**Supplementary 1. Details of Methods**

**Literature Review Methodology**

We searched the literature published in English between 1990 and 2021 in the PubMed database. First, we obtained two guidelines from the database: the “Non-alcoholic Fatty Liver Disease in Patients with Type 2 Diabetes Mellitus: A Position Statement of the Fatty Liver Research Group of the Korean Diabetes Association” and the “Management of Chinese Adults with Type 2 Diabetes and Non-alcoholic Fatty Liver Disease: an Expert Consensus.” We then used the 22 hypoglycemic agents mentioned in these two guidelines (pioglitazone, rosiglitazone, lobeglitazone, metformin, liraglutide, semaglutide, exenatide, dulaglutide, lixisenatide, dapagliflozin, empagliflozin, canagliflozin, ipragliflozin, luseogliflozin, sitagliptin, vildagliptin, linagliptin, saxagliptin, gemigliptin, alogliptin, teneligliptin, and anagliptin) into the following search formula: “((((NAFLD[Title/Abstract]) OR (NASH[Title/Abstract])) OR (non-alcoholic steatohepatitis[Title/Abstract])) OR (non-alcoholic fatty liver disease[Title/Abstract])) AND (“the specific hypoglycemic agents” [Title/Abstract])) AND (fibrosis[Title/Abstract])” with the filters “RCT,” and obtained 39 articles, of which five were duplicates.

**Inclusion and Exclusion Criteria for the Clinical Intervention Studies**

The inclusion criteria were as follows: (1) the study design was a prospective RCT; (2) the study aimed to determine the influence of hypoglycemic agents on liver fibrosis or NASH; (3) the methods of evaluation included biopsy, vibration-controlled transient elastography (VCTE), or magnetic resonance imaging (MRI); and (4) the participants were patients with NAFLD or NASH.
The exclusion criteria were as follows: (1) the study aimed to determine the changes in serological markers, (2) the hypoglycemic agents were not a primary component of the study design or analysis, (3) the participants did not have NAFLD or NASH, and (4) only some of the participants underwent liver biopsy.

**Clinical Intervention Studies Included in the Analysis**

Two authors carried out the course of screening and data collection independently. After the removal of the five duplicates, we read the title, abstract, and full text of the articles obtained, and screened them using the above inclusion and exclusion criteria. Four of the trials were of pioglitazone, one was of rosiglitazone, one was of liraglutide, one was of semaglutide, three were of metformin, one was of dapagliflozin, one was of empagliflozin, and two were of sitagliptin [Supplementary Figure 1]. We then divided the evidence derived from these trials into three categories, according to the method used to evaluate liver fibrosis: histology, VCTE, or MRI.

**Data Collection and Bias Analysis**

We extracted information about participants’ characteristic, the regime of intervention, the evaluating method, and the follow-up time from each study. As for the results, we sorted out the outcomes related to liver fibrosis or NASH, and analyzed them from two aspects, that is: (1) the percentage of participants who benefited from the intervention, and (2) the degree of their improvement if any. However, given the difference in glucometabolic status and baseline liver fibrosis stage of participants, the heterogeneity between those studies became non-negligible and stopped us from synthesizing the outcome, and used the original data instead.
Three authors worked together to evaluate the bias of each study, using version 2 of the Cochrane tool for assessing the risk of bias in a randomized trial (RoB2, The Cochrane Collaboration, USA). Finally, we deliberately get the conclusion about the effect of each hypoglycemic agent according to the strength of evidence, considering the significance of the used indicators and the bias of the study.
Supplementary Figure 1: Flowchart of this study.
### Supplementary Table 1: Quality assessment of included RCTs based on the revised Cochrane risk-of-bias tool for randomized trials.

