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Meta-Analysis

Antidiabetic drugs and non-alcoholic fatty liver disease: A systematic review, meta-analysis and evidence map

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ABSTRACT

Background: The efficacy of antidiabetic agents for the treatment of non-alcoholic fatty liver disease (NAFLD) remains unclear.
Aim: To conduct a meta-analysis to study the efficacy of pioglitazone and three novel anti-diabetic agents: glucagon-like peptide-1 (GLP-1) agonists, sodium-glucose co-transporter-2 (SGLT2) inhibitors, and dipeptidyl-peptidase-4 (DPP4) inhibitors in treating NAFLD.
Methods: Online databases were searched in May 2020 for randomized clinical trials. Results from random-effects meta-analysis are presented as weighted mean differences (WMDs) or standard mean differences (SMDs) and corresponding 95% confidence intervals (CIs).
Results: Twenty-six studies (n=946 NAFLD patients) were included. Reductions in ALT were seen with all four drugs: pioglitazone (MD -38.41, $p<0.001$), SGLT2 inhibitors (MD -16.17, $p<0.001$), GLP-1 agonists (MD -27.98, $p=0.04$) and DPP-4 inhibitors (MD -7.41, $p<0.001$). Pioglitazone (SMD -1.01; $p<0.001$) and GLP-1 agonists (SMD -2.53, $p=0.03$) also demonstrated significant improvements in liver steatosis. SGLT2 inhibitors (SMD -4.64, $p=0.06$) and DPP-4 (SMD -2.49, $p=0.06$) inhibitors trended towards reduced steatosis; however, these results were non-significant.
Conclusion: Pioglitazone demonstrates significant improvements in transaminases and liver histology in both diabetic and non-diabetic NAFLD patients. Early evidence from diabetic NAFLD patients suggests that novel antidiabetics may lead to improvements in liver enzymes and hepatic steatosis, and this should encourage further research into possible utility of these drugs in treating NAFLD.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease globally, affecting up to a third of the general population [1]. More than half of these patients have obesity and type 2 diabetes mellitus (T2DM) [1]. Indeed, the association between NAFLD and T2DM is well established [2,3]. Current guidelines on the management of NAFLD are based on lifestyle modification, with no recommendations for drug treatment [4]. Given the strong association between NAFLD and T2DM, recent trials have sought to assess the usefulness of anti-diabetic agents such as pioglitazone, glucagon-like peptide-1 (GLP-1) agonists, sodium-glucose co-transporter-2 (SGLT-2) and dipeptidyl peptidase-4 (DPP-4) inhibitors in the treatment of NAFLD [5,6].

These trials have; however, yielded inconsistent results due to small sample sizes and varied follow-up durations [1,6,7]. In this study, we conduct a single-arm meta-analysis using data from clinical trials to provide a holistic and well-powered assessment of the efficacy of anti-glycemic agents in the treatment for NAFLD. We aimed to study the NAFLD population as whole, as well as the following subgroups: T2DM patients, non-diabetic patients, and patients with non-alcoholic steatohepatitis (NASH). Our findings are presented in an evidence map which displays the strength and reliability of available evidence, and also highlights current knowledge gaps.

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2. Methods

This study adheres to the reporting guidelines established by the Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) [8].

2.1. Data sources and search strategy

Electronic databases including PubMed Central, Scopus, and Cochrane CENTRAL were searched in May 2020 with no time or language restrictions. Detailed search strategy for each database is provided in **Table S1.** We also searched clinicaltrials.gov using generic, pharmaceutical and trade names of drugs. Bibliographies of relevant published trials, meta-analyses and systematic reviews were also hand-searched to ensure no relevant articles were overlooked. We chose to include data from registered trials as these studies have standardized, prespecified data collection and outcome adjudication methods.

2.2. Study selection

All articles were exported to EndNote Reference Library (Version X9; Clarivate Analytics, Philadelphia, Pennsylvania), where duplicates were identified and removed. The remaining articles were assessed and shortlisted independently by two reviewers (JK and RSM) based on their relevance to the eligibility criteria described herein. Titles and abstracts of articles were reviewed first, after which the full text was read. In case of discrepancies, a third reviewer (MSU) was consulted. Studies were included in our analysis if they met the following prespecified eligibility criteria: (a) they were randomized controlled trials (RCTs); (b) included adults> 18 years of age with or without T2DM; (c) all participants had biopsy or ultrasound proven NAFLD or NASH; (d) evaluated the effect of SGLT-2 inhibitors, DPP-4 inhibitors, GLP-1 agonist and/or pioglitazone on body mass index (BMI), liver enzymes and/or liver histology.

2.3. Data extraction and risk of bias assessment

Data on study, baseline characteristics and outcomes were extracted onto a predesigned form. The following outcomes of interest were extracted from the selected studies: change in (a) Alanine transaminase (ALT) levels; (b) Aspartate transaminase (AST) levels; (c) Gamma glutamyl transferase (GGT) levels; (d) liver fibrosis; (e) liver steatosis; (f) lobular inflammation and (g) BMI.

