

Co-Administering Thiazolidinediones and Sodium-Glucose Cotransporter-2 Inhibitors Attenuates Non-alcoholic Fatty Liver Disease Risk in Type 2 Diabetes: A Nationwide Database Study

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Abstract:

Background: Type 2 diabetes mellitus (T2D) is a risk factor for non-alcoholic fatty liver disease (NAFLD), and identifying antidiabetic drugs that provide fatty liver care is important. This study compared the risk of developing NAFLD in T2D patients taking a sodium-glucose cotransporter-2 inhibitor (SGLT2i) with and without thiazolidinedione (TZD).

Methods: A large retrospective (2014–2017) dataset from the Korean National The Health Information Database was used to form propensity score-matched cohorts of T2D patients (without pre-existing liver conditions) who were receiving an SGLT2i with ($n = 387$) or without TZD ($n = 384$). The risk of developing NAFLD (defined as a Fatty Liver Index [FLI] ≥ 60) was expressed as an adjusted odds ratio (aOR) with 95% confidence intervals (CIs).

Results: Co-administration of TZD and SGLT2i attenuated the risk of developing NAFLD (FLI ≥ 60) relative to SGLT2i without TZD therapy. NAFLD developed in fewer patients in the SGLT2i with TZD group (26/387; 6.72%) than in the SGLT2i without TZD group (43/384; 11.20%), with an estimated unadjusted OR of 0.571 (95% CI, 0.343–0.950) and an aOR of 0.541 (95% CI 0.302–0.971). In the subgroup analysis, none of the variables examined (i.e., age, sex, alcohol use, regular exercise, insulin use, and duration of T2D) had a significant effect on the aORs for developing NAFLD.

Conclusion: Co-administration of TZD with an SGLT2i significantly attenuated the risk of developing NAFLD in T2D patients relative to SGLT2i without TZD therapy.

Keywords: Sodium-glucose cotransporter-2 inhibitor; Thiazolidinedione; Diabetes mellitus, type 2; Non-alcoholic fatty liver disease; Fatty liver index

Keywords: type 2 diabetes, dyslipidemia, SGLT2 inhibitors, thiazolidinedione., NEFLD, Fatty liver index

1. Introduction

Non-alcoholic fatty liver disease (NAFLD), the most common cause of liver disease, ranges from non-alcoholic fatty liver (simple steatosis) to non-alcoholic steatohepatitis (NASH; including mild-to-advanced fibrosis and NASH cirrhosis) and hepatocellular carcinoma [1, 2]. A manifestation of the metabolic syndrome, NAFLD is characterized by excess hepatic fat accumulation in the hepatocytes (defined as the presence of steatosis in >5% of hepatocytes) and is closely associated with insulin resistance [3, 4].

Type 2 diabetes (T2D) is a well-known risk factor for NAFLD [5]. The estimated prevalence of NAFLD in patients with T2D is 55.5% globally and 52.0% in East Asia, which is double its prevalence in the general population [6]. In addition to an increased risk of liver-related morbidity and mortality, NAFLD increases the risk of cardiovascular disease, chronic kidney disease, and overall mortality [7-9]. In Asia, the burden of NAFLD and NASH is expected to increase with an increase in diabetic and obese individuals [10].

Fatty liver management is becoming an important consideration when selecting oral antidiabetic drug (OAD) therapy to treat T2D, although no OAD is currently specifically approved for the treatment of NAFLD. Therefore, it is important to identify the optimal OAD regimen to provide fatty liver care in T2D patients by comparing the effects of various combinations of OADs.

Of the classes of OADs, thiazolidinediones (TZDs) [5, 11, 12] have the greatest effect on NAFLD/NASH and are traditionally considered as first-line treatment in T2D patients with NAFLD [3]. Relatively small randomized clinical trials (RCTs) have shown beneficial histological effects of pioglitazone in patients with NAFLD with or without T2D [13-20]. TZDs interfere with peroxisome-proliferator activated receptor- γ activity, thereby reducing insulin resistance (a major mechanism in the development of NAFLD [4]), decreasing hepatic glucose production, inflammation, and fibrosis, and providing other beneficial effects [5, 11, 21, 22].

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) have also provided significant improvements in liver enzyme levels and other outcomes consistent with reductions in liver fat in small RCTs and cohort studies in T2D patients with [20, 23-29] or without [30-34], NAFLD, but has not yet been shown to improve NASH. The effects of SGLT2is on fatty liver probably involve multiple factors, including reducing excessive weight and fat, improving glycemic control, lowering insulin levels, and reducing inflammation [12, 35] [11-13].