<table>
<thead>
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<th>Authors</th>
<th>Randomization process</th>
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<th>Measurement of the outcome</th>
<th>Selection of the reported result</th>
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<td>Trials using histology</td>
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<tr>
<td>Aithal <em>et al</em></td>
<td>Low risk</td>
<td>Low risk</td>
<td>Some concerns</td>
<td>Low risk</td>
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<td>Ratziu <em>et al</em></td>
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<tr>
<td>Newsome <em>et al</em></td>
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<td>Low risk</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
Lavine *et al*  | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk  
Uygun *et al*  | Low risk | High risk | High risk | Low risk | Some concerns | High risk  
Joy *et al*    | Low risk | Low risk | Low risk | Low risk | Low risk | Some concerns  

**Trials using VCTE or MRI**

Handzlik *et al*  | High risk | High risk | Some concerns | High risk | Low risk | High risk  
Taheri *et al*    | Low risk | High risk | Some concerns | Low risk | Low risk | High risk  
Shimizu *et al*   | Low risk | High risk | Some concerns | Low risk | Low risk | High risk  
Cui *et al*       | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk  

MRI: Magnetic resonance imaging; RCTs: Randomized controlled trials; VCTE: Vibration-controlled transient elastography.
Liver biopsy is the gold standard method of evaluating the hepatic lesions of NAFLD patients. The NAFLD histology scoring system includes a composite of the standardized scores for steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis.

**Histologic Evidence that Hypoglycemic Agents Improve Liver Fibrosis in NAFLD**

*Pioglitazone improves liver fibrosis in patients with NAFLD but not type 2 diabetes (T2D)*

Aithal *et al*[^4] published the results of an RCT of the use of pioglitazone in patients with NAFLD but no diabetes in 2008. The study included a total of 61 patients with biopsy-confirmed NASH and a mean fibrosis stage of 1.9 and excluded those with hepatic steatosis alone. The participants were randomly assigned to two groups, which were administered placebo or pioglitazone (30 mg/day), in addition to consuming a standard diet and performing exercise. The primary outcome was a histologic improvement in fibrosis and hepatocyte injury and the mean duration of follow-up was 12 months.

More participants in the pioglitazone group than in the placebo group showed improvements in fibrosis score (29% vs. 20%, respectively; \( P = 0.05 \)). Benefits of pioglitazone were also shown with respect to other histologic scores, including hepatocyte injury (32% vs. 10%, respectively; \( P = 0.005 \)) and Mallory hyaline (26% vs. 3%, respectively; \( P = 0.004 \)). In addition, there was no significant difference in the incidence of adverse events between the two groups, suggesting that pioglitazone treatment is well tolerated. Thus, the authors concluded that...
12 months of pioglitazone treatment in patients with NAFLD but no diabetes significantly improves liver fibrosis, according to histologic examination.

**Pioglitazone improves liver fibrosis in patients with NAFLD and T2D or prediabetes, according to histologic examination**

Cusi *et al*[^5] published the results of an RCT of the use of pioglitazone in patients with NAFLD and T2D or prediabetes in 2016. They studied 52 patients with T2D and 49 with prediabetes who also had biopsy-confirmed NASH. They had a mean fibrosis stage of 1.0 and a mean NAFLD activity score (NAS) of 4.5, and they were randomly assigned to two groups that were administered placebo or pioglitazone (45 mg/day), in addition to consuming a hypocaloric diet. The mean duration of follow-up was 18 months and the primary outcome was a reduction of at least 2 points in two items in the NAS, without a worsening of fibrosis. The aim of the study was to determine the efficacy and safety of long-term pioglitazone treatment in patients with NASH and prediabetes or T2DM.

