**Early Online**

The European Research Journal 2025 Original Article

DOI: https://doi.org/10.18621/eurj.1631079 *Internal Medicine*

# The impact of dapagliflozin on FIB-4 index over 2 years in patients with type 2 diabetes mellitus

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## ABSTRACT

**Objectives:** Dapagliflozin belongs to the sodium-glucose co-transporter 2 inhibitor drug group used in the treatment of type 2 diabetes. This study aimed to investigate the effects of dapagliflozin and simultaneous dapagliflozin+pioglitazone therapy on the FIB-4 index, associated with liver inflammation and fibrosis, at the end of the first and second years.

**Methods:** This retrospective study, conducted between 01.01.2017 and 01.01.2020, included 386 patients using dapagliflozin alone (DAPA Group) and 122 patients using dapagliflozin in combination with pioglitazone (DAPA+PIO Group). ALT, AST, and FIB-4 index were compared at baseline, at week 52, and at week 104.

**Results:** The DAPA group consisted of 243 females (63%) and 143 males (37%) with a mean age of 59.8±6 years. The DAPA+PIO group consisted of 61 females (50%) and 61 males (50%) with a mean age of 58.3±5 years. No significant differences were observed between the groups in ALT, AST, hemoglobin levels, and platelet counts at the baseline, at the 52nd week, and at the 104th week ($P>0.05$). Statistically significant decreases in fasting blood glucose and HbA1C levels were observed in both groups at baseline, week 52, and week 104 ($P<0.001$). Furthermore, both groups exhibited no statistically significant changes in the FIB-4 index during the first and second years compared to baseline ($P>0.05$).

**Conclusions:** Dapagliflozin, either alone or in combination with pioglitazone, did not alter the FIB-4 index associated with liver fibrosis and inflammation over 1 and 2 years in patients with type 2 diabetes. Despite experimental evidence indicating its potential to reduce liver fibrosis, clinical data remain inconclusive. Future prospective studies with longer durations are necessary for a clearer understanding.

**Keywords:** Type 2 diabetes mellitus, dapagliflozin, pioglitazone, liver, FIB-4 index

In individuals with type 2 diabetes mellitus (T2DM), there is an uptick in metabolic dysfunction- associated steatotic liver disease (MASLD) due to insulin resistance and obesity [1, 2]. Even with liver enzymes within the normal range, it is estimated that up to half of those with T2DM also have MASLD [2]. Both T2DM and Non-alcoholic Fatty Liver Disease (NAFLD) pose risks of progressing to steatohepatitis, liver fibrosis, cirrhosis, and cancer [1]. Furthermore, MASLD is independently linked to an increased risk of cardiovascular disease and death [1, 3, 4]. MASLD is a metabolic condition closely associated with type 2 diabetes. A recent meta-analysis reported that 55.5% of patients with type 2 diabetes had MASLD, and 17% of them had advanced hepatic fibrosis [5]. Per the latest American Diabetes Associa-

**Received:** February 9, 2025 **Accepted:** May 7, 2025 **Available Online:** May 31, 2025 **Published:** XX XX, 2025

**How to cite this article:** Özkan S, Gezer D. The impact of dapagliflozin on FIB-4 index over 2 years in patients with type 2 diabetes mellitus. Eur Res J. 2025. doi: 10.18621/eurj.1631079

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tion guidelines, individuals with prediabetes or T2DM and increased liver enzymes should undergo screening for liver fibrosis using non- invasive methods [6]. Non-invasive imaging tests for detecting MASLD are relatively costly, so assessing fibrosis through non-invasive biomarkers is more advisable [1, 7]. The European Association for the Study of Diabetes, the European Association for the Study of Obesity, and the European Association for the Study of the Liver have sanctioned non-invasive, validated biomarkers amalgamating metabolic and hepatic parameters commonly used in clinical practice [1]. The most widely used biomarkers for fatty liver include the Fatty Liver Index (FLI) and the MASLD Liver Fat Score (NLFS), while for liver fibrosis, the NAFLD Fibrosis Score (NFS) and the Fibrosis-4 (FIB-4) Index are commonly employed [8-11].

