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META-ANALYSIS

Effects of pentoxifylline on nonalcoholic fatty liver disease: A meta-analysis

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Abstract

AIM: To evaluate the effects of pentoxifylline therapy in patients with nonalcoholic fatty liver disease (NAFLD).

METHODS: We searched PubMed, Medline, Google Scholar, Embase, Web of Science, the Cochrane Library and the Chinese Biomedicine Database for all relevant controlled trials of pentoxifylline in patients with NAFLD from 1997 to July 2013. Five studies (3 randomized, double-blind, placebo-controlled trials and 2 prospective cohort studies with concurrent controls) were included in this meta-analysis. Statistical analysis was performed using RevMan 5.0 software.

RESULTS: Five randomized trials of 147 patients with NAFLD/nonalcoholic steatohepatitis (NASH) were included. The results showed that compared to placebo, pentoxifylline therapy resulted in a significant decrease in body weight (P = 0.04), alanine aminotransferase (P < 0.00001), aspartate transaminase (P = 0.0006), glucose (P = 0.0008) and tumor necrosis factor-α (P = 0.007), but did not significantly affect body mass index (P = 0.28), total cholesterol (P = 0.80), triglyceride (P = 0.98), alkaline phosphatase (P = 0.29), γ-glutamyl transferase (P = 0.39) and interleukin-6 (P = 0.38). With regard to histological changes, pentoxifylline only reduced the NAFLD activity score (P < 0.00001) and improved lobular inflammation (P < 0.0001). Improvements in steatosis grade (P = 0.11), ballooning (P = 0.10) and fibrosis (P = 0.50) were not obvious.

CONCLUSION: Pentoxifylline therapy results in weight loss, improved liver function and histological changes in patients with NAFLD/NASH. Therefore, pentoxifylline may be a new treatment option for NAFLD.

Key words: Pentoxifylline; Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Meta-analysis

Core tip: Recently, more researchers have been attempting to identify new treatments for nonalcoholic fatty liver disease (NAFLD), however, no firm conclusions have been reached. Thus, it is necessary to conduct a meta-analysis to assess the efficacy of pentoxifylline. Our analysis showed that pentoxifylline therapy significantly decreased body weight, alanine aminotransferase, aspartate transaminase, glucose and tumor necrosis factor-α. Pentoxifylline also reduced the NAFLD activity score and improved lobular inflammation in NAFLD patients.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a condition of fat accumulation in the liver in the absence of excessive alcohol consumption and any other specific causes of hepatic steatosis[1]. The histological pattern of NAFLD can progress into nonalcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and more rarely, liver carcinoma[2]. NAFLD is now one of the most common liver diseases worldwide. Approximately 20%-30% of patients with NAFLD have histological signs of NASH. The metabolic steps and underlying mechanisms of disease progression remain complex and poorly understood. Diet and lifestyle changes are primary therapies in the management of these patients. For many decades, studies have been aimed at discovering new treatments for NAFLD and many specific treatment strategies have been proposed, such as insulin-sensitizers[3-5], lipid-lowering drugs[6,7], antioxidants[8,9], endocannabinoid receptor antagonists[10], L-carnitine[11] and probiotics[12-14]. However, the current best treatment for the disease is unknown and most of the above treatments are not guideline therapies for NAFLD, because few randomized controlled studies are available. Recently, more attention has been paid to therapeutic strategies that influence the necroinflammatory activity in NAFLD.

Pentoxifylline is a methylxanthine derivative with potent hemorrheologic properties[15] and is commonly used in the treatment of intermittent claudication in western countries[16], based on its effects in enhancing red blood cell flexibility, decreasing blood viscosity, and enhancing aerobic glycolysis and oxygen consumption in ischemic tissues[17]. Furthermore, human and animal studies have shown that pentoxifylline, as a nonspecific phosphodiesterase inhibitor, results in a variety of physiological changes at the cellular level, increases levels of cyclic AMP and decreases tumor necrosis factor (TNF)-α gene transcription[18-20], affecting multiple steps in the cytokine/chemokine pathway. Increased serum TNF-α has been reported in humans and animal models of NAFLD[21,22] and may be important in treating NAFLD.