A larger reduction in fibrosis score was found in the pioglitazone group than in the placebo group (−0.5 vs. 0, respectively; *P* = 0.039), suggesting that pioglitazone improves early liver fibrosis in these patients. In addition, more of the participants in the pioglitazone group achieved the primary outcome (58% vs. 17%, respectively; *P* < 0.001), showed the resolution of NASH (51% vs. 19%, *P* < 0.001), and showed improvements in steatosis (71% vs. 26%, respectively; *P* < 0.001), inflammation (49% vs. 22%, respectively; *P* = 0.004), and ballooning (51% vs. 24%, respectively; *P* = 0.004). Pioglitazone treatment was also associated with larger changes in hepatocyte injury scores: the steatosis score (−1.1 vs. −0.2, *P* < 0.001), inflammation score (−0.6 vs. −0.1, *P* < 0.001), and ballooning score (−0.6 vs. −0.2, *P* = 0.001). The overall incidence of adverse events did not differ between the groups.
Thus, the results of the two RCTs suggest that pioglitazone improves liver fibrosis in patients with NAFLD, whether or not they have T2D or prediabetes.

**Histologic Evidence for Hypoglycemic Agent-Induced Delays in the Progression of Liver Fibrosis in NAFLD**

**Histologic evidence for effects of pioglitazone to improve liver fibrosis and NASH patients with NAFLD but no T2D**

Sanyal et al\(^{[6]}\) published the results of an RCT of the use of pioglitazone and vitamin E in 247 patients with biopsy-confirmed NASH but no T2D in 2010. The participants had a mean fibrosis stage of 1.5 and a mean NAS of 4.9. They were randomly assigned to three groups, which were administered placebo, pioglitazone (30 mg/day), or vitamin E (800 IU/day). The mean duration of follow-up was 96 weeks (22 months) and the primary outcome was histologic improvement in NASH.

The pioglitazone group showed a higher incidence of improvement in liver fibrosis than the placebo group (44% vs. 31%, respectively; \(P = 0.12\)), and a trend toward a larger change in fibrosis score (−0.4 vs. −0.1, respectively; \(P = 0.10\)). Furthermore, more of the participants in the pioglitazone group achieved the primary outcome (34% vs. 19%, respectively; \(P = 0.04\)), showed resolution of NASH (47% vs. 21%, \(P = 0.001\)), and showed improvements in steatosis (69% vs. 31%, respectively; \(P < 0.001\)) and lobular inflammation (60% vs. 35%, respectively; \(P = 0.004\)). Pioglitazone treatment was also associated with larger changes in NAS (−1.9 vs. −0.5, \(P < 0.001\)) and the scores for steatosis, lobular inflammation, and ballooning (−0.8 vs. −0.1, \(P < 0.001\); −0.7 vs. −0.2, \(P < 0.001\); and −0.4 vs. −0.2, respectively; \(P = 0.01\)).
These findings differ from those reported by Aithal et al\(^4\) with respect to the effects of pioglitazone in patients with NAFLD but no T2D. The reason for this is unclear but might be related to the earlier fibrosis stage, lack of hyperglycemia, and/or the lack of diet or exercise regimens in this study.

*Histologic evidence for effects of liraglutide to delay the progression of liver fibrosis and improve NASH in patients with NAFLD, with or without T2D*

The results of the Liraglutide Safety and Efficacy in Patients with NASH (LEAN) trial were published in 2016 by Armstrong et al.\(^7\) A total of 52 patients with biopsy-confirmed NASH were included (32.7% of them with T2D) and randomly assigned to two groups, which were administered placebo or liraglutide (1.8 mg/day). The mean fibrosis stage of the participants was 2.3, and the mean NASs of the two groups were 4.8 and 4.9, respectively. The mean duration of follow-up was 48 weeks (11 months) and the primary outcome was the resolution of NASH without a worsening of fibrosis.

The liraglutide group showed less deterioration in liver fibrosis than the placebo group (9% vs. 36%, respectively; \(P = 0.04\)), although there was no difference in the number of participants in which improvements occurred (26% vs. 14%, \(P = 0.46\)). More participants in the liraglutide group showed resolution of NASH (39% vs. 9%, respectively; \(P = 0.019\)) and an improvement in steatosis (83% vs. 45%, respectively; \(P = 0.009\)). However, there was no significant difference between the two groups with respect to the changes in NAS or the hepatocyte ballooning, steatosis, or lobular inflammation scores. Thus, the results of this trial suggest that liraglutide might delay the progression of liver fibrosis in patients with NAFLD, whether or not they have T2D, but not reverse it.
**Histologic Evidence for an Effect of Hypoglycemic Agents to Improve NASH, While Failing to Improve Liver Fibrosis**

