis and fibrosis, using pre-specified secondary outcome values.

MRI-PDFF and MRE for hepatic steatosis and fibrosis quantification

MRI was performed using a 3.0-T system (Ingenia CX, Philips Medical Systems, Best, Netherlands) at baseline and completion of the 24-week trial. To measure hepatic fat, we employed the MRI-PDFF sequence (mDIXON Quant), and the manufacturer's console automatically produced a fat fraction map. To measure the fat fraction, we drew the largest possible polygonal ROI encompassing both lobes of the liver on a cross-sectional image, while avoiding blood vessels, bile ducts, and distinct hepatic lesions. In the MRI before and after treatment, ROIs were positioned as consistently as possible. For assessing liver fibrosis, we utilized MRE, applying a 2-dimensional gradient-echo sequence and positioning a passive driver on the right upper abdomen of the participant. ROIs were outlined on one slice of the stiffness map, capturing the maximum liver parenchyma while excluding blood vessels, bile ducts, specific hepatic lesions, and the subcapsular region. The mean value of all these measurements was used for analysis.

Body composition analysis

An abdominal fat CT scan (Siemens somatom sensation 64 [Siemens healthcare Gmbh, Erlangen, Germany] or GE Light Speed VCT [GE, Chicago, USA]) was conducted to measure the abdominal subcutaneous fat

area (SFA) and abdominal visceral fat area (VFA). The abdominal fat content was assessed using a 3-mm thick cross-sectional CT scan at the midpoint of the L3 vertebra, with the participants in a supine position. Using the TeraRecon Aquarius software (Aquaris iNtuition Ver.4.4.6 TeraRecon, Foster City, CA, USA), the SFA and VFA values were digitally computed using an attenuation spectrum of −190 to −30 Hounsfield units for SFA and −150 to −50 Hounsfield units for VFA; the results were presented in cm^2. The VFA was calculated by assessing the inner portion of the abdominal cavity, bordered by the abdominal and oblique muscle walls and the rear side of the vertebral body. The residual fat situated between the muscle and the subcutaneous tissue was identified and quantified as the SFA.

Statistical analysis

Overall analysis was based on the per-protocol analysis. Continuous data with or without normal distribution are presented as the average with its SD or the median with its interquartile range (IQR), whereas categorical data are shown as counts and percentages (%). When comparing groups, continuous variables among the three treatment groups were compared using one-way analysis of variance for normal distributions or the Kruskal–Wallis test for non-normal distributions. Categorical variables were analyzed among the three treatment groups using the Chi-square test, or the Fisher's exact test when more than 20% of categories had an expected frequency of less than 5. Comparative analyses between combination therapy and each monotherapy were conducted post hoc using a false discovery rate. Primary and secondary outcomes within each treatment group were analyzed using the Wilcoxson signed rank test. Improvement in liver fat was defined as a ≥ 50% relative decrease in liver fat or as either a relative decrease ≥ 30% or an absolute decrease ≥ 5% in liver fat by MRI-PDFF from baseline to completion of treatment [14, 15]. Improvement in liver stiffness was defined as a relative decrease ≥ 20% in liver stiffness as measured by MRE from baseline to completion of treatment [16]. Univariable and multivariable linear regression analyses were conducted to assess the association of each parameter with the reduction in liver fat and liver stiffness, with multivariable analysis identifying independent determinants.

$P < 0.05$ was considered significant. SAS version 9.3 (SAS Institute, Cary, NC, USA), R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria), and IBM SPSS statistical software for Windows, version 25.0 (IBM, Armonk, NY, USA) were used to perform statistical analyses. All authors had access to study data and approved the final data analysis and submission.

Results

Subject characteristics

A total of 50 participants with type 2 diabetes and MASLD was randomly assigned to receive either PIO (n = 15) or EMPA (n = 17) monotherapy or combination therapy with PIO plus EMPA (n = 18). Six subjects discontinued the study during follow-up and a total of 44 subjects was included in the final analysis (Fig. 1). Baseline characteristics of study participants are summarized in Table 1 and Additional file 1: Table S3. Of the total subjects, 54.5% were male, the mean age was 53.8 years, and the mean BMI was 28.7 kg/m^2. Overall, there were generally no significant differences in baseline clinical characteristics between the three groups. However, despite random assignment, fasting blood glucose levels were lower in the PIO group, and the proportion of insulin users was higher in the EMPA group. At baseline, the median fat fraction, as measured by MRI-PDFF, was 15%, and the median liver stiffness, as measured by MRE, was 2.15, suggesting mild hepatic steatosis without significant fibrosis.

Effects on anthropometric, biochemical, and body composition profiles

Changes in anthropometric, biochemical, and body composition profiles at 24 weeks are presented in Table 2 and Additional file 1: Table S4. Body weight and BMI were significantly reduced only in the EMPA monotherapy group (all $p < 0.001$), while these parameters showed a numerical increase in the PIO monotherapy group, although not to the level of statistical significance (Table 2; Fig. 2A). The tendency toward unfavorable body weight gain observed in the PIO monotherapy group was mitigated when PIO was co-treated with EMPA in the combination group. All treatment groups exhibited significant improvements in HbA1c and HOMA-IR, with no statistical difference between the groups ($p = 0.763$ for HbA1c and $p = 0.499$ for HOMA-IR, regarding differences among the three groups). On the other hand, among the three groups, adiponectin level showed the significantly greatest increase in the combination group ($p = 0.036$ for three group difference).

Visceral fat was significantly reduced in both the EMPA monotherapy and combination therapy groups (all $p < 0.001$), whereas no change was observed in the PIO monotherapy group. The reduction in visceral fat was the largest in the combination group. Subcutaneous fat mostly decreased in the EMPA monotherapy group ($p = 0.004$), while it conversely exhibited a significant increase in the PIO monotherapy group ($p = 0.042$). Unlike the monotherapy groups, the combination therapy group showed a neutral effect on the amount of subcutaneous fat.

