

## Original Article

# The efficacy of sitagliptin for non-alcoholic-fatty liver disease: a meta-analysis of randomized controlled trials

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**Abstract:** Introduction: The efficacy of sitagliptin for non-alcoholic fatty liver disease remains controversial. Therefore, this study was conducted as a systematic review and meta-analysis to explore the influence of sitagliptin versus placebo on the treatment of non-alcoholic fatty liver disease. Methods: PubMed, EMBASE, Web of Science, EBSCO, and Cochrane library databases were searched for dates through December 2018 for randomized controlled trials (RCTs) assessing the efficacy of sitagliptin versus placebo for non-alcoholic fatty liver disease. This meta-analysis is performed using the random-effect model. Results: Five RCTs involving 208 patients are included in the meta-analysis. Overall, compared with control group for non-alcoholic fatty liver disease, sitagliptin treatment has no substantially positive impact on NAS (Std. MD=-0.45; 95% CI=-1.0 to 0.1; P=0.11), steatosis (Std. MD=-0.40; 95% CI=-0.95 to 0.15; P=0.15), fibrosis (Std. MD=0.27; 95% CI=-0.28 to 0.81; P=0.34), ALT (Std. MD=0.19; 95% CI=-0.15 to 0.53; P=0.27), AST (Std. MD=0.35; 95% CI=-0.10 to 0.80; P=0.13), FBS (Std. MD=-1.77; 95% CI=-4.04 to 0.51; P=0.13), HOMA IR (Std. MD=0.03; 95% CI=-0.50 to 0.56; P=0.90), and LDL (Std. MD=0; 95% CI=-0.40 to 0.39; P=1.0). Conclusions: Sitagliptin treatment may produce no favorable efficacy for non-alcoholic fatty liver disease.

**Keywords:** Sitagliptin, non-alcoholic fatty liver disease, randomized controlled trials, meta-analysis

## Introduction

Nonalcoholic fatty liver disease is defined as the hepatic manifestation of a metabolic syndrome and has become an important common cause of liver disease [1-3]. These patients commonly occur in patients with type 2 diabetes mellitus which serves as a leading cause of chronic liver disease [4, 5]. Nonalcoholic steatohepatitis is the progressive form of nonalcoholic fatty liver disease and is characterized by hepatocellular damage, inflammation, and liver fibrosis that can progress to cirrhosis [6-8]. Type 2 diabetes mellitus can also increase the risk of developing cirrhosis, hepatocellular carcinoma, and double the death risk from liver cirrhosis [9]. Liver fat accumulation may result in simple triglyceride accumulation (steatosis), nonalcoholic steatohepatitis, cirrhosis, and even hepatocellular carcinoma [10].

Enzyme dipeptidyl peptidase 4 (DPP-4) shows widespread organ distribution throughout the

body and has pleiotropic effects via its peptidase activity [11, 12]. DPP-4 is associated with the development of various chronic liver diseases such as hepatitis C virus (HCV) infection, nonalcoholic fatty liver disease, and hepatocellular carcinoma. Hepatic DPP-4 expression in patients with nonalcoholic fatty liver disease may have direct relationship with hepatic lipogenesis and liver injury [13]. Sitagliptin is reported to inactivate the hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) released in response to meals through competitively inhibiting DPP-4. Blocking GLP-1 and GIP caused by sitagliptin can increase insulin secretion and suppress glucagon beneficial to lower blood glucose levels. Sitagliptin is reported to improve the features of liver histology in nonalcoholic fatty liver disease patients [14].

However, the benefit of sitagliptin versus placebo for nonalcoholic fatty liver disease has not been well established. Recently, several stud-

ies on the topic have been published, and the results have been conflicting [5, 13, 15, 16]. With accumulating evidence, here a systematic review and meta-analysis of RCTs was performed to explore the efficacy of sitagliptin versus placebo for nonalcoholic fatty liver disease.

## Materials and methods

Ethics approval and patient consent are not required because this is a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis are conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [17].

### Search strategy and study selection

Two investigators independently searched the following databases (inception to December 2018): PubMed, EMBASE, Web of science, EBSCO, and Cochrane library databases. The electronic search strategy is conducted using the following keywords: liver disease or steatohepatitis, and sitagliptin. Reference lists of the screened full-text studies were also checked to identify other potentially eligible trials.

The inclusive selection criteria are as follows: (i) population: patients with non-alcoholic fatty liver disease; (ii) intervention: sitagliptin; (iii) comparison: matched placebo; (iv) study design: RCT.