**Histologic evidence that pioglitazone in combination with vitamin E fails to improve liver fibrosis but does improve NASH in patients with NAFLD and T2D**

Bril *et al*[8] published the results of an RCT of the use of a combination of pioglitazone and vitamin E in patients with NASH and T2D in 2019. A total of 105 T2D patients with biopsy-confirmed NASH were randomly assigned to three groups, which were administered placebo, vitamin E (400 IU twice daily) alone, or a combination of vitamin E (400 IU twice daily) and pioglitazone (45 mg/day). The mean fibrosis stages of the three groups were 1.5, 1.6, and 1.4; and their mean NASs were 4.2, 3.9, and 3.7, respectively. There was a mean duration of follow-up of 18 months and the primary outcome was a reduction of at least 2 points in two items in the NAS, without a worsening of fibrosis.

The fibrosis scores of the vitamin E group and the combination group did not differ from that of the placebo group (vitamin E group: −0.6 vs. −0.3, *P* = 0.39; combination group: −0.6 vs. −0.3, *P* = 0.22). However, whereas more of the participants in the combination group than in the placebo group achieved the primary outcome (54% vs. 19%, respectively; *P* = 0.003), the vitamin E group did not show a difference (31% vs. 19%, respectively; *P* = 0.26). More participants in both treatment groups than in the placebo group showed resolution of NASH (combination group: 43% vs. 12%, respectively; *P* = 0.005; vitamin E group: 33% vs. 12%, respectively; *P* = 0.04), but only the combination treatment was associated with higher incidences of improvements in steatosis and ballooning (87% vs. 46%, respectively; *P* < 0.001 and 61% vs. 35%, respectively; *P* = 0.03) and larger reductions in the inflammation and ballooning scores (−0.6 vs. −0.2, respectively; *P* = 0.018 and −0.6 vs. −0.1, respectively; *P* = 0.022).
Although a separate pioglitazone group was not included in this trial, the results imply that pioglitazone in combination with vitamin E has superior effects to vitamin E alone on the NAS and hepatocyte inflammation and ballooning in patients with NASH and T2D, but not with respect to liver fibrosis.

**Histologic evidence that rosiglitazone improves NASH but does not improve liver fibrosis in patients with NAFLD, whether or not they have T2D**

The results of the Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) trial were published in 2008 by Ratziu et al.[9] A total of 63 patients with biopsy-confirmed NASH were included, 31.7% of whom had diabetes. Of the participants, 71.4% had significant fibrosis (defined as fibrosis stage ≥F2) and their mean NAS was 4. The participants were randomly assigned to two groups that were administered placebo or rosiglitazone (4 mg/day for the first month and 8 mg/day thereafter), and the mean duration of follow-up was 12 months. The trial showed no significant difference between the groups with respect to the improvement in liver fibrosis (0.03 vs. –0.18, P = 0.43), but more of the participants in the rosiglitazone group than in the placebo group showed improvements in steatosis (47% vs. 16%; P = 0.014).

**Histologic evidence that semaglutide improves NASH but not liver fibrosis in patients with NASH, whether or not they have T2D**

Newsome et al.[10] published the results of an RCT of the effects of semaglutide in patients with NASH in 2016. A total of 320 patients with biopsy-confirmed NASH were included, 62.2% of whom had T2D. Of the participants, 71.9% had a fibrosis stage ≥2 and their mean NAS was 4.8–4.9. The participants were randomly assigned to five groups, in which semaglutide was administered once daily at doses of 0.1 mg, 0.2 mg,
or 0.4 mg, or placebo was administered. The mean duration of follow-up was 72 weeks (16.5 months) and the primary outcome was a resolution of NASH without a worsening of fibrosis.