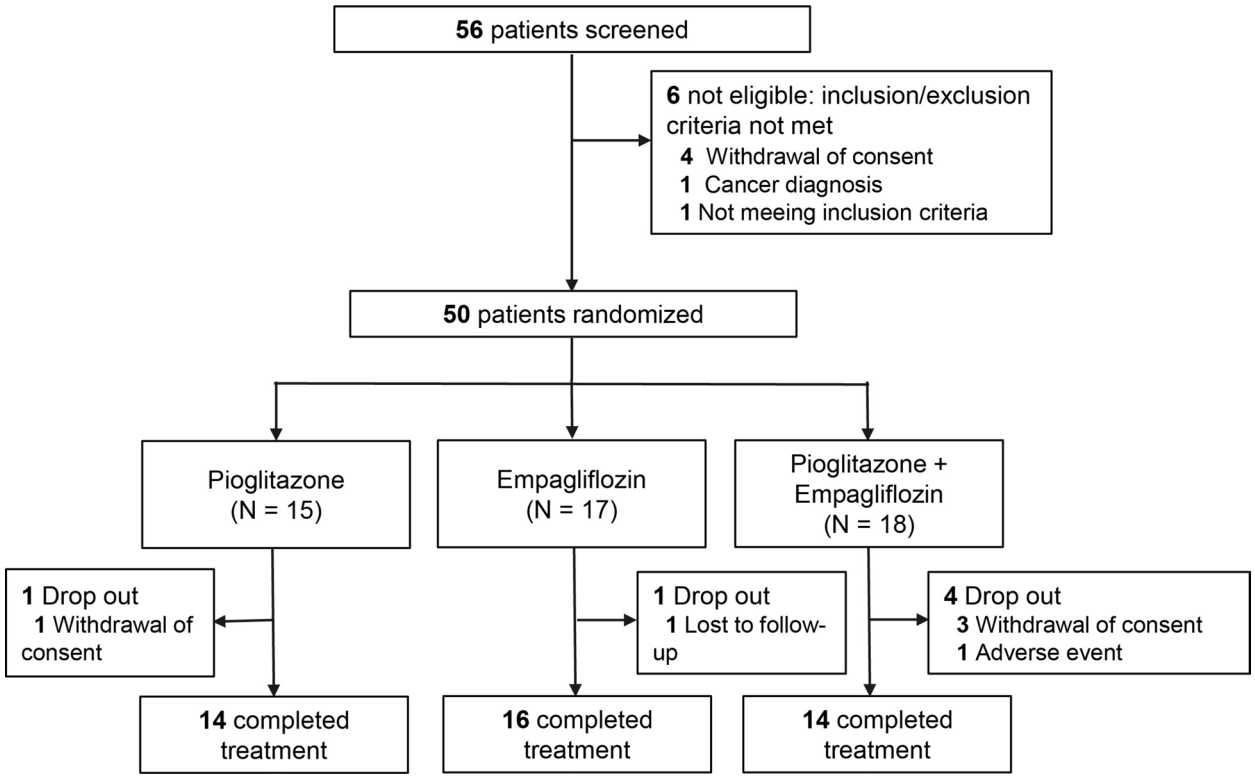

Fig. 1 Study flowchart

Effects on metabolic dysfunction-associated steatotic liver disease

The AST level significantly improved in the PIO and combination groups after 24 weeks, but not in the EMPA group (Table 2; Fig. 2B). ALT and GGT levels and hepatic steatosis index were significantly lowered in all treatment groups at 24 weeks without statistical difference across the three groups (all $p > 0.05$); however, the degree of reduction in these parameters was the most substantial in the combination group (Table 2; Fig. 2C and 2D). Combination therapy showed a 10% decrease in liver fat, the greatest reduction among the groups, albeit with marginal significance for the three-group difference ($p = 0.063$) (Table 2). The proportion of participants with a ≥ 50% relative decrease in liver fat was higher in the combination group than either PIO or EMPA monotherapy group (78.6% vs. 35.7% in PIO and 68.8% in EMPA, $p = 0.050$ for the three-group difference) (Fig. 2E). In addition, participants experiencing a relative reduction ≥ 30% or an absolute reduction ≥ 5% in liver fat were significantly the most prevalent in the combination group (100.0% vs. 57.1% in PIO and 87.5% in EMPA, $p = 0.010$ for the three-group difference) (Fig. 2E). In post hoc comparisons, the improvement in hepatic steatosis observed in the combination group was significantly superior, especially compared to the PIO group (all $p < 0.05$) (Fig. 2E). Liver stiffness was significantly ameliorated only in the PIO and combination groups (Table 2). The combination group was also the only group to show a decrease in the FIB-4 index. In addition, the combination group had the highest proportion of individuals with a relative reduction ≥ 30% in liver fat and ≥ 20% in liver stiffness compared to either PIO or EMPA monotherapy groups (50.0% vs. 21.4% in PIO and vs. 6.3% in EMPA, $p = 0.029$ for the three-group difference), showing particularly superior effects than the EMPA monotherapy group in post hoc analysis ($p = 0.024$) (Fig. 2E).