Although there are no studies on the combined use of TZD and SGLT2i in NAFLD/NASH, such therapies may have beneficial effects. The purpose of this study was to compare the risk of developing NAFLD, assessed using Fatty Liver Index (FLI) values, in T2D patients receiving combination treatment with an SGLT2i and a TZD versus those receiving an SGLT2i without a TZD using a large population dataset derived from the Korean National Health Information Database (NHID).

2. METHODS

2.1 Study database

This retrospective study used 2014–2017 data from the NHID, which is produced by the The National Health Insurance Service (NHIS) and includes data from the National Health Screening Program. The NHIS is a compulsory healthcare plan operated by the Korean government, and it covers approximately 52 million individuals in 2020 [36]. The NHID contains anonymized information on personal characteristics, demographics, health examination details, International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes, claims data, and medical treatment. All NHIS enrollees were eligible to undergo a general health examination at least every two years, with the results of the health examination, as well as the responses to questionnaires on lifestyle and behavior, as recorded in the National Health Screening database.

2.2 Type of data collected

The protocol for the study was approved by the Institutional Review Board (IRB) of the Kangbuk Samsung Hospital (KBSMC 2021-03-003). The requirement for informed consent was waived by the IRB because personal identification information was not included in the data provided to the researchers.

2.3 Study subjects

From the NHID, we identified 129,666 individuals with T2D who received a new prescription for SGLT2i between 2014 and 2016 (index date). After excluding individuals aged ≤ 30 years, those who did not have a national health check-up performed within 2 years before and after the index date, those with type 1 or gestational DM, those with missing data, and those prescribed fewer than two OADs, 46,552 individuals remained (Fig. 1).

Using propensity score matching (PSM), 700 individuals whose SGLT2i regimen included TZD were matched on a 1:1 basis with 700 individuals whose SGLT2i regimen did not include TZD. Individuals with pre-existing conditions that may affect the results, namely FLI ≥ 60 , heavy alcohol consumption (≥ 30 g/day for males, and ≥ 20 g/day for females), and liver cirrhosis were excluded, leaving 387 individuals in the cohort receiving SGLT2i with TZD, and 384 in the cohort receiving SGLT2i without TZD (Fig. 1).

2.4 Definition of NAFLD

Patients with NAFLD were identified based on their FLI, a simple and accurate algorithm for predicting fatty liver, body mass index (BMI), waist circumference, and triglyceride and γ -glutamyl transpeptidase (GGT) levels [37]. FLI values were calculated using the following formula: $FLI = (e^{0.953 \cdot \log_e(\text{triglycerides})} + 0.139 \cdot BMI + 0.718 \cdot \log_e(GGT) + 0.053 \cdot \text{waist circumference} - 15.745) / (1 + e^{0.953 \cdot \log_e(\text{triglycerides})} + 0.139 \cdot BMI + 0.718 \cdot \log_e(GGT) + 0.053 \cdot \text{waist circumference} - 15.745) \square 100$.

The FLI ranges from 0 to 100, with a value of <30 ruling out fatty liver and a value of ≥ 60 indicating the presence of fatty liver (i.e., NAFLD).

2.5 Outcomes and statistical analysis

Values for patient characteristics are expressed as means $\pm$ standard deviation or geometric means with 95% confidence intervals (CIs) for continuous characteristics and as frequency (number and percentage of patients) for categorical characteristics. The statistical significance of between-cohort differences in patient characteristics was analyzed using the t-test for continuous characteristics and chi-square test for categorical characteristics. Mild alcohol consumption was defined as <30 g ethanol per day for males, and <20 g ethanol per day for females; regular exercise was defined as ≥ 5 days of moderate-intensity exercise or ≥ 3 days of high-intensity exercise per week; and low income was defined as the bottom 20% of Korean health insurance premiums.

The primary outcome was the difference in the occurrence of NAFLD (defined as an FLI ≥ 60) between patients receiving an SGLT2i with TZD and those receiving an SGLT2i without TZD. This was expressed as an adjusted odds ratio (aOR) with 95% CIs, which was corrected for all of the variables (Table 1) that were used to balance the two treatment groups when PSM was performed. Secondary outcomes included the aORs of other variables that influenced the development of NAFLD, including high BMI (≥ 25 kg/m²), large waist circumference (≥ 90 cm in males, and ≥ 85 cm in females), elevated triglyceride levels (≥ 150 mg/dL), and elevated GGT levels (≥ 40 IU/L). Subgroup analyses were conducted to assess the effects of age (<65 vs. ≥ 65 years), sex, smoking

status (non-smoker vs. current smoker), alcohol consumption (non-drinker vs. mild drinker), regular exercise (yes vs. no), concomitant insulin use (yes vs. no), number of OADs in their antidiabetic regimen (<3 vs. ≥ 3), and duration of T2D (<5 vs. ≥ 5 years) on the primary and secondary aORs. Logistic Cox-regression models were used to estimate the primary and secondary aORs, Normality was verified using the Kolmogorov-Smirnov test. Statistical significance was set than 0.05. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