### Data extraction and outcome measures

The following information was extracted: author, number of patients, age, female, body mass index, diabetes/duration and detail methods in each group etc. Data was extracted independently by two investigators, and discrepancies are resolved by consensus. The corresponding author was also contacted to obtain data when necessary.

The primary outcomes are nonalcoholic fatty liver disease activity score (NAS), steatosis and fibrosis. Secondary outcomes include alanine aminotransferase (ALT), aspartate-aminotransferase (AST), fasting blood sugar (FBS), homeostatic model assessment insulin resistance (HOMA IR), and low density lipoprotein (LDL).

### Quality assessment in individual studies

Methodological quality of the included studies was independently evaluated using the modi-

fied Jadad scale [18]. There are 3 items for Jadad scale: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score  $\leq 2$  is considered to be of low quality. If the Jadad score  $\geq 3$ , the study is thought to be of high quality [19].

### Statistical analysis

The standard mean difference (Std. MD) with 95% confidence interval (CI) for continuous outcomes (NAS, steatosis, fibrosis, ALT, AST, FBS, HOMA IR, and LDL) was determined. A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the  $I^2$  statistic, and  $I^2 > 50\%$  indicates significant heterogeneity [20]. Whenever significant heterogeneity is present, potential sources of heterogeneity were searched via omitting one study in turn for the meta-analysis or performing subgroup analysis. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

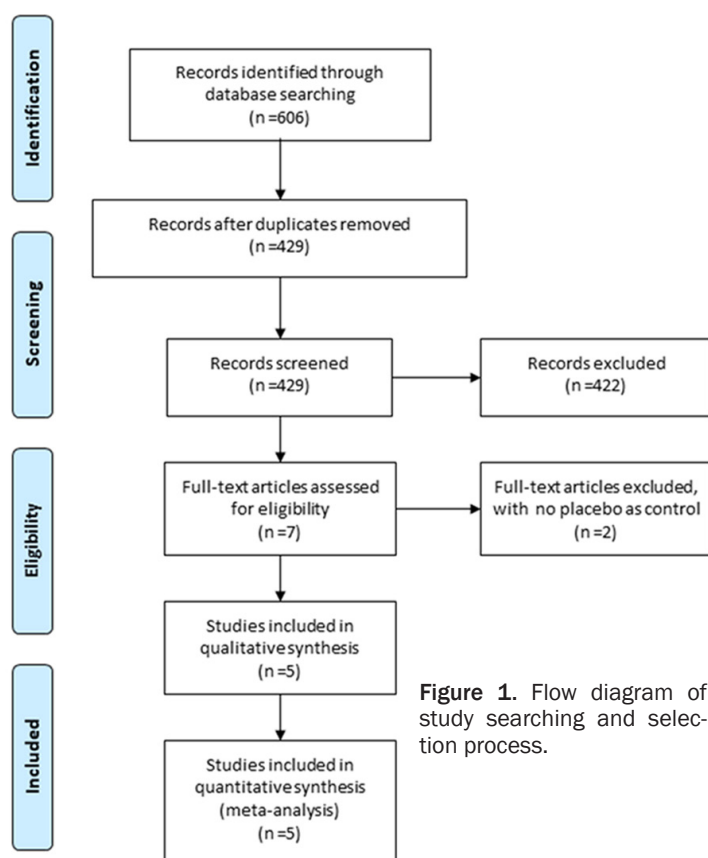
## Results

### Literature search, study characteristics and quality assessment

A detailed flowchart of the search and selection results is shown in **Figure 1**. 606 potentially relevant articles are identified initially. Finally, five RCTs that meet our inclusion criteria are included in the meta-analysis [5, 13, 15, 16, 21].

The baseline characteristics of the five eligible RCTs in the meta-analysis are summarized in **Table 1**. The five studies are published between 2016 and 2018, and sample sizes range from 12 to 72 with a total of 208. Three RCTs report all included patients with diabetes [5, 15, 16], while two RCTs report some of patients with diabetes [13, 21].

Among the five studies included here, two studies report NAS, steatosis, and fibrosis [13, 15], four studies report ALT and AST [5, 13, 15, 21], three studies report FBS [5, 13, 21], and three studies report HOMA IR, and LDL [13, 15, 21]. Jadad scores of the five included studies vary from 3 to 5, and all five studies are considered to be high-quality ones according to quality assessment.