Univariable linear regression models were conducted to identify clinical variables as determinants for the reduction in liver fat and liver stiffness (Additional file 1: Table S5). Other concomitant antidiabetic agents, including insulin, were not significant factors influencing the outcomes. Meanwhile, combination therapy, compared to PIO monotherapy, was significantly more likely to reduce liver fat ($p = 0.012$). In addition, combination therapy, compared to EMPA monotherapy, was more likely to ameliorate liver stiffness with a marginal statistical significance ($p = 0.068$). The superiority of combination therapy over PIO monotherapy in reducing liver fat and over EMPA monotherapy in ameliorating liver stiffness was significant, even after adjusting for baseline fasting

Table 1 Baseline clinical characteristics

	Total (*N* = 44)	PIO (N = 14)	EMPA (N = 16)	PIO + EMPA (N = 14)	*P*-value
Demographic and Anthropometric Profile					
Age (years)	53.8 (12.5)	49.6 (10.2)	56.3 (10.1)	55.1 (16.4)	0.171
Male sex (n, %)	24 (54.5)	8 (57.1)	9 (56.2)	7 (50.0)	0.917
BMI (kg/m^2)	28.7 (3.4)	30.4 (3.1)	27.5 (3.0)	28.4 (3.7)	0.050
Waist circumference (cm)	98 (9)	100 (9)	97 (7)	97 (11)	0.419
Hypertension (n, %)	23 (52.3)	7 (50.0)	11 (68.8)	5 (35.7)	0.191
Dyslipidemia (n, %)	42 (95.5)	14 (100.0)	15 (93.8)	13 (92.9)	0.609
CVD (n, %)	19 (43.2)	3 (21.4)	10 (62.5)	6 (42.9)	0.077
Systolic blood pressure (mmHg)	128 (10)	124 (10)	128 (11)	130 (8)	0.383
Diastolic blood pressure (mmHg)	78 (8)	78 (6)	79 (10)	79 (7)	0.859
Duration of diabetes (yr)[a]	7.0 [4.0, 14.0]	4.0 [3.0, 6.5]	11.5 [6.3, 18.0]	9.0 [4.2, 12.8]	0.073
Glucometabolic Profile					
Fasting glucose (mg/dL)[a]	164 [146, 193]	148 [138, 161]	171 [136, 198]	178 [163, 197]	**0.047**
Fasting insulin (μU/mL)[a]	13.4 [8.7, 20.6]	20.3 [12.1, 23.9]	10.5 [9.1, 14.1]	12.0 [7.2, 17.9]	0.096
HbA1c (%)	8.2 (0.8)	8.0 (0.6)	8.5 (1.0)	8.4 (0.6)	0.155
HOMA-β (%)[a]	44.1 [23.1, 75.8]	77.6 [42.9, 101.0]	39.4 [23.1, 63.2]	39.0 [21.6, 64.0]	**0.049**
HOMA-IR (mg/dL*μIU/mL)[a]	5.3 [3.8, 8.1]	6.5 [4.7, 8.7]	4.6 [3.2, 6.0]	4.7 [3.2, 8.3]	0.300
Adiponectin (μg/mL)[a]	2.6 [2.1, 3.9]	2.5 [2.2, 3.6]	2.6 [2.1, 3.5]	3.6 [1.8, 4.1]	0.713
Leptin (ng/mL)[a]	6.4 [3.2, 10.1]	5.5 [3.1, 10.6]	6.7 [4.1, 8.2]	7.1 [3.4, 13.9]	0.857
Body Composition Variable					
Visceral fat area (cm^2)[a]	186 [154, 214]	175 [156, 243]	197 [159, 210]	183 [138, 199]	0.777
Subcutaneous fat area (cm^2)	191 (79)	213 (74)	167 (72)	197 (88)	0.286
MASLD-Related Parameter					
AST (IU/L)	36 (18)	35 (10)	33 (22)	42 (22)	0.411
ALT (IU/L)[a]	49 [29, 61]	55 [49, 59]	31 [21, 59]	44 [35, 70]	0.207
ALP (IU/L)[a]	66 [58, 76]	69 [56, 80]	67 [64, 76]	64 [58, 75]	0.577
GGT (IU/L)[a]	50 [37, 68]	47 [36, 60]	51 [42, 59]	55 [22, 89]	0.916
Hepatic steatosis index[a]	42.0 [38.9, 46.6]	47.5 [42.7, 49.3]	40.0 [38.3, 42.8]	40.5 [39.5, 44.4]	**0.012**
FIB-4 index	1.39 (1.24)	1.45 (1.36)	1.49 (1.58)	1.21 (0.50)	0.818
Liver fat by MRI-PDFF (%)[a]	15 [11, 22]	15 [10, 20]	19 [13, 23]	14 [13, 26]	0.593
Liver stiffness by MRE (kPa)[a]	2.15 [1.70, 2.40]	2.20 [1.80, 2.85]	2.15 [1.69, 2.35]	2.15 [1.70, 2.35]	0.653
Antidiabetic Medication Use					
Metformin (n, %)	44 (100.0)	14 (100.0)	16 (100.0)	14 (100.0)	NA
Dose of metformin (mg/d)	1000 [1000, 1700]	1000 [1000, 1500]	1000 [1000, 1700]	1500 [1000, 1700]	0.467
Sulfonylurea (n, %)[b]	10 (22.7)	5 (35.7)	3 (18.8)	2 (14.3)	0.358
DPP-4i (n, %)[b]	37 (84.1)	11 (78.6)	15 (93.8)	11 (78.6)	0.416
Insulin (n, %)[b]	10 (22.7)	2 (14.3)	7 (43.8)	1 (7.1)	**0.038**

Data are described as mean (standard deviation), median [interquartile range], or number (%)

Bolds represent statistically significant values ($p < 0.05$)

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase; *BMI* body mass index, *CVD* cardiovascular disease, *DPP-4i* dipeptidyl peptidase-4 inhibitor; *EMPA* empagliflozin, *FIB-4* fibrosis index based on 4 factors, *GGT* gamma-glutamyl transferase, *HbA1c* glycated haemoglobin A1c, *HOMA-β* homeostasis model assessment of β-cell function, *HOMA-IR* homeostatic model assessment of insulin resistance, *MASLD* metabolic dysfunction-associated steatotic liver disease, *MRE* magnetic resonance elastography, *MRI-PDFF* magnetic resonance imaging-proton density fat fraction, *PIO* pioglitazone