2.4. Statistical analysis

Review Manager (V.5.3 Cochrane Collaboration, London, United Kingdom) was used to perform all statistical analysis. Continuous outcomes from each study were pooled using a random-effects model to derive weighted mean differences (WMDs) and corresponding 95% confidence intervals (CIs). If different measurement units were reported by studies for a particular outcome, standard mean difference (SMD) was used. Pooled results were derived for the overall NAFLD cohort, as well as the following subgroups: DM patients, non-DM patients, and NASH patients. The chi-squared test was conducted to test for subgroup differences in efficacy between different drug classes. We chose not to conduct any tests for funnel plot asymmetry as these tests are not recommended by Cochrane guidelines when less than 10 studies are included in the analysis (which is the case for all outcomes in our study). In such cases, the power of the tests is too low to distinguish chance from real asymmetry [9]. Heterogeneity was calculated using I^2 statistics and a value of I^2=25%–50% was considered mild, 50%–75% as moderate and >75% as severe heterogeneity [10]. A p-value <0.05 was considered significant in all cases.

3. Results

Initial search of the two electronic databases yielded 4743 potential studies. After exclusions, 26 studies were included in our analysis. Amongst these 26 studies, 11 evaluated pioglitazone (n=401 participants), 7 evaluated SGLT-2 inhibitors (n=255 participants), four assessed DPP-4 inhibitors (n=110 participants) and 6 assessed GLP-1 agonists (n=179 participants) (**Fig. S1**). Detailed study, baseline characteristics and study references are presented in **Tables S2 and S3.** Detailed forest plots are given in the supplement **(Figs. S2-S14)**

3.1. Pioglitazone (Fig. 1)

3.1.1. Effects on BMI

In the overall cohort, pioglitazone significantly increased BMI (WMD: 0.80, 95% CI [0.42, 1.18]; p<0.001; I^2=67%).

3.1.2. Effect on liver enzymes

Pioglitazone was associated with significant reductions in ALT (WMD: -38.41, 95% CI [-50.31, -26.51]; p<0.001; I^2=74%), AST (WMD: -17.43, 95% CI [-21.88, -12.98]; p<0.001; I^2=53%) and GGT (WMD: -27.57, 95% CI [-43.08, -12.06]; p<0.001; I^2=74%) in the NAFLD population.

3.1.3. Effect on liver histology

In the overall cohort, pioglitazone was associated with significant reduction in fibrosis (SMD: -0.43, 95% CI [-0.74, -0.12]; p=0.007; I^2=77%), steatosis (SMD: -1.01, 95% CI [-1.27, -0.75]; p<0.001; I^2=0%) and inflammation (SMD: -0.78, 95% CI [-1.08, -0.48]; p<0.001; I^2=35%).

3.2. SGLT-2 inhibitors (Fig. 2)

3.2.1. Effect on BMI

SGLT-2 inhibitors were associated with a significant decrease in BMI (WMD: -0.86, 95% CI [-1.15, -0.57]; p<0.001; I^2=7%) in the overall cohort.

3.2.2. Effect on Liver enzymes

SGLT-2 inhibitors significantly reduced ALT (WMD: -16.17, 95% CI [-21.74, -10.60]; p<0.001; I^2=71%) and GGT (WMD: -19.31, 95% CI [-21.13, -17.49]; p<0.001; I^2=0%). However, no significant change in AST levels was observed (WMD: -7.09, 95% CI [-17.03, 2.85]; p=0.16; I^2=100%).

3.2.3. Effect on liver histology

SGLT-2 inhibitors were not associated with any significant change in liver fibrosis (SMD: -0.07, 95% CI [-0.33, 0.19]; p=0.61; I^2=0%) and steatosis (SMD: -4.64, 95% CI [-9.53, 0.25]; p=0.06; I^2=45%) in the overall cohort. Analysis for change in inflammation in the overall cohort could not be performed due to lack of data.

3.3. DPP-4 inhibitors (Fig. 3)

3.3.1. Effect on BMI

DPP-4 inhibitors had no significant changes in BMI (WMD: -0.24, 95% CI [-0.82, 0.34]; p=0.42; I^2=69%) in the overall population.

3.3.2. Effect on liver enzymes

DPP-4 inhibitors significantly reduced ALT (WMD: -7.41, 95% CI [-10.82, -4.00]; p<0.001; I^2=0%). However, no significant changes in AST (WMD: -4.24, 95% CI [-11.69, 3.21]; p=0.26; I^2=52%) and GGT levels (WMD: -2.00, 95% CI [-5.46, 1.46]; p=0.26) were noted. Heterogeneity could not be calculated for the GGT outcome as only one study reported this data.

