The therapeutic efficacy of fenofibrate in nonalcoholic fatty liver disease a meta-analysis of randomized controlled trials

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Research

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Abstract

Objective: To compare the efficacy of fenofibrate therapy in patients with nonalcoholic fatty liver disease (NAFLD) with meta-analysis of randomized controlled trials (RCTs).

Method: PubMed, the Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wang Fang Database and VIP were searched for clinical trials of fenofibrate therapy in treating patients with NAFLD. The latest search was conducted in December 1, 2020. The quality of included RCTs was assessed with the Cochrane risk of bias tool. The data was extracted and analyzed independently by two researchers. REVIEW MANAGER 5.3 was used to perform meta-analysis STATA 12.0 software was used to conduct publication bias and sensitivity analysis. And the evidence strength was evaluated with the GRADE approach.

Result: 12 RCTs with 1272 patients were included. The quality of RCTs was low. The results showed that fenofibrate significantly reduced blood lipid, decreased acute inflammatory damage of liver, and improved the degree of liver fibrosis, but had no effect on insulin resistance. Sensitivity analysis indicated consistent results and there was no significant publication bias. The evidence strength was low.

Conclusion: Although fenofibrate shown positive efficacy on blood lipids, liver function and liver fibrosis for patients with NAFLD, more RCTs with high quality are warranted for further evidence because of the low quality of included RCTs.

Introduction

Nonalcoholic fatty liver disease (NAFLD), the most common liver diseases in the world[1], is defined as the presence of steatosis without a history of excessive alcohol ingestion[2]. NAFLD incorporates a series of histological findings, From individual steatosis to steatosis with inflammation, necrosis, fibrosis or cirrhosis[3]. There are many factors relating to the pathogenesis of NAFLD[4], which includes excessive inappropriate dietary fat intake combined with peripheral insulin resistance, oxidative stress, and innate immunity[5]. NAFLD currently commonly used treatment methods are diet control, strengthening exercises and drug therapy, but because it often occurs with a variety of diseases, such as obesity, type 2 diabetes mellitus(T2DM), dyslipidemia, metabolic syndrome, and cardiovascular disease, which also causes the treatment of NAFLD to be very different. So far, Drugs applicable to all NAFLD patients are still the focus of research.

Fenofibrate, the first-line drugs for reducing blood lipids levels, can activate peroxisome proliferator-activated receptor alpha (PPARα) and produce a variety of biological effects, including controlling the transcription of genes, regulating lipid and glucose metabolism[8]. Studies have found that fenofibrate can improve insulin resistance, dyslipidemia and liver function in patients with NAFLD[10, 11]. However, some scholars have reported the opposite result in their research[12].

To further clarify the efficacy of fenofibrate in non-alcoholic fatty liver, We searched for published randomized controlled trials of fenofibrate in the treatment of NAFLD patients. The effect of fenofibrate in the treatment of NAFLD was evaluated by comparing the expression levels of serum markers related to blood lipids, liver function, liver fibrosis and insulin resistance in the fenofibrate treatment group and the control group.

Materials And Methods

Search strategy

PubMed, the Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wang Fang Database and VIP were searched in December 1, 2020 without language restriction. The relevant articles were searched using the following MeSH in PubMed: “fenofibrate”, “nonalcoholic fatty liver disease” and/or “NAFLD”, “randomized controlled trial or randomized controlled trials as topic”. We also searched manually the reference lists of eligible studies by hand to identify relevant RCTs.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) adult patients with NAFLD, (2) randomized controlled trials using fenofibrat, (3) data of outcome measures. The following studies were excluded: (1) duplicate studies, (2) animal or cell studies, case reports, reviews, conference abstracts, letters, (3) information could not be extracted and was not available.

Data extraction

Data was extracted independently by two authors (Yongyong Zhang and Ying Song) according to the inclusion and exclusion criteria listed above, which included the following: (1) author, publication year, country, sample size, duration, intervention, outcome measures; (2) outcome measures including blood lipid: TG (Triglyceride), TC (Total cholesterol), LDL (Low-density lipoprotein) and HDL (Hyperlipidemia), liver biochemistry: ALT (Alanine aminotransferase), AST (Aspartate transaminase) and GGT (γ-glutamyl transpeptidase), Liver Fibrosis: HA (Hyaluronicacid), LN (Laminin), PC (Procollagen Type) and CVI (Collagen Type IV), Insulin related indicators : Glucose, Regular insulin, ISI (Insulin sensitivity index)[13].