[a] Kruskal–Wallis test was performed for non-normal distributions; otherwise, differences among the three groups for continuous variables were analyzed using one-way analysis of variance for normal distributions

[b] Fisher's exact test was performed for categorical variables, when more than 20% of categories had an expected frequency of less than 5; otherwise, the Chi-square test was used

Table 2 Changes from baseline to week 24 in clinical parameters

	PIO (N = 14)				EMPA (N = 16)				PIO + EMPA (N = 14)				
	Pre	**Post**	**Post–Pre**	***P*- value***	**Pre**	**Post**	**Post–Pre**	***P*-value***	**Pre**	**Post**	**Post–Pre**	***P*-value***	***P*-value for three group difference for Post–Pre values[#]**
Anthropometrics													
BMI (kg/m^2)	30.4 [28.9, 32.3]	31.3 [27.1, 32.7]	0.6 [-0.4, 1.2]	0.442	26.7 [25.4, 29.4]	25.9 [24.2, 27.7]	-1.6 [-1.8, -1.0]	**< 0.001**	28.0 [25.8, 30.3]	28.1 [25.0, 30.1]	-0.1 [-0.1, 0.6]	0.485	**0.003**
Body weight (kg)	84 [78, 89]	84 [75, 89]	2 [-1, 3]	0.414	75 [68, 85]	72 [65, 81]	-4 [-5, -3]	**< 0.001**	76 [67, 85]	76 [68, 84]	-0.4 [-3, 1]	0.583	**0.002**
Waist circumference (cm)	101 [92, 108]	99 [94, 107]	0.8 [-1, 2]	0.550	97 [91, 103]	95 [89, 98]	-2 [-3, -2]	**< 0.001**	98 [89, 103]	95 [88, 108]	0 [-3, 1]	0.449	**0.018**
Systolic blood pressure (mmHg)	128 [119, 131]	125 [121, 127]	-3 [-4, 5]	0.753	130 [124, 134]	124 [113, 134]	-6 [-9, 1]	0.050	129 [125, 133]	126 [115, 134]	-5 [-12, 7]	0.489	0.528
Diastolic blood pressure (mmHg)	78 [74, 82]	78 [71, 80]	-1 [-11, 7]	0.509	80 [72, 87]	80 [77, 84]	-2 [-6, 2]	0.572	77 [75, 84]	77 [75, 81]	-1 [-9, 4]	0.600	0.991
Glucometabolic Profile													
Fasting glucose (mg/dL)	148 [138, 161]	126 [112, 134]	-22 [-35, -18]	**0.001**	171 [136, 198]	114 [92, 126]	-53 [-77, -35]	**< 0.001**	178 [163, 197]	119 [112, 132]	-57 [-69, -41]	**< 0.001**	**0.007**
Fasting insulin (μU/mL)	20.3 [12.1, 23.9]	9.3 [8.2, 14.9]	-8.1 [-11.8, -1.2]	**0.009**	10.5 [9.1, 14.1]	7.8 [5.4, 14.8]	-2.9 [-6.4, 0.3]	0.074	12.0 [7.2, 17.9]	6.1 [3.7, 9.8]	-4.4 [-7.9, -2.5]	**0.002**	0.195
HbA1c (%)	7.9 [7.6, 8.2]	6.7 [6.2, 6.8]	-1.3 [-1.8, -0.5]	**0.003**	8.4 [7.9, 9.3]	7.3 [6.4, 7.8]	-1.3 [-2.5, -0.1]	**0.010**	8.4 [8.2, 8.6]	6.8 [6.3, 7.2]	-1.5 [-2.0, -1.2]	**0.002**	0.763
HOMA-β (%)	77.6 [42.9, 101.0]	67.6 [48.0, 81.5]	-3.8 [-44.1, 17.2]	0.300	39.4 [23.1, 63.2]	82.4 [41.4, 101.0]	23.7 [8.1, 48.5]	**0.015**	39.0 [21.6, 64.0]	47.9 [24.1, 70.8]	3.1 [-3.9, 8.4]	0.221	**0.026**
HOMA-IR (mg/dL*μIU/mL)	6.5 [4.7, 8.7]	3.0 [2.3, 4.9]	-3.2 [-5.0, -1.5]	**0.002**	4.6 [3.2, 6.0]	2.3 [1.1, 4.0]	-2.8 [-3.4, -0.8]	**0.003**	4.7 [3.2, 8.3]	1.9 [1.2, 2.7]	-2.7 [-5.7, -1.5]	**0.001**	0.499
Adiponectin (μg/mL)	2.5 [2.2, 3.6]	10.1 [7.0, 13.7]	7.0 [4.7, 8.7]	**< 0.001**	2.6 [2.1, 3.5]	7.0 [5.8, 11.4]	4.2 [2.8, 7.6]	**< 0.001**	3.6 [1.8, 4.1]	14.8 [9.8, 18.6]	10.1 [6.6, 14.9]	**< 0.001**	**0.036**
Leptin (ng/mL)	5.5 [3.1, 10.6]	8.0 [2.7, 10.4]	0.2 [-1.6, 4.1]	0.626	6.7 [4.1, 8.2]	5.4 [2.8, 6.8]	-1.3 [-2.6, -0.2]	0.211	7.1 [3.4, 13.9]	6.5 [3.4, 11.2]	-0.8 [-3.4, 1.9]	0.583	0.436

Table 2 (continued)