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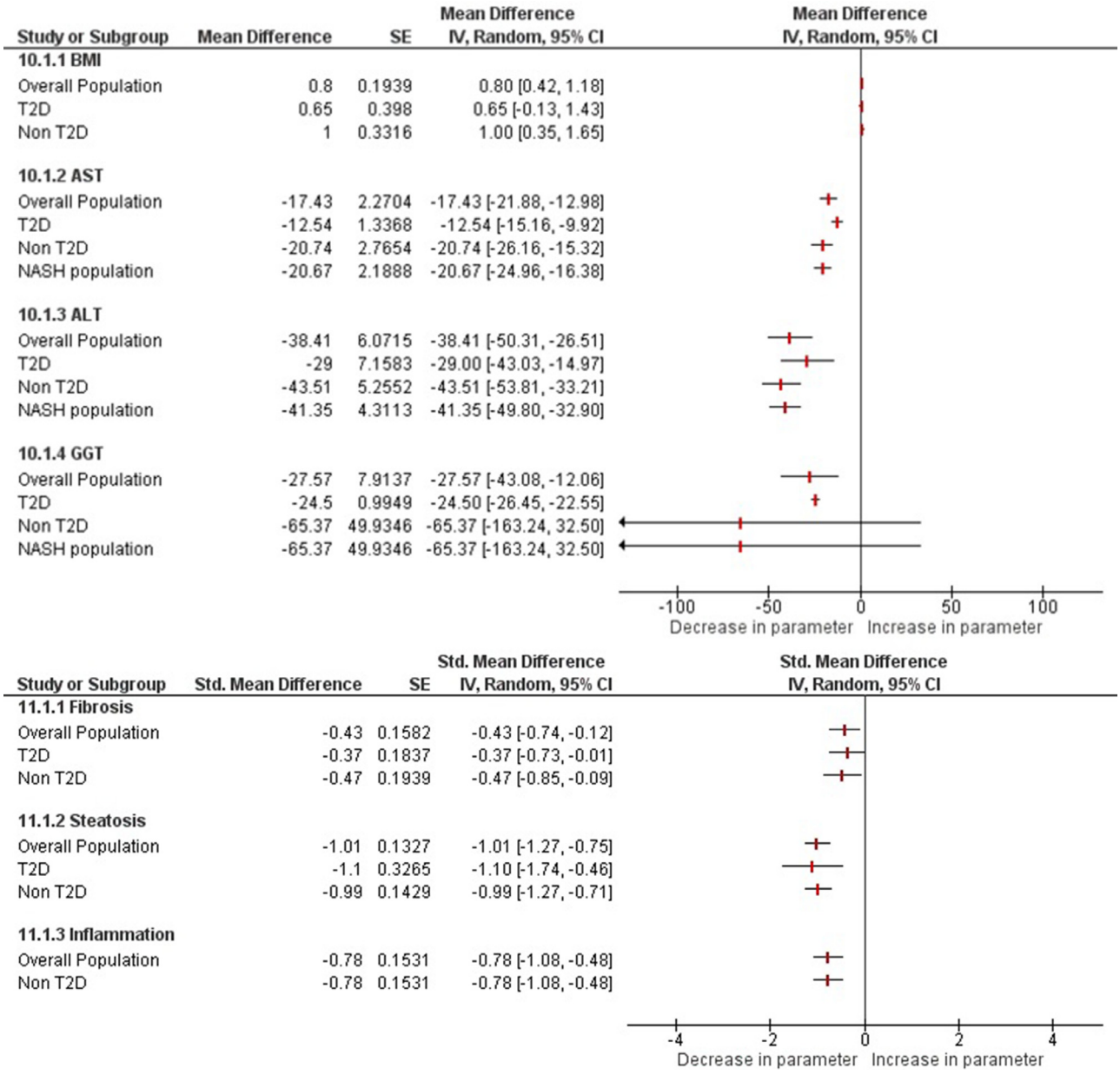

Fig. 1. Summarized Forest Plot detailing results for Pioglitazone.

3.3.3. Effect on liver histology

No significant effect on changes in fibrosis (SMD: -0.03, 95% CI [-0.24, 0.18]; p=0.80; I^2=70%) and steatosis (SMD: -2.49, 95% CI [-5.04, 0.06]; p=0.06; I^2=66%) was detected with DPP-4 inhibitors. Analysis for changes in liver inflammation was not performed due to lack of data.

3.4. GLP-1 agonists (Fig. 4)

3.4.1. Effect on BMI (Fig. S1)

In the overall population, GLP-1 agonists were associated with a significant decrease in BMI (WMD: -1.63, 95% CI [-2.10, -1.16]; p<0.001; I^2=2%).

3.4.2. Effect on liver enzymes

GLP-1 agonists were associated with significant reductions in ALT (WMD: -27.98, 95% CI [-55.33, -0.63]; p=0.04; I^2=75%) and GGT (WMD: -40.65, 95% CI [-77.52, -3.78]; p=0.03; I^2=74%). However, no significant change in AST levels was noted (WMD: -20.23, 95% CI [-46.96, 6.50]; p=0.14; I^2=72%).