Therefore, in the present study, we conducted a meta-analysis of pooled data from studies to assess the effects of pentoxifylline on liver function, cytokines and liver histopathology.

MATERIALS AND METHODS

Search strategy

We searched Pubmed, Medline, Google Scholar, Embase, Web of Science, Chinese Biomedicine Database, and the China Journal Full Text Database with no language restriction. The search terms included: (NASH or NAFLD or nonalcoholic steatohepatitis or nonalcoholic fatty liver disease or fatty liver or steatosis) and (pentoxifylline or oxpentifylline or PTX or POF) and (Fatty Liver [MeSH]) AND Pentoxifylline [MeSH]. We also searched the reference lists of each selected study by hand.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) adult patients of any sex or ethnic origin with NAFLD/NASH; (2) randomized controlled trials or prospective cohort studies using pentoxifylline; and (3) diagnosis of NASH determined by histology or ultrasonography. Patients with other causes of hepatic steatosis or steatofibrosis, such as alcoholic fatty liver disease, viral hepatitis, autoimmune hepatitis, liver decompensation or malignancy were excluded. The trials should have at least one of the following characteristics: BMI, body weight, alanine aminotransferase (ALT), aspartate transaminase (AST), total cholesterol (TC), triglyceride (TG), alkaline phosphatase (AKP), glucose, TNF-α, interleukin (IL)-6 and histology changes. Studies must have objective outcome measures otherwise they were excluded from this review.

Data extraction and methodological quality

Data were extracted independently by four reviewers and included the following: author, publication year, study sign, population, intervention, duration, outcome, and others. Disagreement was resolved by discussion. Agreement between investigators for selection of studies for the meta-analysis was > 95%. All reviewers assessed the quality of the studies. The randomized controlled trials (RCTs) were all high-quality studies, and were scored using the Jadad scale. Prospective cohort studies were regarded as moderate-quality studies.

Statistical analysis

We analyzed the data using Review Manager 5.0. Dichotomous data were presented as OR with 95%CIs. Statistical heterogeneity was measured using the χ^2 test and the inconsistency index (I^2). $P < 0.05$ was considered to indicate statistically significant heterogeneity. If there was obvious heterogeneity, the random effects model was chosen; otherwise, the fixed effects model was adopted.

RESULTS

We initially identified 183 relevant items in PubMed, Medline, Google Scholar, Embase, Web of Science, Chinese Biomedicine Database and China Journal Full Text Database. Publication dates ranged from 1997 to June 2013. After reviewing each publication, we selected five original studies that met the selection criteria. A flow chart is shown in Figure 1.

Table 1 shows the specific information on study design, methodological quality, sample size, intervention, control method, and duration of treatment and follow-up. Two of the included studies were prospective cohort studies with a concurrent control and the other three were RCTs. All the RCTs were double-blinded and included a follow-up period. All the studies gave detailed baseline information. Three studies used placebo as a control and two studies used ursodeoxycholic acid (UDCA): placebo (68.7%) *vs* UDCA (31.3%). The main characteristics of the patients included in the two groups