2.6 Patient characteristics

At the index date, no significant differences in patient characteristics were observed between cohorts receiving SGLT2i with and without TZD (Table 1). In both cohorts, the mean patient age was 58 years, males accounted for 56–57% of the cohort, and the mean duration of T2D was almost 10 years. FLI and the values used to determine FLI (BMI, waist circumference, and triglyceride and GGT levels) did not differ significantly between cohorts. Likewise, there were no significant between-cohort differences in other laboratory values, including lipid and glucose levels, or in the proportions of patients who were smokers, mild alcohol consumers, regular exercisers, or who had hypertension or dyslipidemia. Antidiabetic therapy received before and at the index date did not differ significantly between cohorts, nor did the interval between health check-ups and the index date (Table 1).

3. Result

Co-administration of TZD and SGLT2i reduced the risk of developing NAFLD (i.e., $FLI \geq 60$) relative to SGLT2i without TZD. At regular health checkups after their first prescription for SGLT2i, the proportion of patients who developed NAFLD was lower in the cohort receiving TZD than in the matched cohort not receiving TZD (6.72% vs. 11.2% of patients) [Table 2]. Relative to SGLT2i therapy without a TZD, co-administration of a TZD and an SGLT2i attenuated the odds of having an $FLI \geq 60$, with an unadjusted OR of 0.571 (95% CI 0.343–0.950) and an aOR of 0.541 (95% CI 0.302–0.971).

In subgroup analyses, the aORs for developing NAFLD showed the same results regardless of the variables examined (i.e., age, sex, smoking status, alcohol consumption, regular exercise, concomitant insulin use, number of oral agents in the antidiabetic regimen, and duration of T2D), with none of the variables having a significant effect (Table 2)

In the secondary analysis of the factors that are used to determine the development of NAFLD, patients receiving SGLT2i with a TZD were less likely to have waist circumference ≥ 90 cm in males or ≥ 85 cm in females (aOR 0.778, 95% CI 0.521–1.161), triglyceride levels ≥ 150 mg/dL (aOR 0.626, 95%, CI 0.44–0.89), and GGT levels ≥ 40 IU/L (aOR 0.543, 95%, CI 0.336–0.879) than patients receiving an SGLT2i without a TZD, but were more likely to have a BMI ≥ 25 kg/m² (aOR 2.053, 95% CI 1.306–3.226) [Table 3]. Subgroup analysis of the secondary outcomes indicated that the aORs for these secondary endpoints were not significantly affected by any of the variables examined (Supplemental Fig. S2), with the sole exception of T2D duration in the analysis of the OR for elevated triglyceride levels (interaction $P = 0.03$) [Supplemental Fig. S2C].

4. DISCUSSION

This nationwide cohort study showed that the risk of developing NAFLD (defined as an $FLI \geq 60$) in patients with T2D was attenuated in patients receiving SGLT2i with TZD than in those receiving SGLT2i without TZD as part of their OAD regimen. To the best of our knowledge, this Korean NHI database study is the first to assess the effect of co-administration of an SGLT2i and a TZD on the risk of developing NAFLD in patients with T2D and suggests that such a combination may have a role in the treatment of this condition.

Although the treatment or prevention of NAFLD/NASH is not currently a labeled indication for any currently marketed TZDs, their use is mentioned in several NAFLD/NASH guidelines [3, 38-42] based on the clinical evidence of their benefits available during guideline development. Pioglitazone is recommended for the treatment of liver disease in T2D patients with NAFLD/NASH in the Italian guidelines [38], in selected patients with NASH, particularly those with T2D, in the European guidelines [3], and NASH in patients with insulin resistance in the Japanese guidelines [39]. It is a suggested option for liver biopsy diagnosed NASH in patients with or without T2D in both the Korean [40] and American [41] guidelines and for advanced liver fibrosis in patients with or without T2D in the UK guidelines [42]. Notably, pioglitazone is the only TZD specifically mentioned in any of these guidelines, as other thiazolidines are not widely available or data regarding their effects on NAFLD/NASH are limited.

Perhaps due to a lack of clinical data supporting their use at the time of development of most NAFLD/NASH guidelines, the Japanese guidelines are the only ones that suggest the use of SGLT2i in the treatment of NAFLD/NASH in patients with T2D [39]. Italian guidelines state that SGLT2i are safe to use in patients with liver disease, but do not specifically recommend them as a treatment [38]. Other NAFLD/NASH guidelines [3, 40-42] do not mention the use of SGLT2i in treating these conditions.