Quality assessment

The RCT methodology was evaluated according to the Cochrane Handbook for systematic review of interventions[14]. Risk of bias for assessing the methodological quality of RCTs mainly included six items: random sequence generation (selection bias), allocation concealment (selection bias), blind subjects and test personnel (implementation bias), blindness outcome evaluation (measurement bias), incomplete data (reporting bias), selection of publication (publication bias), and other bias.

Statistical analysis

We selected a random-effects model to perform the pairwise meta-analysis with REVIEW MANAGER 5.3 (Cochrane Collaboration, Copenhagen, Denmark), and STATA software, version 12.0 (Stata Corporation, TX, USA)s was used to conduct publication bias and sensitivity analysis. For each outcome measure, the treatment effect was presented as odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous outcome data and mean difference (MD) with 95% CIs for continuous outcome data. Study heterogeneity was assessed by the statistic of I-square (I^2). Sensitivity analysis was conducted to check the robustness and reliability of pooled outcome results. Publication bias was investigated with the funnel plot, Begg’s rank correlation test, and Egger’s regression test[15]. A p-value<0.05 was considered statistically significant.

Evidence strength with the GRADE approach

According to the GRADE approach[16], the evidence strength on each outcome measure was assessed as high, moderate, low, or very low. The initial evidence from RCTs was “high”, then was rated down according to five factors including high risk of bias, imprecision, inconsistency, indirectness, or publication bias.

Results

Identification of relevant RCTs

Our initial search yielded 872 studies. Among these, 226 of records were excluded from this meta-analysis for duplicate records. After screening the title and abstracts, 35 publications met the crude inclusion criteria and were selected for further assessment. Among them, 2 were excluded for non-human studies, 8 not randomized trials and 13 insufficient data. Finally, a total of 12 eligible RCTs[17-28] with 1272 patients were included for this meta-analysis. The detailed manuscript screening processes are shown in **Figure 1**.

Characteristics of the included studies

All RCTs were published between 2006 and 2020, the primary characteristics of them are described in **Table 1**. 10 RCTs were conducted in China, 1 in Iran and 1 in Greece. The maximum sample size is 180 in a RCT[23] and the minimum sample size is 60 in another RCT[17]. Four RCTs reported patients with diabetes mellitus and report the results (Glucose, insulin or ISI). Overall, all enrolled studies examined the effect of fenofibrate in the treatment of patients with NAFLD.

All trials had two parallel groups and were described as randomized, and allocation concealment was not reported in any of the Chinese studies. The detailed risk of bias, as assessed using the tool from the Cochrane Collaboration, is shown in **Figures 2 and 3**. The overall risk of bias of all included RCTs was high.

Meta-analysis results

All RCTs reported the data of lipids and 12 studies assessed TC and TG in NAFLD patients that treated with fenofibrate compared with control groups **(Figure 4)**. The result showed a statistically significant difference between the experimental and control groups (MD −0.65 and 95% CI [−0.93, −0.36] with P<0.00001 on TG mmol/L; MD −0.97 [−1.29, −0.66] with P<0.00001 on TC mmol/L). 6 RCTs analyzed HDL and LDL also showed significant difference between the experimental group and the control group (MD 0.22 and 95% CI [0.16, 0.29] with P<0.00001 on HDL mmol/L: MD -0.25 and 95% CI [-0.42, -0.09] with P=0.006 on LDL mmol/L).

11 RCTs reported on the effect of fenofibrate on improving liver function of patients, including lowering serum ALT, AST and r-GT **(Figure 5).** Fenofibrate had significant difference between the experimental group and control group (MD -7.67 and 95% CI [-12.93, -2.42] with P=0.004 on ALT U/L: MD -8.48 and 95% CI [-11.83, -5.13] with P<0.00001 on AST U/L: MD -11.73 and 95% CI [-18.90, -4.56] with P=0.001 on r-GT U/L)

5 RCTs provided sufficient data to compare the Serum liver fibrosis (HA, LN, PC□, CVI) of experimental group with control group **(Figure 6).** Results showed a significant decrease in the Serum liver fibrosis after the treatment with fenofibrate (MD -43.49 and 95% CI [-68.84, -18.13] with P=0.0008 on HA μg/L: MD -28.58 and 95% CI [-42.23, -14.94] with P<0.0001 on LN μg/L: MD -18.19 and 95% CI [-30.28, -6.10] with P=0.003 on PC□ μg /L: MD -2.10 and 95% CI [-3.75, -0.46] with P=0.01 on CIV μg /L)

4 RCTs reported the effect of fenofibrate on Insulin resistance (Glucose, Regular insulin, ISI) **(Figure 7).** Fenofibrate had no effect on Insulin resistance (MD -0.45 and 95% CI [-1.30, 0.41] with P=0.30 on Glucose mmol/L; MD -0.09 and 95% CI [-2.03, 1.86] with P=0.93 on insulin mu/L; MD 0.09 and 95% CI [-0.03, 0.20] with P=0.13 on ISI)