**Figure 1.** Flow diagram of study searching and selection process.

#### Primary outcomes: NAS, steatosis, and fibrosis

These outcome data were analyzed with the random-effects model, and compared to control group for non-alcoholic fatty liver disease, sitagliptin treatment has no obvious effect on NAS (Std. MD=-0.45; 95% CI=-1.0 to 0.1;  $P=0.11$ ) with no heterogeneity among the studies ( $I^2=0\%$ , heterogeneity  $P=0.64$ ) (**Figure 2**), steatosis (Std. MD=-0.40; 95% CI=-0.95 to 0.15;  $P=0.15$ ) with no heterogeneity among the studies ( $I^2=0\%$ , heterogeneity  $P=0.70$ ) (**Figure 3**), and fibrosis (Std. MD=0.27; 95% CI=-0.28 to 0.81;  $P=0.34$ ) with no heterogeneity among the studies ( $I^2=0\%$ , heterogeneity  $P=0.87$ ) (**Figure 4**).

#### Sensitivity analysis

No heterogeneity was observed among the included studies for the primary outcomes, and thus sensitivity analysis was not performed via omitting one study in turn to detect heterogeneity.

#### Secondary outcomes

In comparison with control group for non-alcoholic fatty liver disease, sitagliptin treatment shows no substantial impact on ALT (Std. MD=0.19; 95% CI=-0.15 to 0.53;  $P=0.27$ ; **Figure 5**), AST (Std. MD=0.35; 95% CI=-0.10 to 0.80;  $P=0.13$ ; **Figure 6**), FBS (Std. MD=-1.77; 95% CI=-4.04 to 0.51;  $P=0.13$ ; **Figure 7**), HOMA IR (Std. MD=0.03; 95% CI=-0.50 to 0.56;  $P=0.90$ ; **Figure 8**), and LDL (Std. MD=0; 95% CI=-0.40 to 0.39;  $P=1.0$ ; **Figure 9**).

#### Discussion

Currently, there are no approved pharmacologic agents for the treatment of nonalcoholic fatty liver disease. Several anti-diabetic agents have been explored considering the importance of insulin resistance for non-alcoholic fatty liver disease, but the results are variable [14, 22, 23]. Sitagliptin is an oral antidiabetic agent through inhibiting DPP-4, and reduced DPP-4 levels result in reduced lipogenesis and decreased hepatic steatosis [24-26]. In the animal model of mice with non-alcoholic steatohepatitis, sitagliptin is revealed to improve lipid metabolism, attenuate the progression of hepatic fibrosis and decrease platelet aggregation in vitro [27, 28]. Sitagliptin is also found to improve serum ALT, AST, gamma glutamyl transferase levels, and reduce decreased hepatocyte ballooning and non-alcoholic steatohepatitis scores in patients with type diabetes and non-alcoholic steatohepatitis [29, 30].

However, in one RCT investigating 24 week of sitagliptin therapy in patients with non-alcoholic fatty liver disease, the results revealed no significant improvement in liver fat as measured by magnetic resonance imaging in patients with non-alcoholic fatty liver disease [21]. Another study confirmed no improvement in the histologic features of non-alcoholic steatohepatitis with sitagliptin in patients with histologically-proven non-alcoholic steatohepatitis [15].

# Sitagliptin for non-alcoholic fatty liver disease

**Table 1.** Characteristics of included studies

NO	Author	Sitagliptin group						Control group						Jada scores
		Number	Age (years)	Female (n)	Body mass index (kg/m <sup>2</sup> )	Diabetes (n)/ Duration (year)	Methods	Number	Age (years)	Female (n)	Body mass index (kg/m <sup>2</sup> )	Diabetes (n)/ Duration (year)	Methods	
1	Alam 2018	20	41.7±9.1	16	27.6±5.1	11/-	sitagliptin 100 mg once daily for 1 year	20	35.5±6.9	12	25.3±2.8	6/-	matched placebo	5
2	Joy 2017	6	56.7±9.9	3	35.9±6.6	6/6.5 (5.0, 23.0), median (Q1, Q3)	sitagliptin 100 mg daily for 24 weeks	6	54.7±9.8	4	37.4±4.7	6/6.0 (5.0, 6.0), median (Q1, Q3).	matched placebo	3
3	Deng 2017	36	63.7±10.7	8	-	36/-	sitagliptin at a dose of 50 mg and up to 100 mg if necessary once daily for 52 weeks	36	64.1±11.2	10	-	36/-	matched placebo	4
4	Smits 2016	17	61.5±1.7	3	31.4±1.1	17/8.5±1.5	sitagliptin 100 mg for 12 weeks	17	65.8±1.4	4	30.6±0.7	17/8.2±1.2	matched placebo	4
5	Cui 2016	25	52.9±11.9	12	31.9±5.4	12/-	sitagliptin orally 100 mg/day for 24 weeks	25	54.9±11.3	17	31.7±4.7	13/-	matched placebo	3