In addition to improvements in glucose-related outcomes (e.g., glycated hemoglobin, insulin sensitivity, and β -cell function), TZD and SGLT2i combination therapy has been shown to have many other advantages in the treatment of T2D [43]. The potential benefits of combination therapy include reduced risk of cardiovascular events (e.g., stroke, myocardial infarction, cardiovascular death, and heart failure) and renal disease. The use of SGLT2i with TZD may also neutralize fluid retention and fat weight gain associated with TZD treatment [43].

Furthermore, co-administration of TZD and SGLT2i may be expected to have beneficial effects on the risk of NAFLD/NASH relative to the use of either agent alone, given that both drug classes have shown positive effects on liver disease and differ with regard to their mechanisms of action. Although clinical data are limited, combination treatment with an SGLT2i (ipragliflozin) and a TZD (pioglitazone) improved NAFLD- and fat-related outcomes in a 24-week RCT of 44 patients with controlled T2D and comorbid NAFLD [44]. The addition of ipragliflozin to the current treatment with pioglitazone and metformin significantly reduced liver steatosis and excessive fat relative to continued pioglitazone and metformin treatment, including a significantly greater change from baseline in FLI (-9.80 vs 1.05; $P < 0.05$) [44].

The results of the current database study also showed the clinical utility of co-administration of TZD and SGLT2i in improving NAFLD outcomes in patients with T2D. Co-administration of TZD and SGLT2i attenuated the risk of developing NAFLD relative to treatment with an SGLT2i without TZD, with an aOR of 0.541 (95% CI, 0.302–0.971). Notably, none of the variables examined significantly interacted with this primary endpoint, including alcohol consumption, regular exercise, and duration of T2D. Furthermore, co-administration of TZD and SGLT2i diminished the risk of most variables that influence the development of NAFLD, including large waist circumference, elevated triglyceride levels, and elevated GGT levels. The results of this large nationwide PSM cohort study are important given that the few available clinical studies on the effect of OADs on NAFLD are generally short-term and include only a relatively small number of patients.

The results of this study show that co-administration of TZD and SGLT2i attenuates the risk of NAFLD and are supported by those of other large database studies that assessed the effects of TZDs on liver disease. In a UK study using primary-care data from the Clinical Practice Research Datalink database ($n = 5728$ PSM pairs), T2D patients receiving either TZD or a combination of TZD plus sulfonylurea had a significantly lower risk of NAFLD [adjusted hazard ratio (HR) 0.32 and 0.56, respectively] than those receiving sulfonylurea alone [45]. A Taiwan NHI database study of patients with newly diagnosed T2D using or not using TZDs ($n = 5095$ PSM pairs) found that TZDs significantly diminished the risk of cirrhosis relative to not using TZDs (HR 0.39, 95% CI 0.21–0.72) and suggested that TZDs may be able to improve long-term liver-related outcomes [46].

Several limitations should be considered when interpreting the results of this study. As RCTs are time-consuming and expensive to perform, this study used a cohort design to determine whether the risk of developing NAFLD was affected by the co-administration of a TZD and an SGLT2i in the OAD regimens in patients with T2D using data from the Korean NHI. As a result, the data are limited by the inherent limitations of this type of study, such as the possible inaccuracy of patient-reported data, potential miscoding of ICD-10 terms, and the inability to assess patient compliance with their prescribed OAD regimen. Moreover, as the length of use of the study drugs differs between patients, with some patients in the SGLT2i with TZD group potentially only taking a few doses of TZD, it is highly possible that the actual between-group differences in NAFLD and other outcomes may be greater than those reported. Although almost 130,000 individuals who received their first SGLT2i prescription during 2014–2016 were identified, few also received TZD, as the use of such combination therapy was restricted during this period. After excluding patients with pre-existing liver conditions, the size of the propensity-matched cohort was limited to <400 patients. An FLI value of ≥ 60 was used to indicate the presence of NAFLD. Although this was appropriate in this epidemiological study, given the patient information available in the NHID, studies that assess the effect of TZD plus SGLT2i on NAFLD confirmed by standard abdominal ultrasonography criteria, other imaging procedures, or biopsy, may be warranted.

In conclusion, the inclusion of TZD as a part of SGLT2i-containing antidiabetic therapy significantly attenuated the risk of developing NAFLD in individuals with T2D. This suggests that combination treatment with TZD plus and SGLT2i may play a role in the prevention of fatty liver disease in patients with T2D.

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7. REFERENCES

1. Milić S, Lulić D, Štimac D. Non-alcoholic fatty liver disease and obesity: biochemical, metabolic and clinical presentations. *World J Gastroenterol* 2014;20:9330-7.
2. Engin A. Non-alcoholic fatty liver disease. *Adv Exp Med Biol* 2017;960:443-67.
3. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016;64:1388-402.