No difference was identified between the groups with respect to the percentage of participants that achieved an improvement in fibrosis (0.4 mg semaglutide vs. placebo: 43% vs. 33%, \( P = 0.48 \)), but treatment with 0.4 mg semaglutide resulted in more participants achieving the primary outcome than the administration of placebo (59% vs. 17%, \( P < 0.001 \)).

Thus, the three clinical trials show that pioglitazone in combination with vitamin E, rosiglitazone, and semaglutide do not improve liver fibrosis in NAFLD, but do improve NASH, according to histologic evidence.

**Histologic Evidence that Some Hypoglycemic Agents Do Not Have Beneficial Effects on Either Fibrosis or NASH**

**Histologic evidence that metformin does not improve liver fibrosis or NASH in patients with NAFLD but no T2D**

The Treatment of NAFLD in Children and Adolescents (TONIC) trial aimed to determine the effects of vitamin E and metformin in 173 children and adolescents.\(^{[11]}\) The participants had biopsy-confirmed NAFLD, obesity, IR, a mean fibrosis stage of 1.2, and a mean NAS of 4.6. After 96 weeks (22 months), the metformin (1000 mg/day) and control groups showed similar improvements in fibrosis (44% vs. 40%, respectively; \( P = 0.72 \)) and fibrosis score (−0.4 vs. −0.2, respectively; \( P = 0.60 \)). In addition, no differences were found with respect to the resolution of NASH (41% vs. 28%, respectively; \( P = 0.23 \)), steatosis (52% vs. 40%, respectively; \( P = 0.25 \)), or lobular inflammation (46% vs. 43%, respectively; \( P = 0.73 \)).
Uygun et al[12] published the results of an RCT of the use of metformin in patients with clinically diagnosed NASH, but no diabetes, in 2004. The mean fibrosis stage of the combination group (metformin and dietary management) was 0.94 and that in the diet-only group was 1.05, and the mean necro-inflammatory activity grade was 1.41 in either group. Only 23 of the 63 participants underwent liver biopsy after 6 months of the trial, but this showed that the change in fibrosis score during the study period did not differ between the groups (combination group: 0.94 vs. 0.92, \( P = 0.96 \); diet alone group: 1.05 vs. 1.12, \( P = 0.91 \)). However, more participants in the combination group than in the diet-only group tended to show an improvement in necro-inflammatory activity (46% vs. 10%, respectively; \( P = 0.17 \)).

The results of these two trials imply that metformin might not improve liver fibrosis in NASH patients without T2D, according to histologic evidence.

**Histologic evidence that sitagliptin does not improve liver fibrosis or NASH in patients with NAFLD and T2D**

Joy et al[13] published the results of an RCT of the use of sitagliptin in 12 patients with T2D and biopsy-confirmed NASH. The mean fibrosis stage of the participants was 2.2, and the mean NASs were 4.2 and 3.8 in the sitagliptin (100 mg/day) and placebo groups, respectively. After 24 weeks (5.5 months) of follow-up, there were no significant differences in the improvements in the sitagliptin and placebo groups with respect to fibrosis stage or NAS (\( P = 0.82 \) and \( P = 1.00 \), respectively). However, the small sample size limits the validity of these findings.

The evidence of each study was summarized in Supplementary Table 2.

**References**


Supplementary Table 2: Summary of RCTs of the effects of hypoglycemic agents on liver fibrosis in NAFLD, assessed histologically.