The FIB-4 index, initially devised for staging liver disease in HIV-HCV co-infected individuals, has since found application in others with liver disease [12]. It is a score computed using age, aspartate aminotransferase, and platelet count, routinely examined in nearly all patients with liver disease [13]. Studies have demonstrated the efficacy of pioglitazone in reducing fatty liver disease [14]. Dapaglifozin is an oral antidiabetic used in the treatment of T2DM. It works by specifically binding to SGLT-2 in the renal proximal tubule, inhibiting glucose reabsorption via this pathway and increasing urinary glucose excretion [15]. In addition to their glucosuric effect, SGLT-2 inhibitors provide weight loss and reduce body fat. They also have a positive effect on MASLD on the liver by reducing blood pressure, inflammation, and oxidative stress, reducing hyperuricemia, and correcting insulin [15,16]. One experimental study showed that dapagliflozin attenuated hepatic steatosis via the adenosine monophosphate-activated protein kinase (AMPK)-the mechanistic (or mammalian) target of rapamycin (mTOR), promoted autophagy and increased fatty acid oxidation in both in vitro and in vivo models [17].

Dapagliflozin, an SGLT-2 inhibitor, has been proven to diminish fibrosis and hepatic steatosis in a 24-week follow-up study involving patients with liver fibrosis [18]. There is one study showing that in patients with diabetes treated with dapagliflozin, there was a significantly greater reduction in both abdominal visceral adipose tissue and subcutaneous adipose tissue volume with dapagliflozin compared to placebo [19]. There are experimental studies showing that different SGLT-2 inhibitors also improve histologic hepatic steatosis or steatohepatitis in obese mice or rats with T2DM [20, 21]. Only two prospective clinical trials have investigated the effect of SGLT-2 inhibitors on hepatic steatosis in patients with T2DM and NAFLD, but the anti-fibrotic effect of SGLT-2 inhibitors has not been studied in these patients [22, 23].

The objective of our study was to scrutinize the impact of dapagliflozin and combined dapagliflozin-pioglitazone treatment on liver enzymes and the FIB-4 index, associated with fibrosis. Our study encompasses results from a 104-week follow-up, and there's no existing research in the literature examining the effect of dapagliflozin on the FIB-4 index over 2 years.

## METHODS

### Study Participants

This retrospective investigation encompassed 508 individuals diagnosed with type 2 diabetes mellitus, who underwent monitoring at the Internal Medicine Clinic of from January 1, 2017 to January 1, 2020. The required sample size for the study was determined using the G Power software (v 3.1.9.7), resulting in the inclusion of 508 patients, with an effect size of f:0.1, alpha:0.01, and power:0.99. Among the participants, 386 received dapagliflozin alone, while 122 received pioglitazone concurrently with dapagliflozin. Data on fasting blood glucose, white blood cell count, platelet count (PLT), hemoglobin, alanine transaminase (ALT), and aspartate transaminase levels (AST) were gathered at week 0, week 52, and week 104 following the initiation of dapagliflozin and pioglitazone, utilizing the hospital's electronic information system. Patient comorbidities and demographic details were extracted from their medical records.

The FIB-4 index of each harvest was calculated. The formula for FIB-4index is: Age ([yr] ×AST [U/L]) / ((PLT [10(9)/L]) × (ALT [U/L])(1/2)) [13]. The initial body mass index (BMI) values of each patient were calculated by dividing their weight in kilograms by the square of their height in meters.

The study excluded diabetic patients using alternative diabetes medications and insulins, those on antithrombotic drugs, individuals taking medications

impacting platelet count, patients with any hematologic disease, those with chronic liver disease, and individuals using herbal supplements potentially affecting liver function. Patients with alcohol consumption were also excluded because it affects liver enzymes.

Thyroid functions (fT3, fT4, TSH), renal functions (BUN, creatinine, protein in spot urine) were normal in all patients. Patients taking antihyperlipidemic drugs were excluded because they affect liver function tests. Patients over 65 years of age were excluded due to an inaccurate calculation of the FIB-4 Index.

### Laboratory Procedures

The study assessed fasting blood glucose, alanine transaminase, and aspartate transaminase levels, along with hemogram parameters in both groups, utilizing an Abbott Architect 16200 automatic analyzer (Abbott Inc., Princeton, NJ, USA).