	PIO (N = 14)				EMPA (N = 16)				PIO + EMPA (N = 14)				
	Pre	**Post**	**Post–Pre**	***P*- value***	**Pre**	**Post**	**Post–Pre**	***P*-value***	**Pre**	**Post**	**Post–Pre**	***P*-value***	***P*-value for three group difference for Post–Pre values[#]**
Body Composition Variable													
Visceral fat area (cm^2)	175 [156, 243]	177 [142, 213]	-7 [-33, 1]	0.091	197 [159, 210]	160 [145, 172]	-30 [-44, -26]	**< 0.001**	183 [138, 199]	140 [96, 169]	-34 [-46, -19]	**< 0.001**	0.088
Subcutaneous fat area (cm^2)	204 [175, 250]	205 [149, 301]	16 [8, 38]	**0.042**	152 [129, 180]	130 [113, 171]	-11 [-19, -4]	**0.004**	181 [137, 253]	190 [123, 290]	-3 [-14, 33]	0.780	**0.007**
MASLD-Related Parameter													
AST (IU/L)	34 [28, 44]	24 [18, 33]	-9 [-14,-1]	**0.045**	25 [18, 48]	20 [16, 28]	-4 [-18, 1]	0.112	39 [26, 50]	20 [17, 23]	-15 [-31, -10]	**0.001**	**0.049**
ALT (IU/L)	55 [49, 59]	34 [23, 45]	-19 [-26, -6]	**0.001**	31 [21, 59]	21 [17, 39]	-10 [-28, -1]	**0.033**	44 [35, 70]	17 [15, 27]	-22 [-39, -12]	**< 0.001**	0.161
ALP (IU/L)	69 [56, 80]	60 [49, 70]	-7 [-14, -6]	**0.017**	67 [64, 76]	60 [55, 73]	-4 [-12, 0]	**0.021**	64 [58, 75]	57 [52, 64]	-7 [-12, -2]	0.055	0.490
GGT (IU/L)	47 [36, 60]	25 [24, 39]	-15 [-34, -9]	**0.002**	51 [42, 59]	28 [20, 39]	-13 [-28, -5]	**0.007**	55 [22, 89]	24 [16, 38]	-29 [-53, -7]	**0.002**	0.281
Hepatic steatosis index	47.5 [42.7, 49.3]	43.2 [39.7, 47.7]	-1.6 [-3.7, -0.5]	**0.025**	40.0 [38.3, 42.8]	37.1 [35.5, 39.0]	-2.9 [-4.6, -1.3]	**< 0.001**	40.5 [39.5, 44.4]	39.9 [36.0, 43.8]	-4.5 [-5.5, 0.2]	**0.049**	0.706
FIB-4 index	0.94 [0.67, 1.71]	1.04 [0.56, 1.77]	0.02 [-0.15, 0.15]	0.952	1.02 [0.82, 1.53]	1.07 [0.80, 1.25]	0.01 [-0.26, 0.10]	0.660	1.08 [0.95, 1.47]	0.96 [0.64, 1.45]	-0.20 [-0.32, -0.03]	**0.025**	0.230
Liver fat by MRI-PDFF (%)	15 [10, 20]	12 [4, 17]	-7 [-10, -3]	**0.025**	19 [13, 23]	8 [5, 12]	-9 [-12, -5]	**0.001**	14 [13, 26]	4 [3, 9]	-10 [-12, -9]	**0.001**	0.063
Liver stiffness by MRE (kPa)	2.20 [1.80, 2.85]	1.95 [1.72, 2.45]	-0.25 [-0.50, 0.00]	**0.034**	2.15 [1.69, 2.35]	2.05 [1.78, 2.42]	0.00 [-0.40, 0.12]	0.530	2.15 [1.70, 2.35]	1.70 [1.52, 2.03]	-0.35 [-0.60, 0.00]	**0.015**	0.210

Bolds represent statistically significant values ($p < 0.05$)

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *CVD* cardiovascular disease, *EMPA* empagliflozin, *FIB-4* fibrosis index based on 4 factors, *GGT* gamma-glutamyl transferase, *HbA1c* glycated haemoglobin A1c, *HOMA-β* homeostasis model assessment of β-cell function, *HOMA-IR* homeostatic model assessment of insulin resistance, *MASLD* metabolic dysfunction-associated steatotic liver disease; *MRE* magnetic resonance elastography, *MRI-PDFF* magnetic resonance imaging-proton density fat fraction, *PIO* pioglitazone