6 RCTs reported the total effective rate of fenofibrate treatment (**Figure 8)**. The evaluation criteria included relief or disappearance of clinical symptoms, Recovery of liver function and blood lipid levels, and B-ultrasound examination of liver morphology returning to normal or improving. The results revealed that fenofibrate has a significant effect for NAFLD patients compare with control groups (OR 3.32 and 95% CI [2.23, 4.93] with P < 0.00001)

Sensitivity analysis, publication bias, and evidence strength

Sensitivity analysis indicated consistent results. The funnel plot, Begg's rank correlation test, and Egger's regression test were performed for publication bias and there was no significant publication bias among the included RCTs (Table 2). The evidence strength of meta-analysis was low because of the high risk of bias of included RCTs and the significant heterogeneity.

Discussion

The metabolic syndrome, NAFLD commonly occurs in persons at all ages and become a global public health issues[29], and there is no registered drug for the treatment of NAFLD. Currently, people often advocate lifestyle intervention[30, 31], but it is difficult to maintain, so there is a kind of need to improve therapeutics for this condition. studies have shown the effect of fenofibrate reduceing liver enzyme levels, blood lipid levels and Serum liver fibrosis, improveing insulin resistance[32, 33]. However, no exact conclusion has been reached on the efficacy of various NAFLD treatments so far.

Our results reveal that patients in the treatment group shows a significant improvement after treatment with fenofibrate compare with patients in the control group, with a decrease in their blood lipid levels, a reduction in liver function impairment, and a degree of improvement in liver fibrosis, and the differences between the two groups were statistically significant. However, there was no improvement in insulin resistance in the treatment group, as opposed to previous reports.

All included articles analyzed the blood lipids of fenofibrate-treated NAFLD patients compared with the control group. First, fenofibrate is a drug that can regulate hexahydroglycerate lipids, which can block the production of TG and very low-density lipoprotein and promote its catabolism, thereby reducing the content of TC and TG. At the same time, fenofibrate also selectively activates peroxisome proliferator activated receptor (PPAR) alpha, improves mitochondrial energy metabolism, promotes beta-oxidation of fatty acids, and enhances the activity of lipoprotein metabolism enzymes, thereby promoting liver and plasma Lipolysis, reduce TG, TC, LDL and increase HDL levels. Secondly, our Meta-analysis showed that fenofibrate therapy significantly decreased ALT, AST, r-GT, which indicates that fenofibrate have the function of restoring liver damage and improving liver function. Liver fibrosis is a necessary process for the liver to develop into cirrhosis, which is mainly manifested by the excessive deposition of extracellular matrix (ECM) in liver cells. HA, LN, PC□ and CVI are the main components of ECM, which can reflect the progress of liver fibrosis. Our results show that compared with the control group, the fibrosis indicators LN, HA, PCIII and CIV of the treatment group were significantly reduced, which indicates that fenofibrate has the effect of improving liver function and reducing the degree of liver fibrosis. Some studies have confirmed that fenofibrate can improve insulin resistance and pancreatic β-cell function, but this is completely contrary to what we have studied. The most likely reason is that only four of the articles we consulted in the study involved insulin resistance and did not fully reflect the effect of fenofibrate on insulin resistance. Our meta-analysis confirmed the role of fenofibrate in the treatment of non-alcoholic fatty liver, and provided a basis for clinical treatment, but we still need to be cautious in the treatment of diabetes.

The limitations of this study should be mentioned. Most authors did not provide adequate information of the handler or allocation hiding, or blinding method. The sample size for inclusion in the study is also relatively small, which may influence the credibility of the assessment.

Conclusion

Although fenofibrate shown positive efficacy on blood lipids, liver function and liver fibrosis for patients with NAFLD, more RCTs with high quality are warranted for further evidence because of the low quality of included RCTs.

List Of Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate transaminase
CIs	Confidence intervals
CVI	Collagen Type IV
GGT	γ-glutamyl transpeptidase
HA	Hyaluronicacid
HDL	Hyperlipidemia
I^2	I-square
ISI	Insulin sensitivity index
LDL	Low-density lipoprotein
LN	Laminin
MD	Mean difference
NAFLD	Nonalcoholic fatty liver disease
ORs	Odds ratios
PC	Procollagen Type
PPARα	Peroxisome proliferator-activated receptor alpha
RCTs	Randomized controlled trials
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglyceride

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

Not applicable.

Availability of data and materials

The data of included RCTs and meta-analysis used to support the findings of this study is available from the corresponding author upon request.