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>Hypoglycemic agents (dosage)</th>
<th>Duration (months)</th>
<th>Subjects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved fibrosis and NASH</td>
<td>Pioglitazone (30 mg/day)</td>
<td>12</td>
<td>Without DM</td>
<td>[4]</td>
</tr>
<tr>
<td></td>
<td>Pioglitazone (45 mg/day)</td>
<td>18</td>
<td>51.5% with T2D and 48.5% with prediabetes</td>
<td>[5]</td>
</tr>
<tr>
<td>Might delay the progress of fibrosis, and</td>
<td>Pioglitazone (30 mg/day)</td>
<td>22</td>
<td>Without DM</td>
<td>[6]</td>
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<tr>
<td>improved NASH</td>
<td>Liraglutide (1.8 mg/day)</td>
<td>11</td>
<td>32.7% with T2D</td>
<td>[7]</td>
</tr>
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<td>Failed to improve fibrosis, but improved</td>
<td>Pioglitazone (45 mg/day with</td>
<td>18</td>
<td>T2D</td>
<td>[8]</td>
</tr>
<tr>
<td>Treatment</td>
<td>Duration</td>
<td>T2D With Other Conditions</td>
<td>Result</td>
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<tr>
<td>Rosiglitazone (8 mg/day)</td>
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<td>31.7%</td>
<td>71.4% with significant fibrosis (fibrosis stage ≥ F2) and a mean NAS of 4</td>
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<tr>
<td>Semaglutide (0.4 mg/day)</td>
<td>16.5</td>
<td>62.2%</td>
<td>71.9% with significant fibrosis (fibrosis stage ≥ F2) and a mean NAS of 4.8–4.9</td>
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<tr>
<td>Metformin (1000 mg/day)</td>
<td>22</td>
<td>Without DM</td>
<td>A mean fibrosis stage of 1.2 and a mean NAS of 4</td>
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</tr>
<tr>
<td>Metformin (1700 mg/day)</td>
<td>6</td>
<td>Without DM</td>
<td>A mean fibrosis stage of 0.94–1.05 and a mean necro-inflammatory activity of 1.41</td>
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</tr>
<tr>
<td>Sitagliptin (100 mg/day)</td>
<td>5.5</td>
<td>T2D</td>
<td>A mean fibrosis stage of 2.2 and a mean NAS of 3.8–4.2</td>
<td></td>
</tr>
</tbody>
</table>

DM: Diabetes mellitus; NAFLD: Non-alcoholic fatty liver disease; NAS: NAFLD activity score; NASH: Non-alcoholic steatohepatitis; RCTs:
Randomized controlled trials; T2D: Type 2 diabetes.

**Supplementary 3. Details of Clinical Trials Studying the VCTE and MRI Evidence for the Effects of Hypoglycemic Agents on Liver Fibrosis in NAFLD**

Liver biopsy is the gold standard method of evaluating NAFLD, but this is an invasive method that is of limited clinical use. The non-invasive substitute methods include VCTE, including liver stiffness measurement (LSM) and magnetic resonance elastography (MRE) to evaluate hepatic fibrosis; and VCTE, including controlled attenuation parameter (CAP) and MRI-proton density fat fraction (MRI-PDFF) to evaluate hepatic steatosis.[1]

**VCTE-derived evidence for hypoglycemic agent-induced amelioration of liver fibrosis in NAFLD**

**VCTE-derived evidence for an amelioration of liver fibrosis in patients with NAFLD and type 2 diabetes (T2D) or prediabetes**

Handzlik et al.[2] published an evaluation of the use of metformin in patients with NAFLD in 2019. A total of 42 participants with CAP and clinically diagnosed NAFLD were included, of whom 64.3% had T2D or prediabetes. They were randomly assigned to a dietary intervention alone or a combination of dietary therapy and metformin (starting at 500 mg/day and increasing to 2000 mg/day).

Five months of combination therapy resulted in significant reductions in LSM (6.2 kPa vs. 5.2 kPa, \( P < 0.05 \)) and CAP (319 dB/m vs. 295 dB/m, \( P < 0.05 \)), whereas dietary therapy alone did not induce significant changes. This implies that a combination of metformin and diet improves liver fibrosis and steatosis in patients with NAFLD and T2D or prediabetes, according to VCTE.