[#] *P*-value of Kruskal–Wallis test for the difference between three groups

[*] Wilcoxon signed-rank test was performed

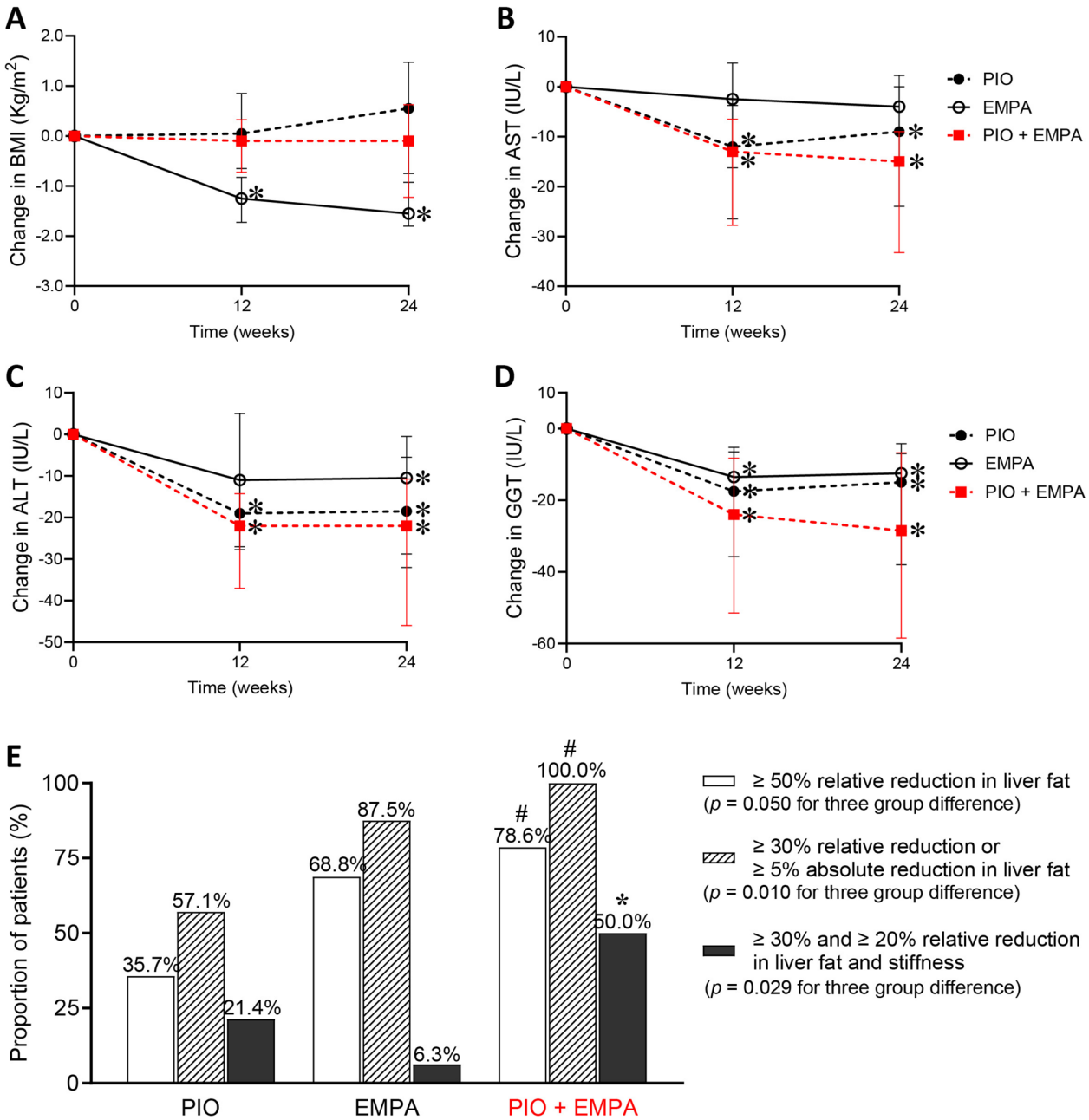

Fig. 2 Changes in (**A**) BMI, (**B**) AST, (**C**) ALT, and (**D**) GGT from baseline after 12 and 24 weeks in the PIO, EMPA, and combination groups. **E** Proportion of patients with a relative reduction ≥ 50% in liver fat, a relative reduction ≥ 30% or an absolute reduction ≥ 5% in liver fat, and a relative reduction ≥ 30% in liver fat and ≥ 20% in liver stiffness at 24 weeks. Liver fat and stiffness were evaluated using MRI-PDFF and MRE, respectively (**E**). $^{*}P < 0.05$ from baseline (**A**–**D**). $^{\#}P < 0.05$ vs. PIO monotherapy (**E**). $^{*}P < 0.05$ vs. EMPA monotherapy (**E**). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; EMPA, empagliflozin; GGT, gamma-glutamyl transferase; PIO, pioglitazone

glucose and insulin use, which showed imbalances among the three groups at baseline (Additional file 1: Table S6).

Depending on the duration of medication use, changes from baseline to week 12 and from week 12 to week 24 were analyzed. (Additional file 1: Table S7). In both the PIO monotherapy group and the combination therapy group that included pioglitazone, improvements in AST, ALT, GGT, and hepatic steatosis index were already significant at 12 weeks compared to baseline. Further decrease in HbA1c and AST from 12 to 24 weeks were observed only in the combination therapy group, suggesting that combining TZD with SGLT2 inhibitor may

lead to additional pathophysiological benefits beyond the initial 12-week effects of TZD alone. The efficacy of EMPA monotherapy on ALT and hepatic steatosis index were not significant during the first 12 weeks but became significant at 24 weeks. To achieve sufficient effects of SGLT2 inhibitor use on hepatic steatosis, a continued use over at least 24 weeks might be necessary.

Collectively, combination therapy compensated for the inadequate effects of the PIO monotherapy in reducing liver fat accumulation and those of the EMPA monotherapy in ameliorating liver stiffness, exhibiting optimal results in both hepatic steatosis and stiffness among the three groups.

Adverse events

Safety profiles were favorable in all treatment groups (Additional file 1: Table S8). One serious adverse event (AE) occurred in the combination group; the participant was diagnosed with renal cell carcinoma on MRI, leading to withdrawal from the study. One participant from the PIO group and one participant from the combination group experienced symptoms of diarrhea and heartburn, respectively. In the PIO group, one case of facial pain and one of mental cloudiness accompanied by weight loss were reported. In the PIO group, one participant reported frequent urination, while in the combination group, one participant had symptoms of urinary tract infection and another had perineal pruritis. Skin pruritis was observed in one participant from the combination group. No participant experienced AEs that necessitated discontinuation of medication, and no severe AEs occurred.

Discussion

In this 24-week, randomized, active-controlled trial, combination therapy of PIO (15 mg/day) and EMPA (10 mg/day) showed superior benefits for MASLD compared to either monotherapy. Combination therapy resulted in the largest improvement in liver fat and stiffness among the three treatment groups. The degrees of reduction in the AST, ALT, GGT, and hepatic steatosis index were the most pronounced in the combination group, and the FIB-4 index significantly decreased only in the combination group. In addition, the proportion of participants showing a reduction in liver fat fraction above the threshold or an improvement in liver stiffness accompanied by a reduction in liver fat was the highest in the combination group. While PIO and EMPA individually increased and decreased the amount of subcutaneous fat, respectively, the combination therapy did not affect subcutaneous fat deposits. Instead, the combination therapy only reduced visceral fat, showing the greatest reduction in that fat among the three groups. Combination therapy was generally well-tolerated.