Competing interests

All authors declare that there is no conflict of interest.

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Authors' contributions

SQL and YYZ designed the review protocol. PW and PXJ carried out the literature search. YYZ and YS contributed to data extraction and quality assessment. YYZ and YLJ conducted data analysis. JTL and YLJ provided statistical supports for meta-analysis. YYZ drafted the manuscript. SQL and YLJ revised the manuscript. All authors read and approved the final manuscript.

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Not applicable.

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Tables

Table 1: Characteristics of eligible RCTs

RCT	Year	Country	Sample size		Intervention	Control	Follow-up (week)	With diabetes	Outcomes
			T(M/F)	(M/F)					
Malek	2017	Iran.	30	30	Fn	Exercise	12	Unknow	1,2,4,5,12
Vasilios	2006	Greece	61	63	At +Fn	At	54	Unknow	1,2,3,4,5,6,7,12
Ruan	2018	China	44(26/18)	43(24/19)	PPC + Fn	PPC	12	Yes	4,5,8,9,10
Liu	2017	China	49	49	Fn	placebo	8	Yes	1,2,4,5,8,9,10,11
Ma	2017	China	37(28/9)	31(23/8)	PPC + Fn	PPC	4	Unknow	1,2,3,4,5,
Huang	2012	China	45(29/16)	41(23/18)	Fn	PPC	12	Unknow	1,2,4,5,6,7,
Zhang	2014	China	90(58/32)	90(53/37)	Fn	placebo	12	Yes	1,2,3,4,5,6,7,8,9,10,11,12,13,14
Liu	2013	China	48(38/10)	47(35/12)	Fn	placebo	8	Yes	1,2,3,4,5,6,7,8,9,10,11,12,13,14
Zhang	2020	China	50	50	DNP+ Fn	DNP	12	Unknow	1,2,3,4,5,6,7,8,9,10
Zhuang	2019	China	86	70	bicyclol+ Fn	bicyclol	12	Unknow	1,2,4,5,
Zhuang	2010	China	76	66	Fn	PPC	12	Unknow	1,2,3,4,5,7
Deng	2013	China	38	38	Fn	TPE	12	Unknow	1,2,4,5,6,7

T: treatment, C: control, PPC: PolyenePhosphatidylcholine Capsules, DNP: Danning Tablet, Fn: Fenofibrate, At: Atorvastatin, TPE: Tiopronin Enteric-coated Tablets

1:AST, 2:ALT, 3:r-GT, 4:TC, 5:TG, 6:HDL, 7:LDL, 8:PC, 9:LN, 10:HA, 11:CVI, 12:Glucose, 13:insulin, 14:ISI

Table 2: Publication bias analysis with Begg's test and Egger’s test

Outcome	No. of RCTs	Begg's test		Egger's test	
		z	P-value	t	P-value
TC	12	1.44	0.150	-1.80	0.103
TG	12	1.58	0.115	-1.40	0.191
HDL	6	0.38	0.707	-0.21	0.845
LDL	7	1.20	0.230	-1.27	0.261
AST	11	0.00	1.000	-0.11	0.912
ALT	11	0.31	0.755	0.11	0.916
r-GT	6	1.13	0.260	-1.18	0.305
HA	5	1.71	0.086	-2.46	0.091
LN	5	1.71	0.086	-1.83	0.164
PC	5	2.20	0.027	-2.97	0.059
CIV	3	0.00	1.000	-0.51	0.698
Glucose	4	0.34	0.734	-0.09	0.937
insulin	2	0.00	1.000	NA	NA
ISI	2	0.00	1.000	NA	NA
total effective rate	6	1.50	0.133	1.77	0.152

NA, not available.