3.4.3. Effect on liver histology

Use of GLP-1 agonists was associated with a significant reduction in steatosis (SMD: -2.53, 95% CI [-4.77, -0.30]; p=0.03; I^2=82%). Analysis for fibrosis and inflammation was not performed due to lack of data.

3.5. Subgroup analysis

We stratified our results into the following subgroups: studies with T2DM patients, studies with non-diabetic patients, and studies with NASH patients exclusively. The results of subgroup analysis are presented in Table 1. The strength and certainty of evidence in each subgroup is displayed in the evidence map in Fig. 5. Fig. 5 also displays 'evidence free zones' where trial data is not available.

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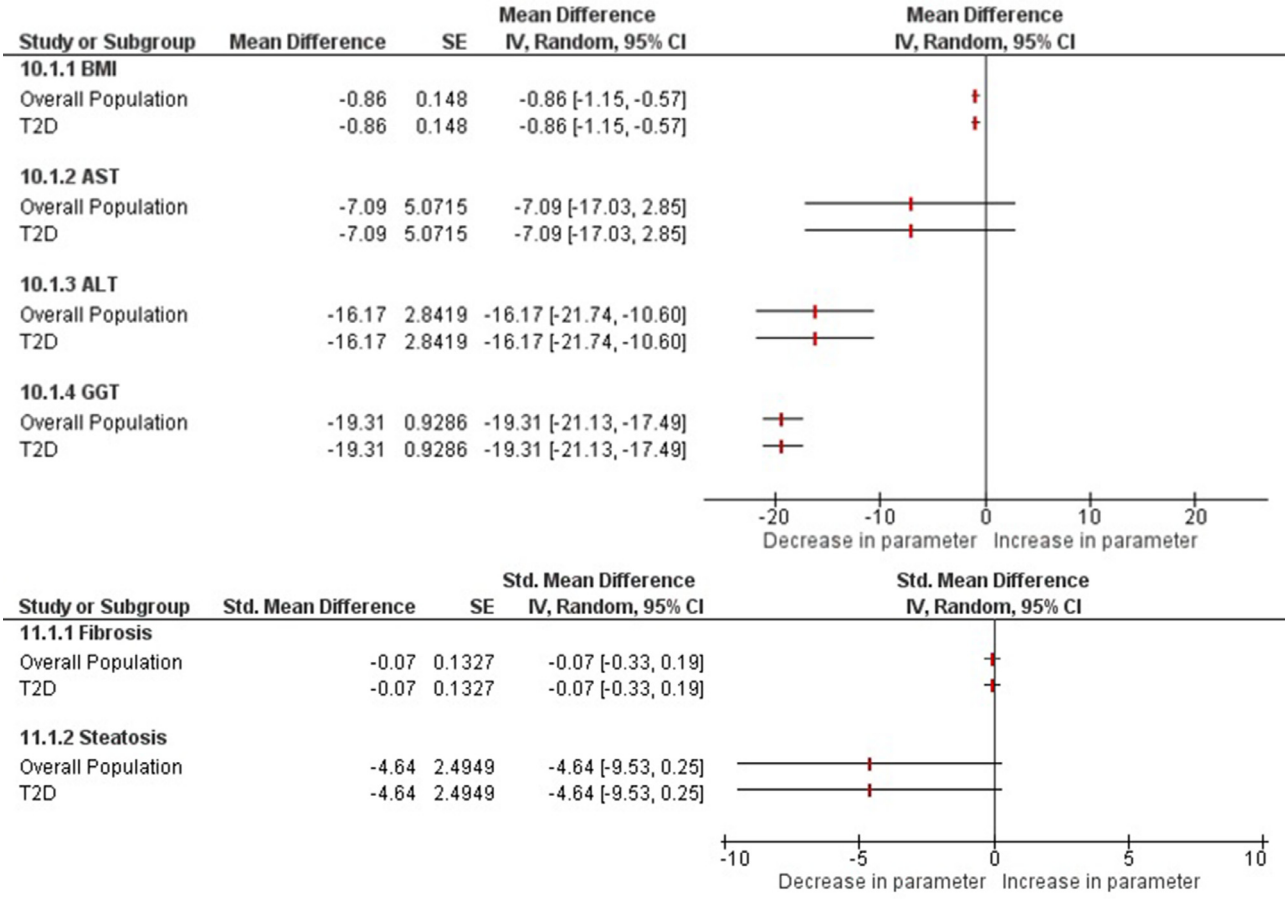

Fig. 2. Summarized Forest Plot detailing results for SGLT-2 inhibitors.

3.6. Comparison of drugs

Supplementary Table S4 displays the pairwise comparison of drugs for each outcome in NAFLD patients. However, this analysis is purely exploratory. Although the results offer early insight, they should be viewed with caution because (1) it is based on a study-level subgroup analysis rather than a head-to-head comparison; and (2) current data are limited for many outcomes.