## Sitagliptin for non-alcoholic fatty liver disease

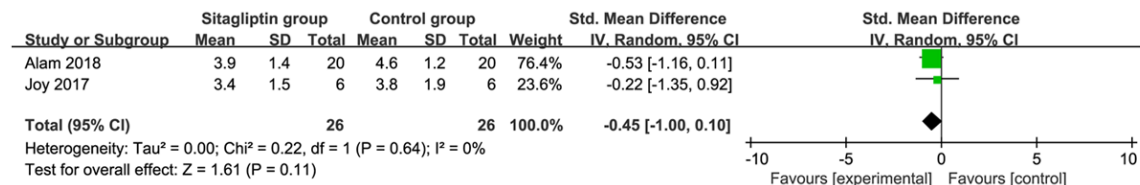


Figure 2. Forest plot for the meta-analysis of NAS.

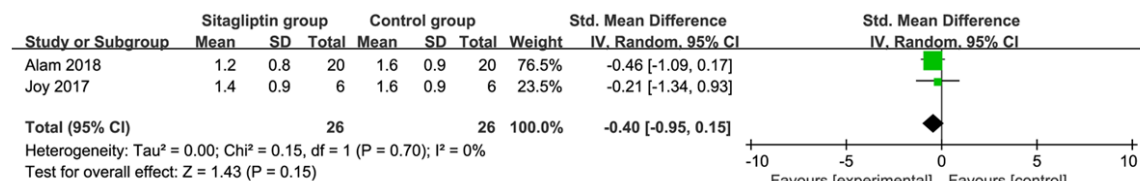


Figure 3. Forest plot for the meta-analysis of steatosis.

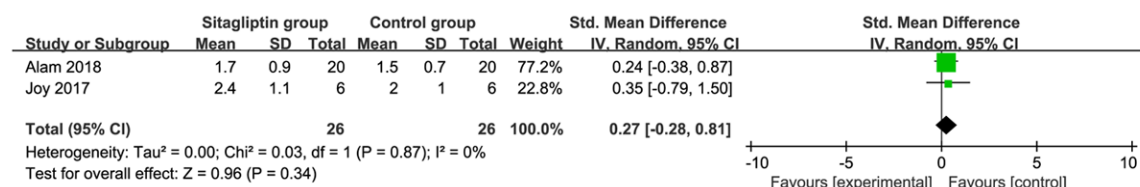


Figure 4. Forest plot for the meta-analysis of fibrosis.

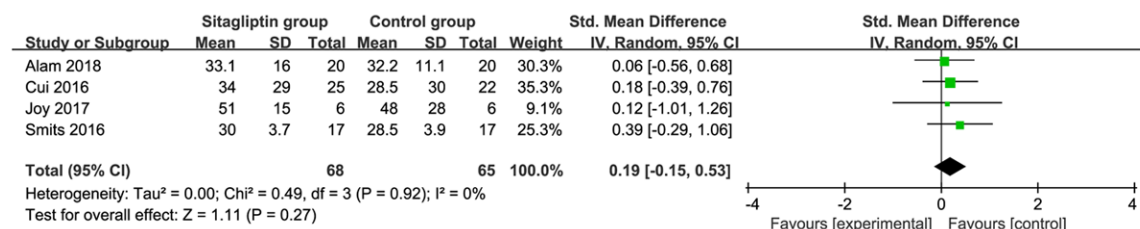


Figure 5. Forest plot for the meta-analysis of ALT (U/L).

This meta-analysis includes five RCTs and the results reveal no significantly favorable impact on NAS, steatosis, fibrosis, ALT, AST, FBS, HOMA IR, and LDL in patients with non-alcoholic fatty liver disease.

These results are consistent with a large RCT regarding the effects of another incretin-based antidiabetic agent, the GLP-1 analogue liraglutide, liraglutide treatment for 48 weeks find no improvements in fibrosis score, HOMA-IR, free fatty acids, or liver enzymes (apart from GGT) [31]. The addition of sitagliptin to patients with DM2 type 2 diabetes shows no substantial reduction in HbA1C [32]. One RCT demonstrates no improvement in visceral adipose tis-

sue or subcutaneous peripheral adipose tissue with sitagliptin treatment for patients with non-alcoholic steatohepatitis and type 2 diabetes [15]. These indicate that sitagliptin may have no remarkably positive impact on insulin resistance and non-alcoholic fatty liver disease.