The individual effects of TZD on MASLD have been previously studied [6, 17]. PIO belongs to the TZD class that stimulates a nuclear receptor, PPAR-γ, expressed in adipose tissue, muscle, and the liver [10]. Activation of PPAR-γ by TZDs attenuates insulin resistance in adipose tissue, muscle, and the liver, with the effects being particularly pronounced in adipose tissue due to the highest level of PPAR-γ expression in adipocytes [10]. Amelioration of insulin resistance in adipose tissue alters the production of adipokines: it decreases pro-inflammatory cytokines and increases anti-inflammatory adipokines such as adiponectin [18]. The favorable changes in the adipokine profile induced by TZDs may systemically attenuate proinflammatory and profibrogenic process in MASH [18]. Additionally, when insulin resistance in adipose tissue is decreased, the suppression of lipolysis in adipose tissue and the promotion of redistributing lipid from muscle and liver to peripheral adipocytes can occur [10]. Therefore, the use of PIO can contribute to reducing liver fat while potentially increasing total body adiposity [10]. In clinical trials of TZD for MASH with histological confirmation, there were improvements in steatosis, inflammation, and fibrosis, but the results varied between individual studies, some of which had a restricted number of participants [17]. A recent meta-analysis partially compensated for the limitations of small sample sizes in individual studies, due to the challenges associated with histological assessment [19]. It demonstrated that PIO had significant positive impact on steatosis, inflammation, and hepatocyte ballooning, while no significant changes were found in fibrosis grade [19]. In this study, steatosis and liver stiffness confirmed by MRI were also improved in the PIO group. Liver stiffness measured using MRE in this study reflects not only the severity of fibrosis but also correlate with lobular inflammation and hepatocyte ballooning [20]. Therefore, the reduction in liver stiffness observed in the PIO group likely reflects improvements in these histological parameters. Regarding concerns about increased adiposity in extrahepatic adipose tissue, we did not observe significant body weight gain in the PIO group, possibly due to the relatively low dose of PIO of 15 mg/day, which is less than the dose used in previous studies [10, 17].

Considering the effects of SGLT2 inhibitor separately, positive results have been observed in indicators related to MASLD. SGLT2 inhibitors, including EMPA, facilitate caloric loss and body weight reduction through glycosuria, leading to improvement in hyperglycemia, adiposity, and systemic insulin resistance [9]. In addition to the total body fat reduction, suppression of hepatic de novo lipid synthesis due to decreases in both glucose and

insulin contributes to the attenuation of hepatic steatosis by SGLT2 inhibitor [9, 21]. SGLT2 inhibitors may also alleviate oxidative stress, inflammation, and insulin resistance in MASH, in association with the mitigation of obesity and glucose toxicity [9, 22]. A systematic analysis of studies on the effects of SGLT2 inhibitors on MASLD revealed that SGLT2 inhibitors consistently demonstrated improvement, particularly in steatosis measured by various modalities [22]. Additionally, some studies on MASH showed improvement in hepatic fibrosis with SGLT2 inhibitors, mostly assessed by noninvasive indices and liver biopsy in a limited studies [9, 22, 23].

The combination effect on MASLD in this study may be due to reasons beyond the glucose-lowering effects of the combined use of two antidiabetics. If the combination group had shown a significantly greater improvement in glycemic control, it could have contributed to better MASH outcomes than monotherapies [24]. However, in this study, the reduction in HbA1c in the combination group was not statistically more pronounced than in the monotherapy groups. This might be attributed to the baseline condition where hyperglycemia was not severe [25]. Instead, the enhanced efficacy of the combination therapy in MASH is likely due to the synergistic amplification of one drug's positive mechanism when paired with the other. First, the combination group showed the most significant rise in adiponectin, which benefits MASH [18]. This increase likely resulted from two aspects: the enhanced insulin sensitivity of adipocytes due to PPAR-γ activation from PIO use and the further attenuation of insulin resistance associated with adiposity improvement by EMPA use [26]. Second, the decrease in visceral fat was the most evident in the combination group. Visceral fat releases FFA to the liver, which act as ligands for Toll-like receptor 4 and upregulate cytokine production [27]. This process contributes to inflammatory responses associated with MASLD [27]. Additionally, the combination treatment showed a neutral effect on subcutaneous fat, in contrast to the PIO and EMPA monotherapies. Subcutaneous fat reflects a proper expansion of nonpathogenic adipocytes and is considered protective [28]. However, paradoxically, inflamed subcutaneous fat in the obese condition is associated with systemic insulin resistance [29]. For subcutaneous fat, both increasing and decreasing changes might be undesirable. Third, in a recent study, the increased hepatic SGLT2 expression in MASH and the excessive glucose uptake through this transporter were suppressed by SGLT2 inhibitors, potentially contributing to the improvement of MASH [30]. Considering that hepatic SGLT2 expression increased due to high-fat, high-glucose, and inflammatory stimuli [30], the reduction in circulating FFA and proinflammatory adipokines, resulting from improved adipocyte insulin resistance by PIO [10, 18], might also have potentiated the hepatic SGLT2-targeted mechanism for MASH amelioration. Previously, the combination effect of TZD and SGLT2 inhibitor was investigated using PIO and tofogliflozin; the combined use demonstrated greater improvement in steatosis than the use of SGLT2 inhibitor alone, but no combination effects were confirmed in hepatic stiffness [31]. However, the combination effects were assessed in the study through an add-on method and there was no active control group [31]. To the best of our knowledge, this study is the first to investigate the effects on MASLD with concurrent initiation of both TZD and SGLT2 inhibitor using active controls.