### Statistical Analysis

A specialized statistical software (SPSS for Windows version 22, IBM Corporation, Armonk, NY, USA) was employed to analyze the collected data. Analytical methods, including the Shapiro-Wilk test or Kolmogorov-Smirnov, and visual approaches, such as probability plots and histograms, were utilized to ascertain the normal distribution of variables. Categorical parameters are expressed as number (n) and percentage (%), while demographic data and other parameters are presented as the median and interquartile range (IQR). The Mann-Whitney U test determined significant differences between the DAPA and DAPA+PIO groups. Changes over time in evaluated parameters were assessed using the Friedman test, and the Wilcoxon test was applied to determine the significance of pairwise differences. A total type-1 error level of 5% was set for statistical significance.

## RESULTS

Among the 508 participants in the study, 386 individuals were prescribed dapagliflozin as the sole antidiabetic therapy, while 122 were concurrently prescribed pioglitazone with dapagliflozin. The DAPA group comprised 243 females (63%) and 143 males (37%), with an average age of 59.8±6 years, receiving dapagliflozin exclusively. The DAPA+PIO group, consisting of 61 females (50%) and 61 males (50%) with an average age of 58.3±5 years, utilized pioglitazone concurrently with dapagliflozin. No significant age difference was observed between the two groups (P=0.127). BMI values of the patients were between 20-29.3 and were similar between the two groups (P=0.742). Furthermore, Table 1 provides details on

**Table 1. Demographic characteristics and clinical findings in the DAPA and DAPA+PIO Group**

| Parameters | | DAPA Group (n=386) | DAPA+PIO Group (n=122) |
|---|---|---|---|
| **Gender** | Female | 243 (63%) | 61 (50%) |
| | Male | 143 (37%) | 61 (50%) |
| **Age (years)** | | 59.8±6 | 58.3±5 |
| **Hypertension** | No | 212 (54.9%) | 67 (54.9%) |
| | Yes | 174 (45.1%) | 55 (45.1 %) |
| **Hyperlipidemia** | No | 276 (71.5%) | 78 (64.5 %) |
| | Yes | 110 (28.5%) | 43 (35.5 %) |
| **Coronary artery disease** | No | 355 (92%) | 116 (95.1%) |
| | Yes | 31 (8%) | 6 (4.9%) |
| **Cerebrovascular disease** | No | 383 (99.2%) | 121 (99.2%) |
| | Yes | 3 (0.8%) | 1 (0.8%) |

Data are shown as mean±standard deviation or n (%). DAPA group=Group receiving dapagliflozin alone, DAPA+PIO Group=Group receiving pioglitazone simultaneously with dapagliflozin