4. Fujii H, Kawada N, NAFLD JSGO. The role of insulin resistance and diabetes in non-alcoholic fatty liver disease. *Int J Mol Sci* 2020;21:3863.
5. Targher G, Corey KE, Byrne CD, Roden M. The complex link between NAFLD and type 2 diabetes mellitus - mechanisms and treatments. *Nat Rev Gastroenterol Hepatol* 2021;18:599-612.
6. Younossi ZM, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. *J Hepatol* 2019;71:793-801.
7. Zou B, Yeo YH, Cheung R, Ingelsson E, Nguyen MH. Fatty liver index and development of cardiovascular disease: Findings from the UK Biobank. *Dig Dis Sci* 2021;66:2092-100.
8. Abenavoli L. Non-alcoholic fatty liver disease and cardiovascular disease: a close relationship. *J Gastrointestin Liver Dis* 2021;30:183-4.
9. Cernea S, Raz I. NAFLD in type 2 diabetes mellitus: Still many challenging questions. *Diabetes Metab Res Rev* 2021;37:e3386.
10. Estes C, Chan HLY, Chien RN, Chuang WL, Fung J, Goh GB, et al. Modelling NAFLD disease burden in four Asian regions-2019-2030. *Aliment Pharmacol Ther* 2020;51:801-11.
11. Ferguson D, Finck BN. Emerging therapeutic approaches for the treatment of NAFLD and type 2 diabetes mellitus. *Nat Rev Endocrinol* 2021;17:484-95.
12. Esler WP, Bence KK. Metabolic targets in non-alcoholic fatty liver disease. *Cell Mol Gastroenterol Hepatol* 2019;8:247-67.
13. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, et al. A placebo-controlled trial of pioglitazone in subjects with non-alcoholic steatohepatitis. *N Engl J Med* 2006;355:2297-307.
14. Aithal GP, Thomas JA, Kaye PV, Lawson A, Ryder SD, Spendlove I, et al. Randomized, placebo controlled trial of pioglitazone in nondiabetic subjects with non-alcoholic steatohepatitis. *Gastroenterology* 2008;135:1176-84.
15. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for non-alcoholic steatohepatitis. *N Engl J Med* 2010;362:1675-85.
16. Sharma BC, Kumar A, Garg V, Reddy RS, Sakhuja P, Sarin SK. A randomized controlled trial comparing efficacy of pentoxifylline and pioglitazone on metabolic factors and liver histology in patients with non-alcoholic steatohepatitis. *J Clin Exp Hepatol* 2012;2:333-7.
17. Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, et al. Long-term pioglitazone treatment for patients with non-alcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. *Ann Intern Med* 2016;165:305-15.
18. Razavizade M, Jamali R, Arj A, Matini SM, Moraveji A, Taherkhani E. The effect of pioglitazone and metformin on liver function tests, insulin resistance, and liver fat content in non-alcoholic Fatty liver disease: a randomized double blinded clinical trial. *Hepat Mon* 2013;13:e9270.
19. Lee YH, Kim JH, Kim SR, Jin HY, Rhee EJ, Cho YM, et al. Lobeglitazone, a novel thiazolidinedione, improves non-alcoholic fatty liver disease in type 2 diabetes: Its efficacy and predictive factors related to responsiveness. *J Korean Med Sci* 2017;32:60-9.
20. Kinoshita T, Shimoda M, Nakashima K, Fushimi Y, Hirata Y, Tanabe A, et al. Comparison of the effects of three kinds of glucose-lowering drugs on non-alcoholic fatty liver disease in patients with type 2 diabetes: A randomized, open-label, three-arm, active control study. *J Diabetes Investig* 2020;11:1612-22.
21. Bansal G, Thanikachalam PV, Maurya RK, Chawla P, Ramamurthy S. An overview on medicinal perspective of thiazolidine-2,4-dione: A remarkable scaffold in the treatment of type 2 diabetes. *J Adv Res* 2020;23:163-205.
22. Long N, Le Gresley A, Wren SP. Thiazolidinediones: An in-depth study of their synthesis and application to medicinal chemistry in the treatment of diabetes mellitus. *ChemMedChem* 2021;16:1716-35.
23. Kuchay MS, Krishan S, Mishra SK, Farooqui KJ, Singh MK, Wasir JS, et al. Effect of empagliflozin on liver fat in patients with type 2 diabetes and non-alcoholic fatty liver disease: A randomized controlled trial (E-LIFT Trial). *Diabetes Care* 2018;41:1801-8.
24. Ito D, Shimizu S, Inoue K, Saito D, Yanagisawa M, Inukai K, et al. Comparison of ipragliflozin