Figures

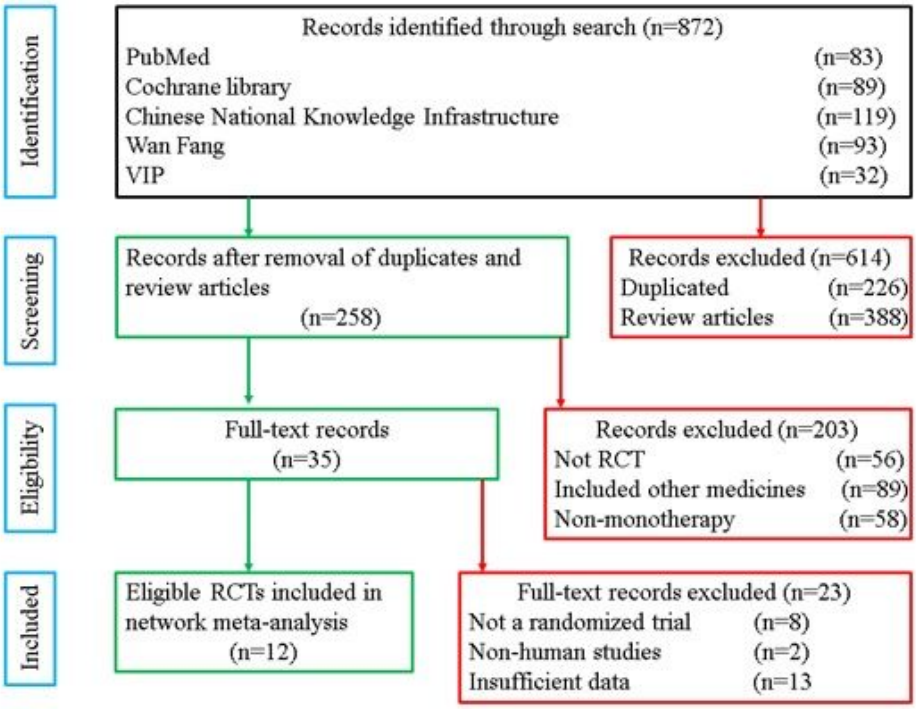

Figure 1

Flow chart of study selection process.

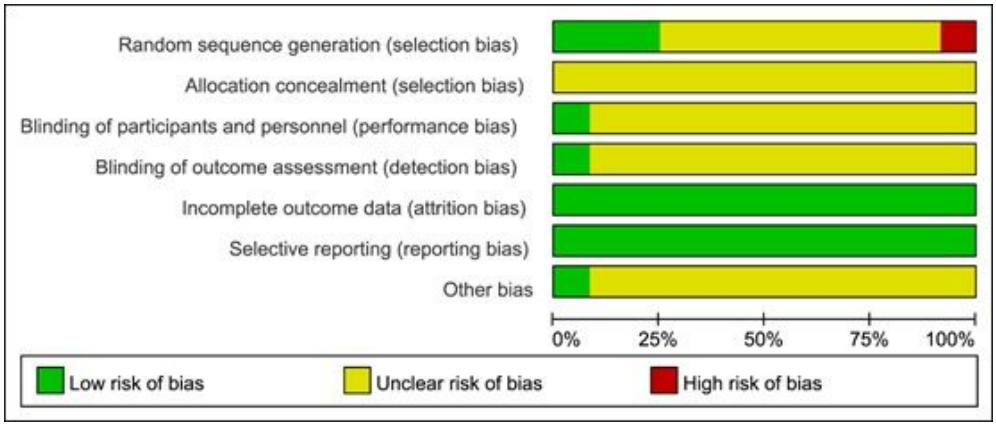

Figure 2

Overall risk of bias of all included RCTs.