4. Discussion

To the best of our knowledge, this is the first meta-analysis that provides a quantitative assessment of the efficacies of four antidiabetic agents (pioglitazone, GLP-1 agonists, SGLT-2, and DPP-4 inhibitors) in the management of NAFLD. We sought to study the effect of these drugs in four populations: all NAFLD patients, NAFLD patients with DM, NAFLD patients without DM, and patients with NASH. In this systematic review, we also highlight areas where evidence is currently lacking (Fig. 5).

4.1. Effect on BMI

The results of this study show expected changes in BMI amongst the NAFLD population. Pioglitazone significantly raised BMI whereas SGLT-2 inhibitors and GLP-1 analogs were shown to significantly decrease BMI. In contrast, DPP-4 inhibitors showed no significant changes in BMI.

4.2. Effect on liver enzyme levels

All four drugs demonstrated significant reductions in ALT. Pioglitazone also showed reductions in AST levels. Although SGLT-2 inhibitors, GLP-1 agonists and DPP-4 inhibitors demonstrated a trend towards lower AST levels, the results were not statistically significant, likely due to limited data. All drug classes, apart from DPP-4 inhibitors, showed reduction in GGT levels.

In harmony with our findings, a trial [11] and two pilot studies [12,13] showed significant decrease in ALT and AST levels with pioglitazone, which increased again to levels of statistical significance after a few weeks off treatment [13]. Unlike pioglitazone, the effect of SGLT-2 inhibitors on liver enzyme levels has previously remained unclear. Ito D et al demonstrated favorable reductions in ALT, AST and GGT levels with SGLT-2 inhibitors in T2DM patients [6]. Contradictorily, a trial assessing NAFLD outcomes with luseugliflozin showed that the decrease in ALT levels was non-significant [14]. Our pooled analysis demonstrates encouraging modulations in liver enzymes with SGLT-2 inhibitors in patients with NAFLD, and this should encourage further research assessing the applicability of these agents in the treatment of NAFLD. The efficacy of DPP-4 inhibitors in improving ALT levels has remained inconclusive. Two trials on sitagliptin report no significant reductions; whereas, an RCT on vildagliptin demonstrated improvement in ALT levels [15–17]. While our results suggest possible reductions in ALT and AST with DPP-4 inhibitors, the effect noted was significantly less than pioglitazone and SGLT-2 inhibitors. Consistent with our analysis, the LEAN trial reports

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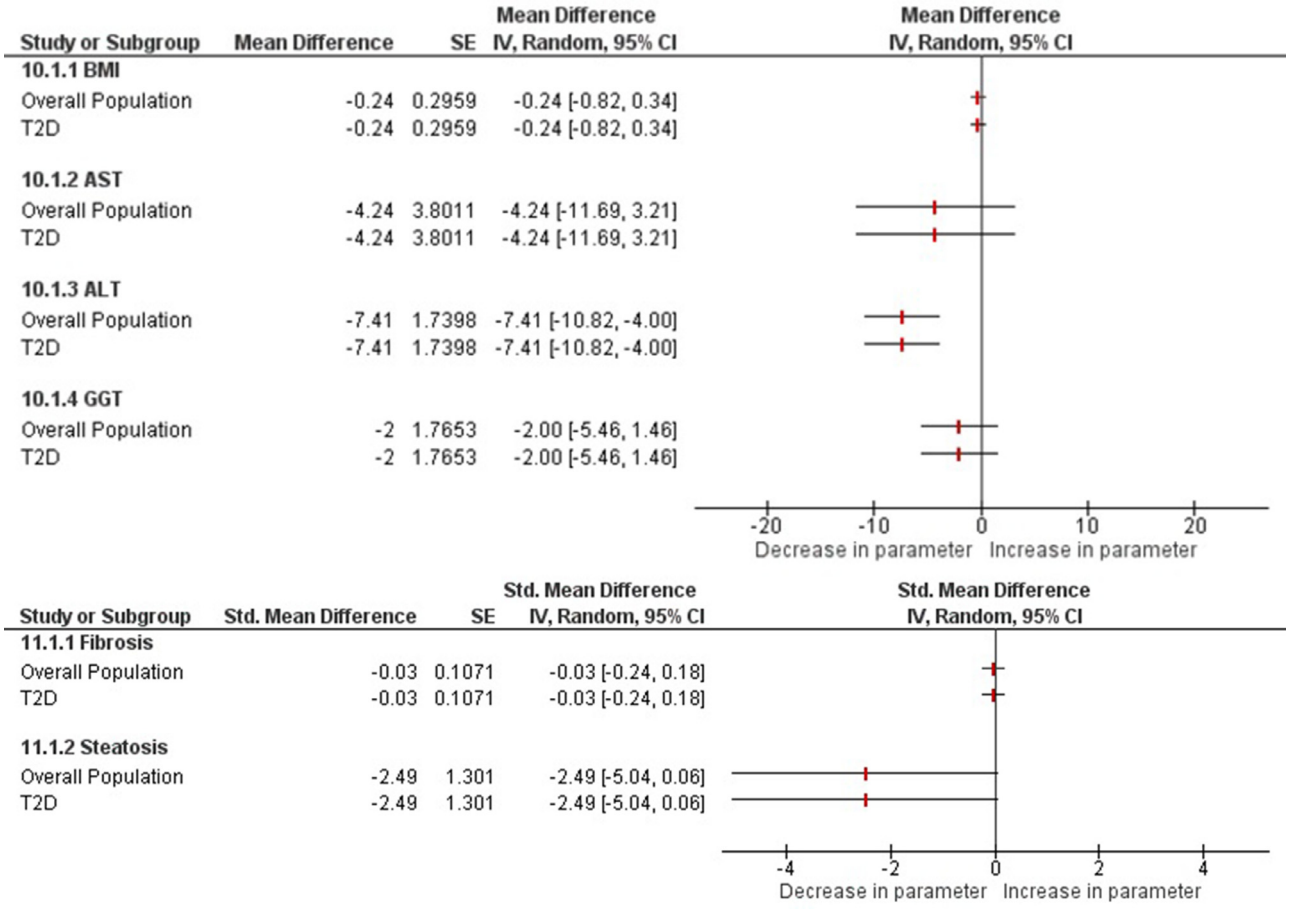