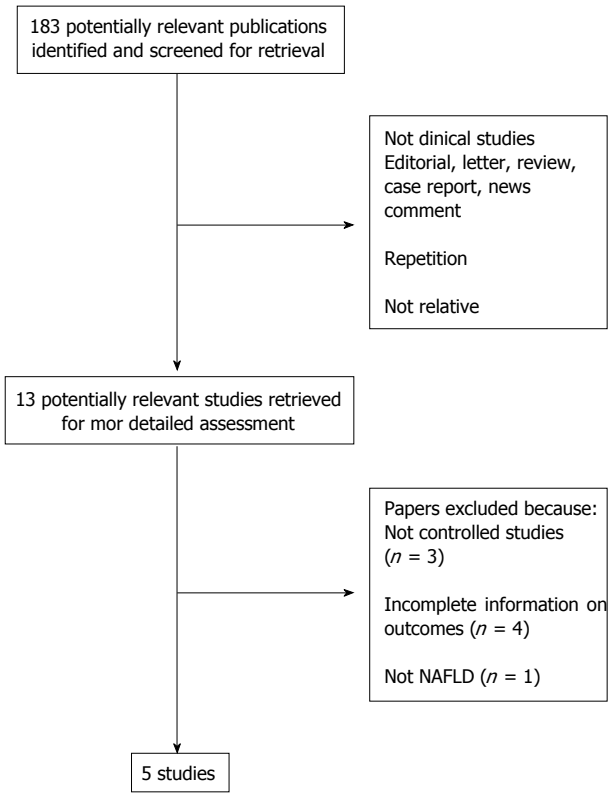


Figure 1 Selection of studies.

were well matched in all studies.

Two studies[23,25] evaluated changes in BMI after pentoxifylline treatment or placebo and showed no significant difference [weighted mean difference (WMD) 1.43, 95%CI: -1.19 to 4.05, $P = 0.28$]. The included studies were homogeneous ($I^2 = 0\%$, $P = 0.32$, Figure 2A).

Two studies[23,27] assessed the reduction of body weight in the experimental group and control group. The results showed a statistically significant difference between the experimental and control groups (WMD: -1.1, 95%CI: -2.16 to -0.05, $P = 0.04$). The included studies were homogeneous ($I^2 = 0\%$, $P = 0.44$) (Figure 2A).

Four studies[23-25,27] reported the effect of pentoxifylline on serum ALT reduction, however, compared with the control group, this reduction was not significantly different in the experimental group (WMD: -7.16, 95%CI: -19.67 to 5.34, $P = 0.26$). Significant heterogeneity among the studies was observed ($I^2 = 64\%$, $P = 0.04$, Figure 2B). Subgroup analyses were performed in order to evaluate the effect of the different controls. Two studies used placebo as the control and pentoxifylline was found to have a significantly better effect on reducing ALT (WMD: -13.64, 95%CI: -19.61 to -7.66, $P < 0.00001$). The studies were homogeneous ($I^2 = 0\%$, $P = 0.42$, Figure 2B). The other two studies used UDCA and the data were not significantly different (WMD: 7.51, 95%CI: -19.36 to 34.38, $P = 0.58$). The studies were homogeneous ($I^2 = 49\%$, $P = 0.58$, Figure 2B).

Three studies[23,24,27] assessed the effect of pentoxifylline on the level of serum AST and showed a significant difference in the treated group compared with the placebo group (WMD: -9.70, 95%CI: -15.24 to -4.16, $P = 0.0006$). The included studies were homogeneous ($I^2 = 0\%$, $P = 0.66$, Figure 2B).

Three studies[23-25] analyzed TC and TG in NAFLD/NASH patients treated with pentoxifylline compared with placebo, and two studies analyzed AKP and γ-glutamyl transferase (GGT). Pentoxifylline had no effect on normalizing TC (WMD: 0.26, 95%CI: -0.30 to 0.83, $P = 0.36$); TG (WMD: -0.07, 95%CI: -0.47 to 0.33, $P = 0.73$); AKP (WMD: -20.87, 95%CI: -59.33 to 17.59, $P = 0.29$); and GGT (WMD: -5.2, 95%CI: -17.05 to 6.64, $P = 0.39$). The included studies in all four analyses were homogeneous (TC: $I^2 = 0\%$, $P = 0.42$; TG: $I^2 = 0\%$, $P = 0.49$; AKP: $I^2 = 0\%$, $P = 0.96$; GGT: $I^2 = 0\%$, $P = 0.81$) (Figure 2B).

Three studies[24,25,27] reported the effect of pentoxifylline on serum glucose. Pentoxifylline had a significantly better effect on decreasing serum glucose (WMD: -8.27, 95%CI: -14.28 to -2.25, $P = 0.007$). The included studies were all homogeneous ($I^2 = 55\%$, $P = 0.11$) (Figure 2B).