This meta-analysis also has some important limitations. First, the analysis is based on five RCTs, and two of them have a relatively small sample size ( $n < 100$ ). Overestimation of the treatment effect was more likely in smaller trials compared with larger samples. Although there was no heterogeneity, sitagliptin treatment may produce variable impact in patients with the comorbidity of diabetes or not. Finally,

# Sitagliptin for non-alcoholic fatty liver disease

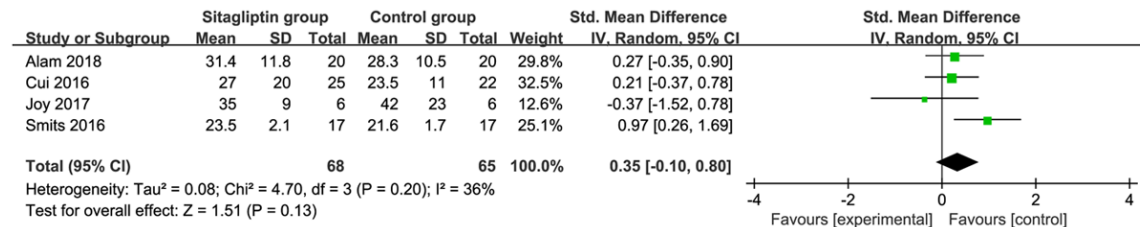


Figure 6. Forest plot for the meta-analysis of AST (U/L).

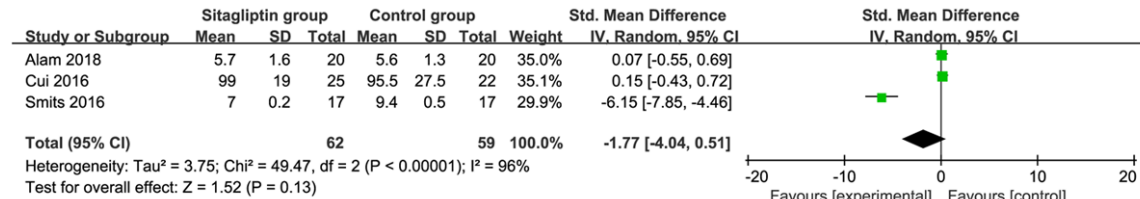


Figure 7. Forest plot for the meta-analysis of FBS (mmol/L).

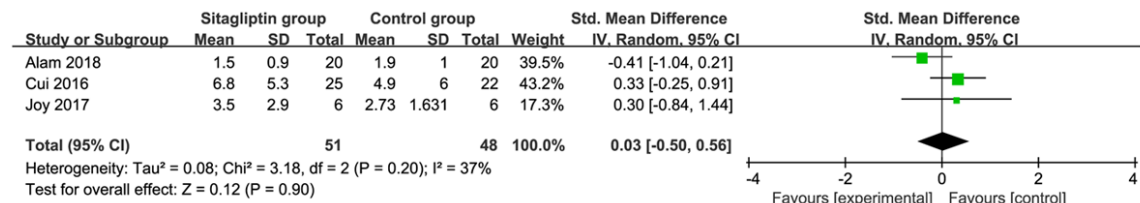


Figure 8. Forest plot for the meta-analysis of HOMA IR.

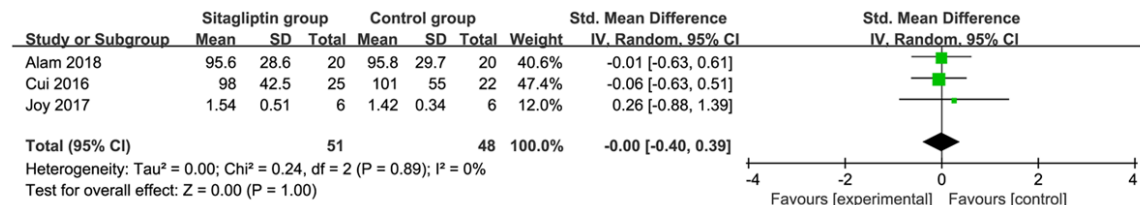


Figure 9. Forest plot for the meta-analysis of LDL.

treatment duration ranges from 12 weeks to 1 year, and the duration may be not sufficient to produce the positive results.

## Conclusions

Sitagliptin treatment may provide no additional benefits for non-alcoholic fatty liver disease.

## Disclosure of conflict of interest

None.

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