Fig. 3. Summarized Forest Plot detailing results for DPP-4 inhibitors.

Table 1
Effect of antidiabetic drugs in each subgroup of the NAFLD population.

	Pioglitazone		SGLT-2 inhibitors		DPP-4 inhibitors		GLP-1 agonists	
	Effect size [95% CI]	N	Effect size [95% CI]	N	Effect size [95% CI]	N	Effect size [95%CI]	N
DM population								
ALT	WMD: -29 [-43.03,-14.97]	150	WMD: -16.17 [-21.74,-10.59]	103	WMD: -7.41[-10.82,-4.00]	74	WMD: -27.98[-55.33,-0.64]	107
AST	WMD: -12.54 [-15.16,-9.91]	110	WMD: -7.09 [-17.03,2.86]	87	WMD: -4.24 [-11.69,3.21]	52	WMD: -20.23[-46.96,6.50]	107
GGT	WMD: -24.5 [-26.45,-22.55]	34	WMD: -19.31 [-21.13,-17.49]	87	WMD: -2 [-5.46,1.46]	25	WMD: -40.65[-77.52,-3.78]	78
FIBROSIS	SMD: -0.37 [-0.73,-0.00]	84	SMD: -0.07 [-0.33,0.19]	65	SMD: -0.03 [-0.24,0.19]	52	SMD: 0.02[0.00,0.04]	24
STEATOSIS	SMD: -1.1 [-1.74,-0.46]	50	SMD: -4.64 [-9.53,0.25]	153	SMD: -2.49 [-5.04,0.06]	52	SMD: -4.47[-9.26,0.32]	79
INFLAMMATION	NA	NA	NA	NA	NA	NA	SMD: -0.2[10.79,10.39]	26
BMI	WMD: 0.65 [-0.13,1.43]	76	WMD: -0.86 [-1.15,-0.56]	71	WMD: -0.24 [-0.82,0.34]	52	WMD: -1.66[-2.27,-1.04]	109
Non-DM population								
ALT	WMD: -43.51 [-53.81,-33.22]	219	NA	NA	NA	NA	NA	NA
AST	WMD: -20.74 [-26.16,-15.33]	222	NA	NA	NA	NA	NA	NA
GGT	WMD: -65.37 [-163.24,32.51]	117	NA	NA	NA	NA	NA	NA
FIBROSIS	SMD: -0.47 [-0.85,-0.08]	214	NA	NA	NA	NA	NA	NA
STEATOSIS	SMD: -0.99 [-1.27,-0.71]	182	NA	NA	NA	NA	SMD: -1.57[-2.47,-0.67]	48
INFLAMMATION	SMD: -0.78 [-1.08,-0.48]	214	NA	NA	NA	NA	NA	NA
BMI	WMD: 1 [0.35,1.65]	219	NA	NA	NA	NA	WMD: -1.9[-2.99,-0.81]	48
NASH population								
ALT	WMD: -41.35 [-49.80,-32.98]	295	NA	NA	NA	NA	WMD: -26.6[-63.13,9.93]	26
AST	WMD: -20.67 [-24.96,-16.38]	295	NA	NA	NA	NA	WMD: -15.8[-44.61,13.01]	26
GGT	WMD: -65.37 [-163.24,32.51]	117	NA	NA	NA	NA	WMD: -33.7[-58.30,-9.10]	26
FIBROSIS	NA	NA	NA	NA	NA	NA	NA	NA
STEATOSIS	NA	NA	NA	NA	NA	NA	NA	NA
INFLAMMATION	NA	NA	NA	NA	NA	NA	NA	NA
BMI	NA	NA	NA	NA	NA	NA	NA	NA