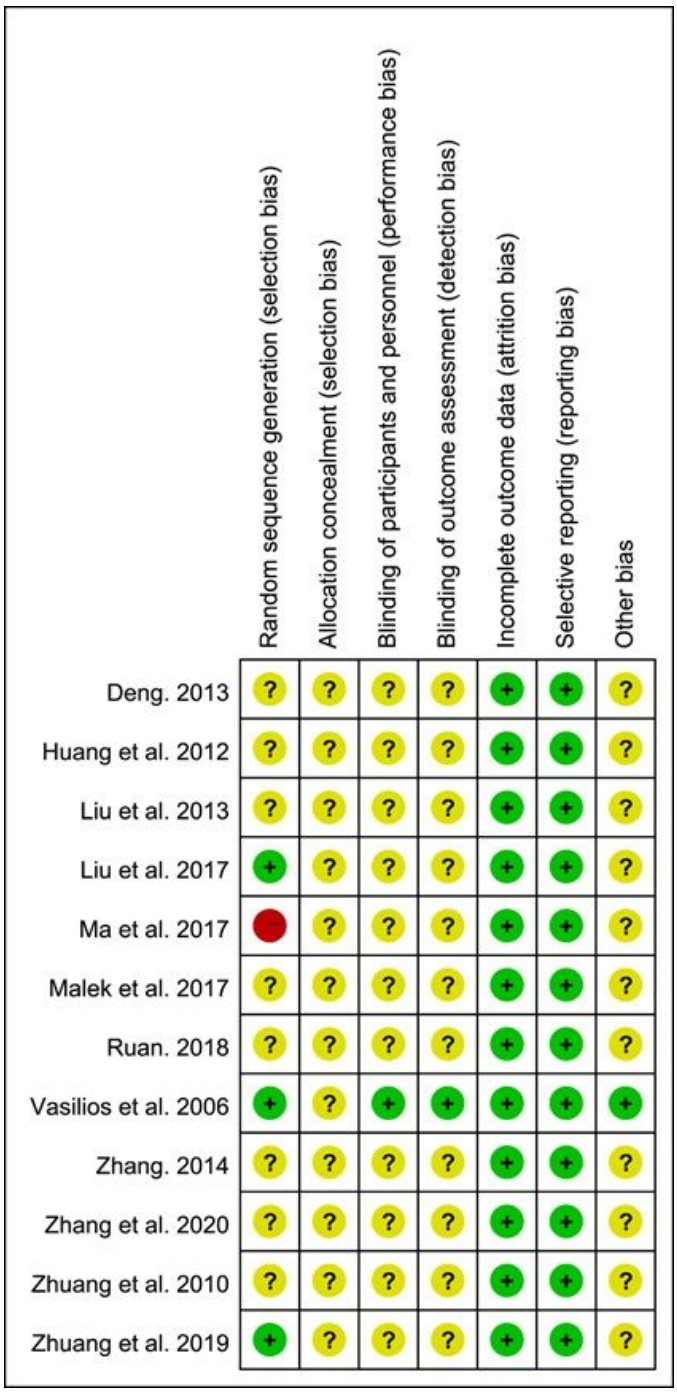

Figure 3

Risk of bias of each included RCT.

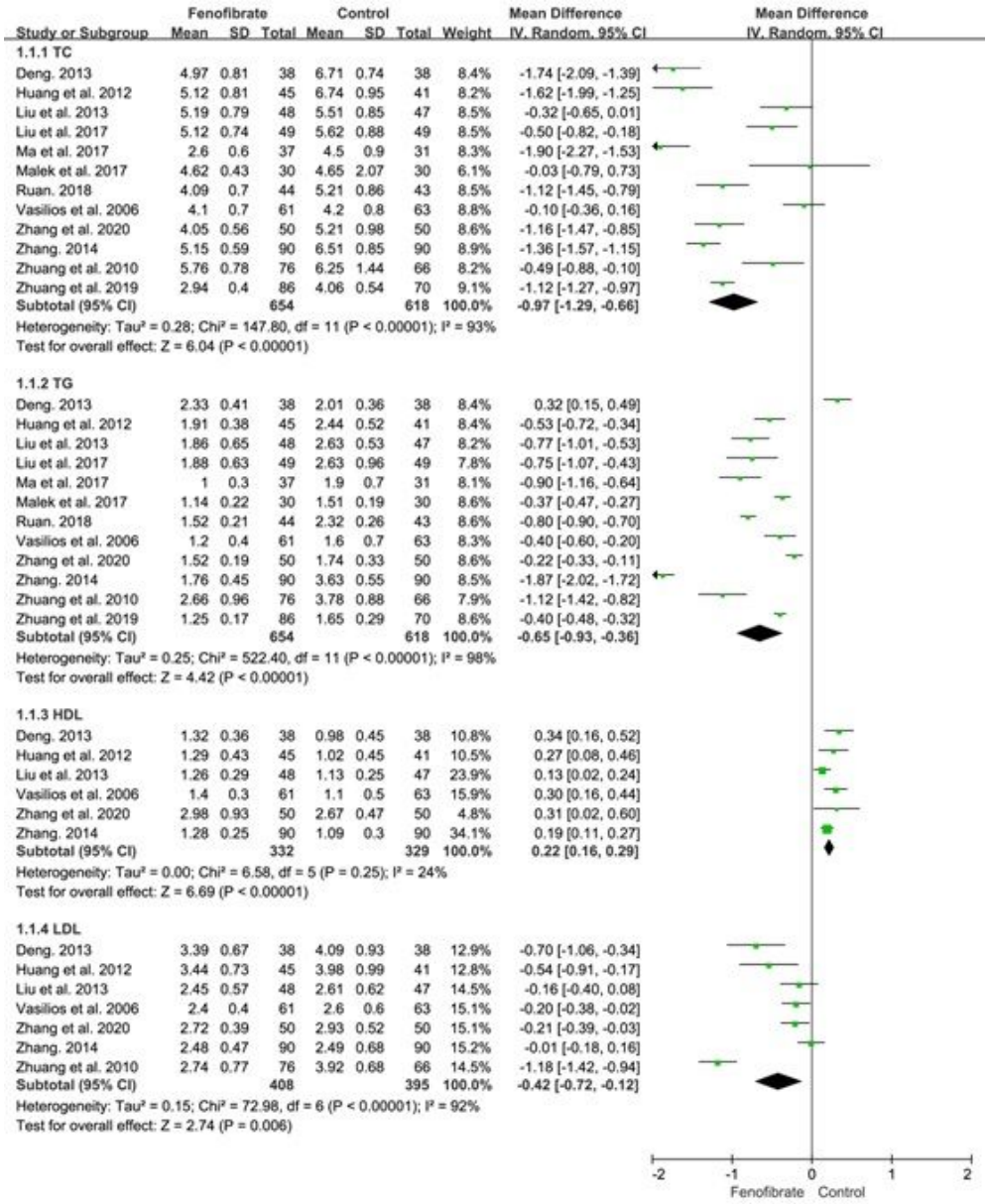

Figure 4

Forest plot in terms of the blood lipid levels of patients.