**Table 2. Comparison of blood parameters at baseline, week 52, and week 104 in the DAPA group and the DAPA+PIO group**

| Parameters | Weeks | DAPA Group (n=386) | DAPA+PIO Group (n=122) | P value |
|---|---|---|---|---|
| **BMI (kg/m$^2$)** | Baseline | 24.9 (23.8-26.5) | 24.6 (23.8-26.3) | 0.742 |
| **ALT (IU/L)** | Baseline | 20 (15-27) | 19 (15-31) | 0.576 |
| | Week 52 | 21 (16-30) | 20 (14-26) | 0.148 |
| | Week 104 | 20 (15-27) | 19 (15-26) | 0.911 |
| | **P value** | 0.170 | 0.125 | |
| **AST (IU/L)** | Baseline | 18 (14-24) | 19 (14-25) | 0.731 |
| | Week 52 | 19 (15-25) | 19 (15-24) | 0.500 |
| | Week 104 | 19 (15-25) | 20 (15-26) | 0.325 |
| | **P value** | 0.257 | 0.656 | |
| **White blood cell (10$^3$/mm$^3$)** | Baseline | 7.8 (6.5-9.2) | 7.9 (6.8-9.9) | 0.213 |
| | Week 52 | 8.0 (6.7-9.6) | 7.9 (6.8-9.8) | 0.941 |
| | Week 104 | 8.3 (6.8-10.0) | 8.0 (6.8-9.9) | 0.788 |
| | **P value** | **0.004*** | 0.695 | |
| **Hemoglobin (g/dL)** | Baseline | 13.6 (12.5-14.7) | 13.8 (12.4-15.2) | 0.378 |
| | Week 52 | 13.8 (12.6-15.0) | 13.6 (12.3-15.0) | 0.641 |
| | Week 104 | 13.7-12.7-15.0) | 13.6 (12.4-15.0) | 0.743 |
| | **P value** | 0.278 | 0.628 | |
| **Platelets (×10$^9$/mL)** | Baseline | 270 (229-320) | 266 (227-311) | 0.610 |
| | Week 52 | 273 (226-317) | 266 (214-315) | 0.467 |
| | Week 104 | 269 (227-317) | 262 (220-310) | 0.519 |
| | **P value** | 0.188 | 0.589 | |
| **FIB-4 index** | Baseline | 0.92 (0.68-1.21) | 0.84 (0.62-1.20) | 0.699 |
| | Week 52 | 0.93 (0.70-1.27) | 0.87 (0.70-1.28) | 0.965 |
| | Week 104 | 0.95 (0.73-1.22) | 0.97 (0.69-1.30) | 0.847 |
| | **P value** | 0.124 | 0.150 | |
| **Fasting blood sugar (mg/dL)** | Baseline | 213 (157-276) | 226 (169-290) | 0.154 |
| | Week 52 | 178 (137-247) | 169 (142-243) | 0.843 |
| | Week 104 | 181 (141-238) | 191 (131-231) | 0.816 |
| | **P value** | **<0.001*** | **<0.001*** | |
| **HbA1c (%)** | Baseline | 9.2 (7.9-10.6) | 9.6 (8.4-10.9) | 0.074 |
| | Week 52 | 8.5 (7.4-9.6) | 8.4 (7.3-9.5) | 0.611 |
| | Week 104 | 8.3 (7.2-9.8) | 8.1 (7.1-9.3) | 0.257 |
| | **P value** | **<0.001*** | **<0.001*** | |
| **LDL (mg/dL)** | Baseline | 115 (91-143) | 111 (89-133) | 0.108 |
| | Week 52 | 109 (86-131) | 101 (80-126) | 0.066 |
| | Week 104 | 106 (85-130) | 100 (80-130) | 0.254 |
| | **P value** | **<0.001*** | **<0.001*** | |
| **Triglyceride (mg/dL)** | Baseline | 181(140-268) | 199 (143-300) | 0.237 |
| | Week 52 | 175 (136)-262) | 182 (134-300) | 0.675 |
| | Week 104 | 174 (130-256) | 175 (125-250) | 0.510 |
| | **P value** | **<0.001*** | **<0.001*** | |

Data are shown as median (interquartile range). DAPA group=Group receiving dapagliflozin alone, DAPA+PIO Group=Group receiving pioglitazone simultaneously with dapagliflozin. AST=Aspartate Aminotransferase, ALT=Alanine Aminotransferase, BMI=Body Mass Index, LDL=low density lipoprotein

*P<0.05 (Comparison between pre and post treatment), Friedman test

patient comorbidities.

A noteworthy disparity in white blood cell levels emerged between week 52 and week 104 in the DAPA group (P=0.004). A pairwise comparison disclosed a substantial increase in white blood cell count within the DAPA group after the first year compared to the baseline (P=0.003). In the DAPA+PIO group, no significant difference in white blood cell counts was noted in the first and second years compared to the baseline (P=0.695). Levels of ALT, AST, hemoglobin, and platelets were assessed at the baseline, in the 52nd week, and in the 104th week for both the DAPA and DAPA+PIO groups, revealing no significant differences between the two groups (P>0.05). HbA1C, fasting blood glucose, triglyceride and LDL levels of patients decreased significantly at 1 and 2 years compared to baseline (P<0.001). Additionally, there were no statistically significant alterations in the FIB-4 index for both groups during the initial and second years compared to the baseline (P>0.05). For detailed statistical outcomes, please consult Table 2.

## DISCUSSION

Our study is the first in the literature to retrospectively investigate the effect of dapagliflozin onliver fibrosis with a 2-year follow-up using the FIB-4 index. In our study, we did not observe a statistically significant change in the FIB-4 index compared to the baseline in the first and second years for the group receiving dapagliflozin alone or dapagliflozin and pioglitazone concomitantly.