**VCTE-derived evidence that empagliflozin improves liver fibrosis in patients with NAFLD but no T2D**
Taheri et al[3] published the results of an RCT of the use of empagliflozin (10 mg/day) in 100 patients with NAFLD but no T2D in 2020. After 24 weeks (5.5 months), empagliflozin treatment caused a significantly larger reduction in LSM ($P = 0.039$) than placebo administration, but the differences in NAFLD fibrosis score, fibrosis-4 index, and aspartate aminotransferase activity to platelet count ratio index were not significant. There was also no significant difference in the change in CAP between the two groups ($P = 0.396$), but subgroup analysis of participants with significant steatosis at baseline (CAP $\geq 302$ dB/m) showed that steatosis significantly improved in the empagliflozin group (37.2% vs. 17%, $P = 0.035$).

VCTE-derived evidence that dapagliflozin improves liver fibrosis in patients with NAFLD and T2D

Shimizu et al[4] published an evaluation of the effects of dapagliflozin (5 mg/day) in 57 patients with NAFLD and T2D in 2019. After 24 weeks (5.5 months), there were no significant differences between the groups with respect to the changes in LSM, but in the 14 participants with substantial liver fibrosis (defined as LSM $> 8.0$ kPa), LSM decreased significantly in the dapagliflozin group ($P = 0.0158$). Furthermore, dapagliflozin administration was associated with a larger reduction in CAP than the placebo ($P = 0.0479$).

MRI-Derived Evidence that Sitagliptin does not Improve Steatosis or Fibrosis

Cui et al[5] published the results of an RCT of the use of sitagliptin in 50 patients with NAFLD and pre-diabetes or early T2D in 2016. 24 weeks (5.5 months) of sitagliptin (100 mg/day) treatment was not superior to placebo with respect to improvements in MRE (mean difference = $-0.2\%$, $P = 0.26$) and MRI-PDFF (mean difference = $-1.3\%$, $P = 0.4$).
Supplementary Table 3 shows the summary of RCTs of the effects of hypoglycemic agents on liver fibrosis NAFLD, assessed using VCTE or MRI.

References


Supplementary Table 3: Summary of RCTs of the effects of hypoglycemic agents on liver fibrosis NAFLD, assessed using VCTE or MRI.

<table>
<thead>
<tr>
<th>Methods</th>
<th>Conclusion</th>
<th>Hypoglycemic agents (dosage)</th>
<th>Duration of follow-up (months)</th>
<th>Subjects</th>
<th>Baseline liver fibrosis and steatosis assessed by VCTE or MRI</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCTE</td>
<td>Improved fibrosis and steatosis</td>
<td>Metformin (2000 mg/day)</td>
<td>5</td>
<td>64.3% with T2D or prediabetes</td>
<td>A mean LSM of 5.6–6.2 kPa and a mean CAP of 316 dB/m</td>
<td>[2]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Empagliflozin (10 mg/day)</td>
<td>5.5</td>
<td>Without DM</td>
<td>A mean LSM of 5.56–6.03 kPa and a mean CAP of 304.6–306.5 dB/m</td>
<td>[3]</td>
</tr>
<tr>
<td></td>
<td>Improved significant fibrosis</td>
<td>Dapagliflozin</td>
<td>5.5</td>
<td>T2D</td>
<td>A mean LSM of 6.10–7.20 kPa and a mean CAP of</td>
<td>[4]</td>
</tr>
<tr>
<td>MRI</td>
<td>Failed to improve fibrosis and steatosis</td>
<td>Sitagliptin (100 mg/day)</td>
<td>5.5</td>
<td>T2D or prediabetes</td>
<td>A mean MRE of 2.6–2.8% and a mean MRI-PDFF of 16.6–18.1%</td>
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</tbody>
</table>

CAP: Controlled attenuation parameter; DM: Diabetes mellitus; LSM: Liver stiffness measurement; MRE: Magnetic resonance elastography; MRI: Magnetic resonance imaging; MRI-PDFF: Magnetic resonance imaging-proton density fat fraction; NAFLD: Non-alcoholic fatty liver disease; RCTs: Randomized controlled trials; T2D: Type 2 diabetes; VCTE: Vibration-controlled transient elastography.