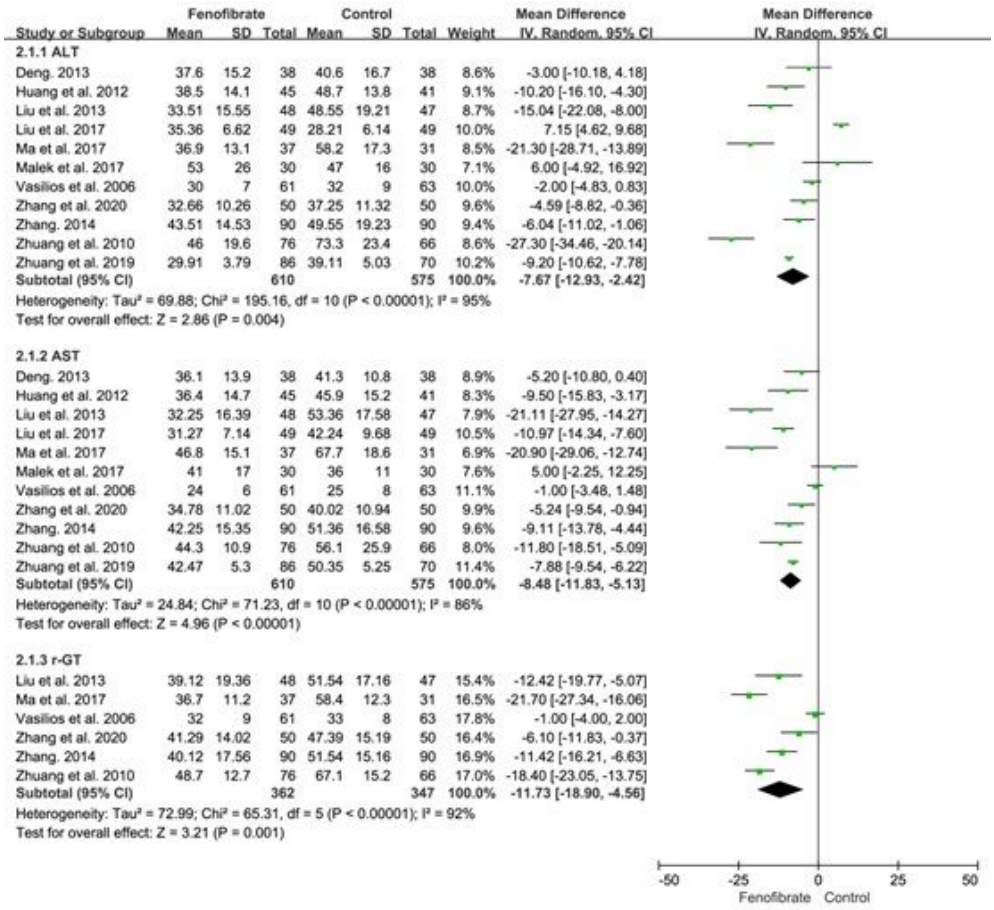

Figure 5

Forest plot in terms of the liver function of patients

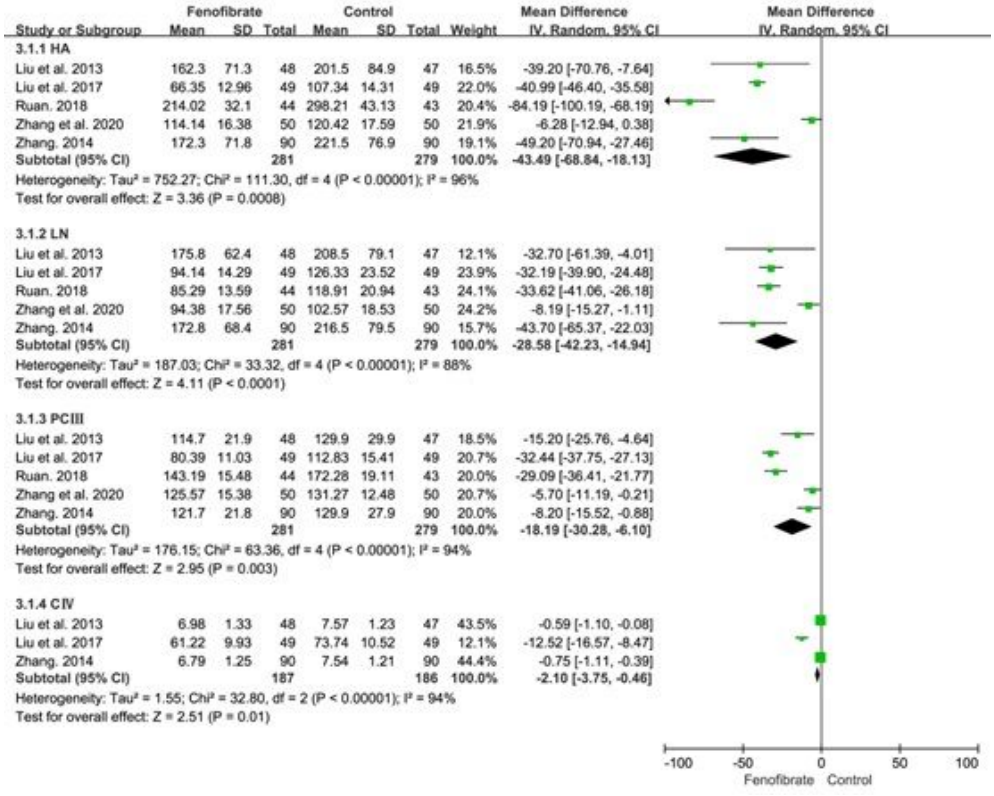

Figure 6

Forest plot in terms of the liver fibrosis of patients