- and pioglitazone effects on non-alcoholic fatty liver disease in patients with type 2 diabetes: A randomized, 24-week, open-label, active-controlled trial. *Diabetes Care* 2017;40:1364-72.
25. Eriksson JW, Lundkvist P, Jansson PA, Johansson L, Kvarnström M, Moris L, et al. Effects of dapagliflozin and n-3 carboxylic acids on non-alcoholic fatty liver disease in people with type 2 diabetes: a double-blind randomised placebo-controlled study. *Diabetologia* 2018;61:1923-34.
26. Shimizu M, Suzuki K, Kato K, Jojima T, Iijima T, Murohisa T, et al. Evaluation of the effects of dapagliflozin, a sodium-glucose cotransporter-2 inhibitor, on hepatic steatosis and fibrosis using transient elastography in patients with type 2 diabetes and non-alcoholic fatty liver disease. *Diabetes Obes Metab* 2019;21:285-92.
27. Choi D-H, Jung C-H, Mok J-O, Kim C-H, Kang S-K, Kim B-Y. Effect of dapagliflozin on alanine aminotransferase improvement in type 2 diabetes mellitus with non-alcoholic fatty liver disease. *Endocrinol Metab (Seoul)* 2018;33:387.
28. Cho KY, Nakamura A, Omori K, Takase T, Miya A, Yamamoto K, et al. Favorable effect of sodium-glucose cotransporter 2 inhibitor, dapagliflozin, on non-alcoholic fatty liver disease compared with pioglitazone. *J Diabetes Investig* 2021;12:1272-7.
29. Wong C, Yaow CYL, Ng CH, Chin YH, Low YF, Lim AYL, et al. Sodium-glucose cotransporter 2 inhibitors for non-alcoholic fatty liver disease in Asian patients with type 2 diabetes: A meta analysis. *Front Endocrinol (Lausanne)* 2020;11:609135.
30. Sattar N, Fitchett D, Hantel S, George JT, Zinman B. Empagliflozin is associated with improvements in liver enzymes potentially consistent with reductions in liver fat: results from randomised trials including the EMPA-REG OUTCOME® trial. *Diabetologia* 2018;61:2155-63.
31. Bolinder J, Ljunggren Ö, Kullberg J, Johansson L, Wilding J, Langkilde AM, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. *J Clin Endocrinol Metab* 2012;97:1020-31.
32. Cusi K, Bril F, Barb D, Polidori D, Sha S, Ghosh A, et al. Effect of canagliflozin treatment on hepatic triglyceride content and glucose metabolism in patients with type 2 diabetes. *Diabetes Obes Metab* 2019;21:812-21.
33. Leiter LA, Forst T, Polidori D, Balis DA, Xie J, Sha S. Effect of canagliflozin on liver function tests in patients with type 2 diabetes. *Diabetes Metab* 2016;42:25-32.
34. Wilding JP, Charpentier G, Hollander P, González-Gálvez G, Mathieu C, Vercruysse F, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. *Int J Clin Pract* 2013;67:1267-82.
35. Chrysavgis L, Papatheodoridi AM, Chatzigeorgiou A, Cholongitas E. The impact of sodium glucose cotransporter 2 inhibitors on non-alcoholic fatty liver disease. *J Gastroenterol Hepatol* 2021;36:893-909.
36. Shin DW, Cho, J., Park, J.H., Cho, B. National General Health Screening Program in Korea: history, current status, and future direction. *Precision Fut Med* 2022;6:9-31.
37. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol* 2006;6:33.
38. Associazione Italiana per lo Studio del Fegato (AISF), Società Italiana di Diabetologia (SID) and Società Italiana dell'Obesità (SIO). Non-alcoholic fatty liver disease in adults 2021: A clinical practice guideline of the Italian Association for the Study of the Liver (AISF), the Italian Society of Diabetology (SID) and the Italian Society of Obesity (SIO). *Dig Liver Dis* 2022;54:170-82.
39. Tokushige K, Ikejima K, Ono M, Eguchi Y, Kamada Y, Itoh Y, et al. Evidence-based clinical practice guidelines for non-alcoholic fatty liver disease/non-alcoholic steatohepatitis 2020. *J Gastroenterol* 2021;56:951-63.
40. Kang SH, Lee HW, Yoo JJ, Cho Y, Kim SU, Lee TH, et al. KASL clinical practice guidelines: Management of non-alcoholic fatty liver disease. *Clin Mol Hepatol* 2021;27:363-401.
41. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and