There are few studies in the literature examining the effect of dapagliflozin on the FIB-4 index. The results of this study are also controversial. In the comparison study of dapagliflozin and teneligliptin, the FIB-4 index showed similarity between the two groups, with no statistically significant difference found [24]. Dapagliflozin 5 mg was used in this study and the patients had BMI over 23. In a separate study, pioglitazone and dapagliflozin exhibited no notable impact on the FIB-4 index in type 2 diabetic patients at the 24-week follow-up [25]. The doses of pioglitazone and dapagliflozin used in this study are unclear, and the study patients consisted of patients with BMI 23 and above. An experimental study involving 11 patients with diabetes and NASH demonstrated that dapagliflozin reduced the FIB-4 index [26]. A recent meta-analysis suggested that standard treatment doses of SGLT-2 inhibitors may not be adequate to reduce liver fibrosis and fatty liver in NASH patients. However, it was acknowledged that the study results might have been influenced by the use of these drugs in high doses, potentially increasing the likelihood of side effects and reducing patient tolerability [27]. In our study, no change in the FIB-4 index was observed between the group using only dapagliflozin and the group using dapagliflozin-pioglitazone concomitantly at the 104-week follow-up. Our research is the initial one in the literature to evaluate the impact of dapagliflozin on the FIB-4 index, examining liver fibrosis over 104 weeks. Similar to other studies, the present study demonstrated that the use of dapagliflozin alone or concurrently with pioglitazone did not impact the FIB-4 index in the liver over two years.

In our study, patients were selected from those receiving 10 mg dapagliflozin. Other studies used dapagliflozin doses of 5-10mg. We do not know whether the difference in the drug doses used affects the FIB-4 index because there are no available studies.

Our study was performed in patients with a BMI 20-29.3. Considering the weight loss and adipose tissue reducing effects of dapagliflozin, we think that the fact that the BMI of the patients was in the normal range may have affected the results of the study. In addition, our patient population included patients taking antihypertensive drugs, which may have affected the study results. Therefore, new large prospective studies in obese individuals are needed.

Previous studies have indicated significant reductions in AST, ALT, and GGT in the dapagliflozin group after 24 weeks [18]. Some studies have suggested that dapagliflozin lowers ALT and AST levels [28, 29]. A recent meta-analysis, including 43 randomized controlled trials, indicated that serum ALT levels decreased by 0.21 IU/L (95% CI 0.33-0.10) following treatment with SGLT2 inhibitors [30]. However, this study also included SGLT-2 inhibitors other than dapagliflozin. In our study, no change was noted in ALT and AST levels after 2 years of dapagliflozin use. These results may be attributed to the absence of a 2-year follow-up study for dapagliflozin use in the literature. Long-term studies are necessary to elucidate this matter. In our study, dapagliflozin was found to cause a statistically significant increase in white blood cell

counts starting from the 1st year during the 2-year follow-up (P=0.004). Since no studies on this subject were identified in a comprehensive literature review, we cannot comment on whether these results hold clinical importance. We believe that these results may become clearer with new studies to be conducted in the future.

### Limitations

Our study presents several notable limitations. The first one is the retrospective design of the study. The second important limitation is that the effect of weight loss on FIB-4 index, ALT and AST levels could not be evaluated considering the height and weight of the patients. Although the patients had body mass index data at the beginning of the study, BMI data at the 1st and 2nd follow-up years could not be obtained. The third important limitation is that antihypertensives and additional medications used for coronary artery disease may also affect liver function. The last important limitation is the lack of previous liver imaging.

## CONCLUSION

In patients with type 2 diabetes, dapagliflozin alone did not modify the FIB-4 index, associated with liver fibrosis and inflammation, in 1 year and 2 years compared to concurrent dapagliflozin use with pioglitazone. Although experimental studies show that dapagliflozin improves liver fibrosis, the matter has not yet been clarified in clinical studies. There is no 2-year follow-up study in the literature. Therefore, this needs to be elucidated in new prospective studies.

*Ethical Statement*

This study was approved by the Mersin University Clinical Research Ethics Committee (Decision no. 2023/861, date: 13.12.2023). Since the study was retrospective, written informed consent was not required.

*Authors' Contribution*

Study Conception: SÖ; Study Design: SÖ, DG; Supervision: SÖ, DG; Funding: SÖ; Materials: SÖ; Data Collection and/or Processing: SÖ, DG; Statistical Analysis and/or Data Interpretation: SÖ; Literature Review: DG; Manuscript Preparation: SÖ and Critical Review: SÖ, DG.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

*Financing*

The authors disclosed that they did not receive any grant during the conduction or writing of this study.

*Acknowledgement*

I would like to thank Associate Professor Serkan TAŞ for his valuable guidance and support throughout the project.

*Editor's note*

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