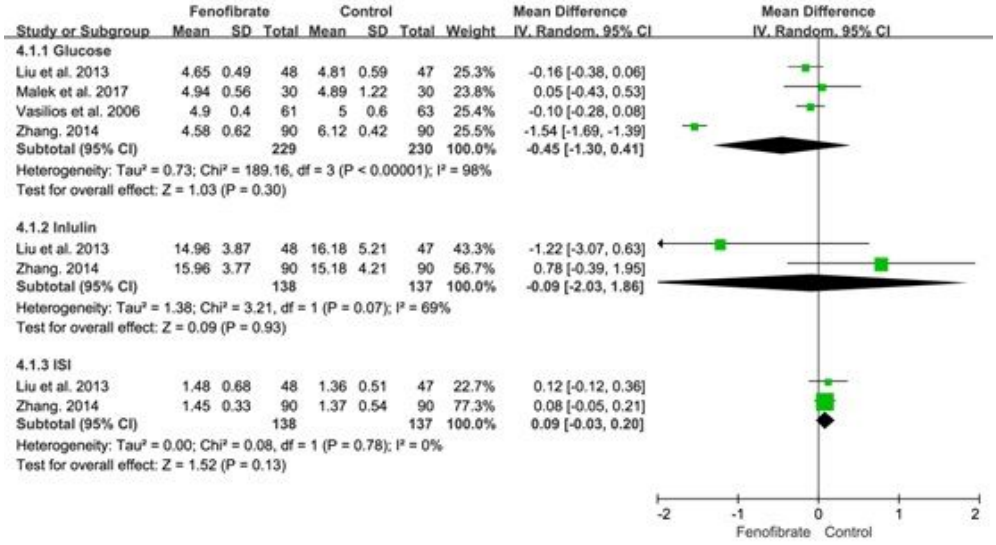

Figure 7

Forest plot in terms of the insulin related indicators of patients

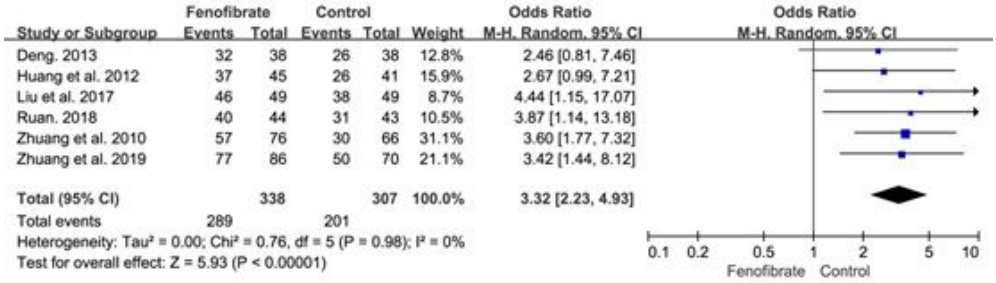

Figure 8

Forest plot in terms of the total effective rate of patients