- management of non-alcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018;67:328-57.
42. Glen J, Floros L, Day C, Pryke R. Non-alcoholic fatty liver disease (NAFLD): summary of NICE guidance. *Bmj* 2016;354:i4428.
43. DeFronzo RA, Chilton R, Norton L, Clarke G, Ryder RE, Abdul-Ghani M. Revitalization of pioglitazone: the optimum agent to be combined with a sodium-glucose cotransporter-2 inhibitor. *Diabetes Obes Metab* 2016;18:454-62.
44. Han E, Lee YH, Lee BW, Kang ES, Cha BS. Ipragliflozin additively ameliorates non-alcoholic fatty liver disease in patients with type 2 diabetes controlled with metformin and pioglitazone: a 24-week randomized controlled trial. *J Clin Med* 2020;9:
45. van Dalem J, Driessen JHM, Burden AM, Stehouwer CDA, Klungel OH, de Vries F, et al. Thiazolidinediones and glucagon-like peptide-1 receptor agonists and the risk of non-alcoholic fatty liver disease: A cohort study. *Hepatology* 2021;74:2467-77.
46. Yen FS, Yang YC, Hwu CM, Wei JC, Huang YH, Hou MC, et al. Liver-related long-term outcomes of thiazolidinedione use in persons with type 2 diabetes. *Liver Int* 2020;40:1089-97.

Figures and Tables

Figure legend

Fig. 1. Selection of study cohorts of patients receiving a sodium-glucose cotransporter-2 inhibitor (SGLT2i) with or without a thiazolidinedione (TZD). ICD-10, International Classification of Diseases Tenth Revision.

Table 1. Patient Characteristics at the Index Date in the Propensity Score-Matched Study Cohorts

Parameter	SGLT2i with TZD (n = 387)	SGLT2i without TZD (n = 384)	P value
Age, year	58.07 ± 9.57	58.06 ± 9.36	0.9854
Sex, male	222 (57.36)	216 (56.25)	0.7548
Height, cm	162.95 ± 8.72	162.93 ± 8.7	0.9829
Weight, kg	65.99 ± 9.56	66.81 ± 9.87	0.2414
Body mass index, kg/m ²	24.82 ± 2.79	25.12 ± 2.79	0.1349
Waist circumference, cm	84.35 ± 6.92	85.05 ± 6.8	0.1551
Systolic blood pressure, mm Hg	124.91 ± 14.07	125.27 ± 14.13	0.7183
Diastolic blood pressure, mm Hg	76.27 ± 9.34	76.11 ± 8.99	0.8063
Income, low	61 (15.76)	74 (19.27)	0.2000
Tobacco smoking status			0.3585
Non-smoker	225 (58.14)	207 (53.91)	
Former smoker	90 (23.26)	106 (27.6)	
Current smoker	72 (18.6)	71 (18.49)	
Alcohol consumption status			0.4016
Non-drinker	262 (67.7)	249 (64.84)	
Mild drinker	125 (32.3)	135 (35.16)	
Regular exercise	98 (25.32)	97 (25.26)	0.9841
Duration of diabetes mellitus, year	9.84 ± 3.78	9.88 ± 4.05	0.8975
Co-morbidities			
Hypertension	224 (57.88)	235 (61.2)	0.3482
Dyslipidemia	277 (71.58)	286 (74.48)	0.3639
Laboratory values			
Glucose, mg/dL	163.43 ± 58.4	166.83 ± 56.21	0.4102
Total cholesterol, mg/dL	172.5 ± 41.01	169.95 ± 38.94	0.3772
High-density lipoprotein cholesterol, mg/dL	51.03 ± 24.93	49.32 ± 11.75	0.2239
Low-density lipoprotein cholesterol, mg/dL	96.36 ± 35.48	95.29 ± 35.85	0.6779
Triglycerides, mg/dL	116.6 (110.96–122.53)	114.47 (109.23–119.95)	0.5961
AST, IU/L	23.34 (22.36–24.36)	23.67 (22.79–24.57)	0.6296
ALT, IU/L	24.37 (23.2–25.59)	24.68 (23.42–26.01)	0.7235
GGT, IU/L	25.62 (24.11–27.23)	26.11 (24.78–27.51)	0.6466
Glomerular filtration rate, mL/min	88.79 ± 24.62	89.48 ± 25.74	0.7014

Fatty liver index	31.18 ± 16.28	32.30 ± 16.09	0.3359
Antidiabetics received within 1 year prior to the index date			
Insulin	65 (16.8)	57 (14.84)	0.4577
Sulfonylurea	258 (66.67)	254 (66.15)	0.8783
Metformin	350 (90.44)	353 (91.93)	0.4664
Meglitinide	9 (2.33)	6 (1.56)	0.4431
TZD	340 (87.86)	336 (87.5)	0.8807
Dipeptidyl peptidase-4 inhibitor	308 (79.59)	317 (82.55)	0.2933
α-Glucosidase inhibitor	42 (10.85)	41 (10.68)	0.9373
GLP-1 agonist	0	2 (0.52)	0.1552
Antidiabetics received at the index date ^a			
Insulin	28 (7.24)	17 (4.43)	0.0963
GLP-1 agonist	0	0	
≥3 oral agents	339 (87.6)	330 (85.94)	0.4965
Index year ^a			0.4222
2014	53 (13.7)	61 (15.89)	
2015	192 (49.61)	198 (51.56)	
2016	142 (36.69)	125 (32.55)	
Interval between check-ups and index date ^a			
Previous check-up and index date, days	346.98 ± 229.31	352.6 ± 219.38	0.7284
Index date and next check-up, days	342.74 ± 218.59	348.81 ± 220.25	0.7010
Values expressed as mean ± standard deviation, geometric mean (95% confidence intervals), or number (%).			
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; GLP-1, glucagon-like peptide 1; SGLT2i, sodium-glucose co-transporter-2 inhibitor; TZD, thiazolidinedione.			
^a Date of first SGLT2i prescription.			