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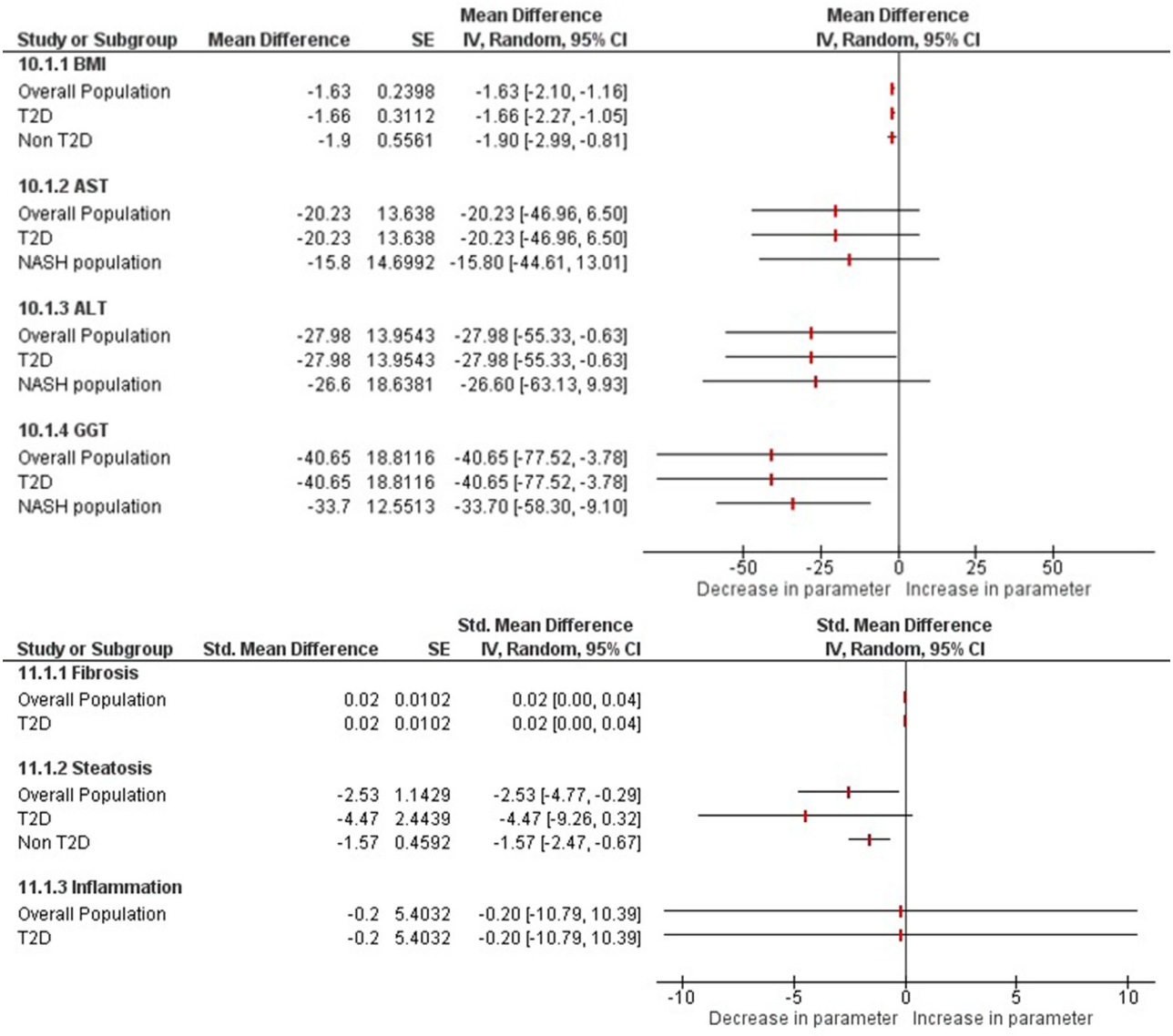

Fig. 4. Summarized Forest Plot detailing results for GLP-1 agonists.

significant improvement in the levels of ALT and GGT with GLP-1 analogs [18].

4.3. Changes in liver histology

Our study demonstrates significant improvements in liver steatosis, fibrosis and parenchymal inflammation with pioglitazone. Previous meta-analyses have also reported beneficial effects of pioglitazone on liver histology in patients with NAFLD [19–21]. Liver histology data were scarce for drug classes other than pioglitazone. Consistent with a previous study [22], GLP-1 analogs showed significant improvements in hepatic steatosis in our study. Evidence of improvements in liver fibrosis and parenchymal inflammation was not seen with GLP-1 agonists; however, current data in this area are very limited. SGLT-2 inhibitors and DPP-4 inhibitors demonstrated a trend towards reduced steatosis; but this result was non-significant. No evidence of improvement in liver fibrosis was seen with SGLT-2 inhibitors and DPP-4 inhibitors, and no studies reported data on parenchymal inflammation for these drugs. This entails the need to conduct high-quality, adequately powered RCTs of sufficient duration in the future, with endpoints pertaining to liver histology, particularly for the newer anti-diabetic agents.