This study has limitations. First, due to a small sample size, caution is required when interpreting its results [32]. A major limitation of small studies is their potential to yield imprecise findings [32]. They may fail to show statistical significance even when a relationship is genuinely meaningful [32]. In addition, ensuring reliability in statistical analysis by adjusting various variables, requires a sufficient number of subjects [32]. Nevertheless, small randomized controlled trials (RCTs) are efficient in terms of time and cost and minimize participants' exposure to potential risks associated with testing unproven hypotheses [32, 33]. Furthermore, the research experience and findings from a small RCT can serve as a foundation for conducting more extensive studies [32, 33]. Second, although this study confirmed the effects of 24-week combination therapy on MASH, it could not assess the impact and safety of extended treatment, or on liver-related long-term outcomes in MASH, such as cirrhosis and hepatic decompensation [7]. Despite these limitations, the current study still provides meaningful information as an exploratory study. Before the confirmatory research with a large number of participants demonstrated the efficacy of 96-week pioglitazone treatment in steatohepatitis [34], small pilot studies with even fewer than 20 total subjects were conducted, with the shortest duration being 24 weeks [10, 34, 35]. Therefore, this study is expected to serve as a foundational study for future studies on larger scales and over longer durations regarding the combined therapy of TZD and SGLT2 inhibitor in treating MASLD. Third, the results were not confirmed by liver biopsy, the definite method for evaluating MASH [7]. Fourth, despite randomization, there were statistical differences in clinical variables including baseline fasting glucose and the proportion of insulin users between the treatment groups. Hyperglycemia and glucotoxicity aggravate pro-inflammatory and pro-fibrogenic process in the liver, which contribute to the occurrence and progression of MASLD [36]. Insulin therapy affects hepatic insulin sensitivity and liver fat [37]. Thus, the imbalance in baseline fasting glucose and insulin use might have led to a bias in the results.

Statistical adjustment with these factors was conducted to minimize residual confounding, although this approach cannot entirely eliminate such bias, and the superiority of combination therapy over monotherapies was still observed. Additionally, with no significant differences in baseline HbA1c, duration of diabetes, and comorbidities among the three groups, we inferred generally well-balanced baseline glycemic status and diabetes severity between treatment groups. Fifth, efficacies of antidiabetic drugs differ between ethnicities [38, 39]. Therefore, there is limited generalizability of the effects of the combination therapy on MASLD observed in this study.

Conclusions

In conclusion, we demonstrated that combination therapy of PIO with EMPA showed synergistic benefits for hepatic steatosis and stiffness in individuals with type 2 diabetes and MASLD compared to either drug as a monotherapy. Combination therapy mitigated the unwanted effects of monotherapies including weight gain and changes in subcutaneous fat and potentiated the desirable effects of monotherapies such as reduction in visceral fat and increase in adiponectin level. Future studies are needed to validate the effects of TZD and SGLT2 inhibitor combination therapy on MASLD in individuals with type 2 diabetes, employing larger and more diverse populations, longer time periods, and across multiple institutions.

Abbreviations

NAFLD	Non-alcoholic fatty liver disease
SLD	Steatotic liver disease
MASLD	Metabolic dysfunction-associated steatotic liver disease
MASH	Metabolic dysfunction-associated steatohepatitis
NASH	Non-alcoholic steatohepatitis
TZD	Thiazolidinedione
PPAR	Peroxisome proliferator-activated receptor
SGLT2	Sodium-glucose cotransporter 2
EMPA	Empagliflozin
MRI-PDFF	Magnetic resonance imaging- proton density fat fraction
MRE	Magnetic resonance elastography
US	Ultrasonography
CT	Computed tomography
SD	Standard deviation
ROI	Region of interest
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
GGT	Gamma-glutamyl transferase
HbA1c	Glycated hemoglobin A1c
HOMA-β	Homeostasis model assessment of β-cell function
HOMA-IR	Homeostatic model assessment for insulin resistance
CRP	C-reactive protein
FIB-4	Fibrosis index based on 4 factors
SFA	Subcutaneous fat area
VFA	Visceral fat area
IQR	Interquartile range
AE	Adverse event
FFA	Free fatty acid
RCT	Randomized controlled trial

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04017-x.

Supplementary Material 1.

Additional file 1: Fig. S1. Study design. Tables S1–S8. Table S1. Exclusion criteria. Table S2. Clinical research timeline. Table S3. Baseline clinical characteristics for other parameters. Table S4. Changes from baseline to week 24 in other clinical parameters. Table S5. Univariable linear regression models for changes in liver fat and stiffness at 24 weeks. Table S6. Effects of combination therapy compared to monotherapy on improvements in liver fat and stiffness. Table S7. Changes in glucometabolic and liver-related parameters from baseline to week 12 and from week 12 to week 24. Table S8. Adverse events.

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Authors' contributions

Conceptualization: M.L., Y.C., J.B., B-S.C. Methodology: M.L., Y.C., H.R., J.B., B.-S.C. Validation: S.H. Formal analysis: M.L., S.H., H.R., M.H.Y. Investigation: M.L., S.H., H.R., M.H.Y., B.-S.C. Resources: B.-S.C. Data curation: M.L., S.H., Y-h.L., B-S.C. Writing - Original Draft: M.L. Writing - Review & Editing: Y-h.L., B-W.L., E.S.K. B.-S.C. Visualization: M.L., Supervision: B.-S.C. Project administration: B.-S.C. Funding acquisition: M.L., B.-S.C. All authors read and approved the final manuscript.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

All participants provided written informed consent and the Ethics Committee of the Yonsei University College of Medicine approved this study (4-2018-0655), which conforms to the ethical principles of the 1975 Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

M.L. has received lecture honoraria from JW Pharmaceutical Corporation, Boryung Corporation, Eli Lilly and Company, Merck Sharp & Dohme, HK inno.N, Servier Korea, Handok Inc., Daewoong Pharmaceutical, KUKJE PHARM CO.,LTD, and GC Biopharma Corporation. All other authors have no conflicts to disclose; no other relationships or activities that could appear to have influenced the submitted work.

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