Table 2. Overall And Subgroup Analyses of the Frequency and Adjusted Odds Ratios for NAFLD

Variable	Subgroup	No. of pts with FLI ≥60/no. of pts in subgroup (%)		aOR for FLI ≥60 (95% CI)		P value for interaction
		SGLT2i with TZD (n = 387)	SGLT2i without TZD (n = 384)	SGLT2i with TZD	SGLT2i without TZD	
Overall		26/387 (6.72)	43/384 (11.20)	0.541 (0.302–0.971)	1 (ref)	
Subgroup analysis						
Age	<65 years	21/286 (7.34)	33/283 (11.66)	0.565 (0.291–1.095)	1 (ref)	0.7889
	≥65 years	5/101 (4.95)	10/101 (9.9)	0.467 (0.136–1.605)	1 (ref)	
Sex	Male	20/222 (9.01)	30/216 (13.89)	0.545 (0.273–1.087)	1 (ref)	0.9722
	Female	6/165 (3.64)	13/168 (7.74)	0.532 (0.178–1.591)	1 (ref)	
Tobacco smoking	Non-smoker	19/315 (6.03)	32/313 (10.22)	0.588 (0.298–1.161)	1 (ref)	0.8318
	Current smoker	7/72 (9.72)	11/71 (15.49)	0.508 (0.158–1.637)	1 (ref)	
Alcohol consumption	Non-drinker	15/262 (5.73)	23/249 (9.24)	0.565 (0.26–1.23)	1 (ref)	0.8682
	Mild drinker	11/125 (8.8)	20/135 (14.81)	0.511 (0.207–1.26)	1 (ref)	
Regular exercise	No	19/289 (6.57)	31/287 (10.80)	0.598 (0.303–1.178)	1 (ref)	0.5781
	Yes	7/98 (7.14)	12/97 (12.37)	0.412 (0.132–1.28)	1 (ref)	
Insulin use	No	23/359 (6.41)	42/367 (11.44)	0.498 (0.272–0.912)	1 (ref)	0.2543
	Yes	3/28 (10.71)	1/17 (5.88)	2.426 (0.17–34.68)	1 (ref)	
No. of OADs	<3	5/48 (10.42)	10/54 (18.52)	0.569 (0.132–2.449)	1 (ref)	0.9418
	≥3	21/339 (6.19)	33/330 (10.00)	0.536 (0.283–1.016)	1 (ref)	
Duration of T2D	<5 yr	7/50 (14.00)	9/57 (15.79)	0.92 (0.242–3.504)	1 (ref)	0.3938
	≥5 yr	19/337 (5.64)	34/327 (10.40)	0.481 (0.25–0.926)	1 (ref)	
NAFLD defined as FLI ≥60.						
aOR, adjusted odd ratio; FLI, fatty liver index; NAFLD, non-alcoholic fatty liver disease; OAD, oral antidiabetic drug; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes mellitus; TZD, thiazolidinedione.						

Table 3. Secondary Outcomes: Analysis of the Frequency and Adjusted Odds Ratios of Variables that Influence the Risk of NAFLD

Variable	No. of pts with outcome (%)	Adjusted OR (95% CI)
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	SGLT2i with TZD (n = 387)	SGLT2i without TZD (n = 384)	SGLT2i with TZD	SGLT2i without TZD
BMI ≥ 25 kg/m ²	182 (47.03)	163 (42.45)	2.053 (1.306–3.226)	1 (ref)
Waist circumference ≥ 90 cm (male)/ ≥ 85 cm (female)	113 (29.2)	132 (34.38)	0.778 (0.521– 1.161)	1 (ref)
Triglycerides ≥ 150 mg/dL	96 (24.81)	126 (32.81)	0.626 (0.44– 0.89)	1 (ref)
GGT ≥ 40 IU/L	53 (13.44)	75 (19.53)	0.543 (0.336–0.879)	1 (ref)
NAFLD defined as FLI ≥ 60 . aOR, adjusted odd ratio; BMI, body mass index; GGT, γ -glutamyl transpeptidase; NAFLD, non-alcoholic fatty liver disease; SGLT2i, sodium-glucose co-transporter-2 inhibitor; TZD, thiazolidinedione.				