4.4. Subgroup analysis

Sufficient evidence exists for the benefits of pioglitazone on liver enzymes and histology in diabetics as well as non-diabetics. Pioglitazone also demonstrated potential improvements in liver enzymes amongst patients with NASH; however, evidence regarding its effects on liver histology in this population is limited. GLP-1 agonists demonstrated improvements in steatosis amongst non-diabetic NAFLD patients, and possible improvements in liver enzyme levels in the NASH population; however, data on other markers are lacking. Currently, no data exists regarding the effects of SGLT-2 inhibitors and DPP-4 inhibitors amongst non-diabetic NAFLD patients and patients with NASH, and this knowledge gap needs to be filled by future trials.

5. Limitations

Our study has certain limitations that should be considered. Firstly, it is possible that concomitant use of other antidiabetics could have confounded our results. However, until placebo-controlled trials evaluating these drugs in NAFLD patients emerge, the current single-arm analysis can provide valuable early

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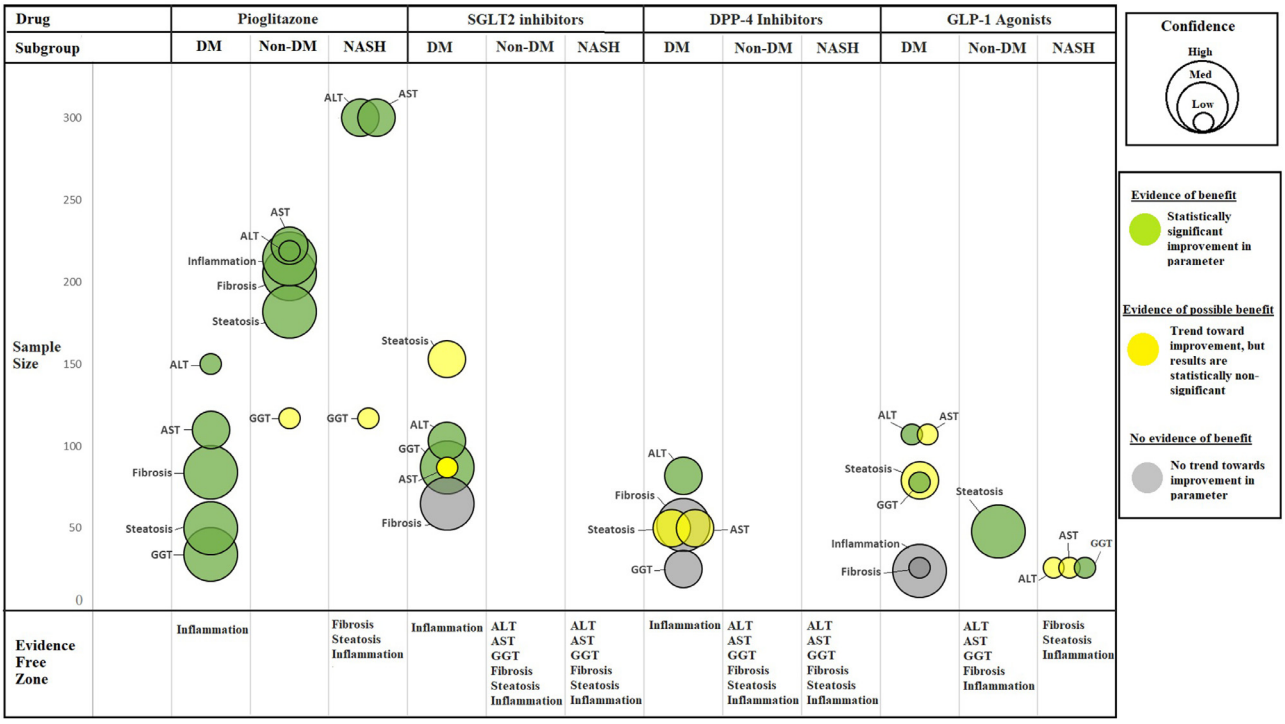

Fig. 5. Evidence map displaying the strength and certainty of evidence, and the evidence-free areas.

insight. Secondly, certain outcomes in our study had wide confidence intervals and high heterogeneity, indicating low reliability. This can be attributed to the fact that data for certain outcomes were available only from small-sized studies with varying results.

6. Conclusions

Pioglitazone demonstrates significant improvements in liver enzyme levels and liver histology in both diabetic and non-diabetic NAFLD patients. Currently, there are limited data on the usefulness of novel antidiabetics (SGLT-2 inhibitors, DPP-4 inhibitors, and GLP-1 agonists) in the treatment of NAFLD patients. Early evidence suggests possible improvements in liver enzymes and hepatic steatosis with these drug classes, and this should encourage further research into possible utility of these drugs in treating NAFLD.

Conflict of interest

The authors whose names are listed immediately below this declare no conflict of interest. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. All authors had access to the data and a role in writing the manuscript. All authors have reviewed the manuscript and approved it in its current form.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2020.08.021.

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