Four[23,24,26,27] and three[23,24,27] studies, respectively, analyzed the cytokines: TNF-α and IL-6. Pentoxifylline significantly reduced TNF-α (WMD: -0.66, 95%CI: -1.14 to -0.18, $P = 0.007$) but not IL-6 (WMD: 1.35, 95%CI: -5.75 to 8.44, $P = 0.71$). Homogeneity among the studies was observed for TNF-α, but not for IL-6 (TNF-α: $I^2 = 11\%$, $P = 0.34$; IL-6: $I^2 = 69\%$, $P = 0.04$) (Figure 2C).

Three studies[25-27] provided sufficient data to compare the effects of pentoxifylline with placebo and showed a significant decrease in the NAFLD activity score (NAS) after treatment with pentoxifylline (WMD: -1.16, 95%CI: -1.51 to -0.81, $P < 0.00001$). Homogeneity among studies was observed ($I^2 = 10\%$, $P = 0.33$, Figure 2D).

Two studies[26,27] evaluated steatosis grade, lobular inflammation, ballooning and fibrosis before and after treatment. A significant improvement in lobular inflammation and ballooning was observed after treatment with pentoxifylline compared with placebo (steatosis grade: WMD: -0.49, 95%CI: -1.09 to 0.11, $P = 0.11$; lobular inflammation: WMD: -0.43, 95%CI: -0.64 to -0.23, $P < 0.0001$; ballooning: WMD: -0.32, 95%CI: -0.71 to 0.06, $P = 0.10$; fibrosis: WMD: -0.24, 95%CI: -0.92 to 0.45, $P = 0.50$). Significant heterogeneity was observed, with the exception of lobular inflammation (steatosis grade: $I^2 = 88\%$, $P = 0.004$; lobular inflammation: $I^2 = 0\%$, $P = 0.58$; ballooning: $I^2 = 78\%$, $P = 0.03$; Fibrosis: $I^2 = 85\%$, $P = 0.01$) (Figure 2D).

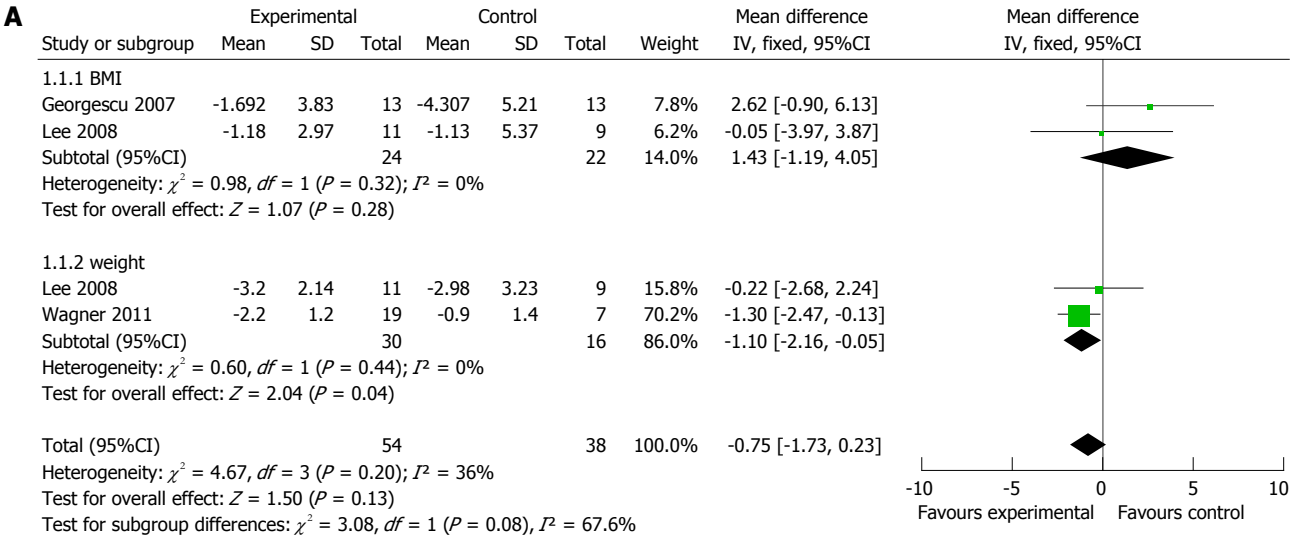
DISCUSSION

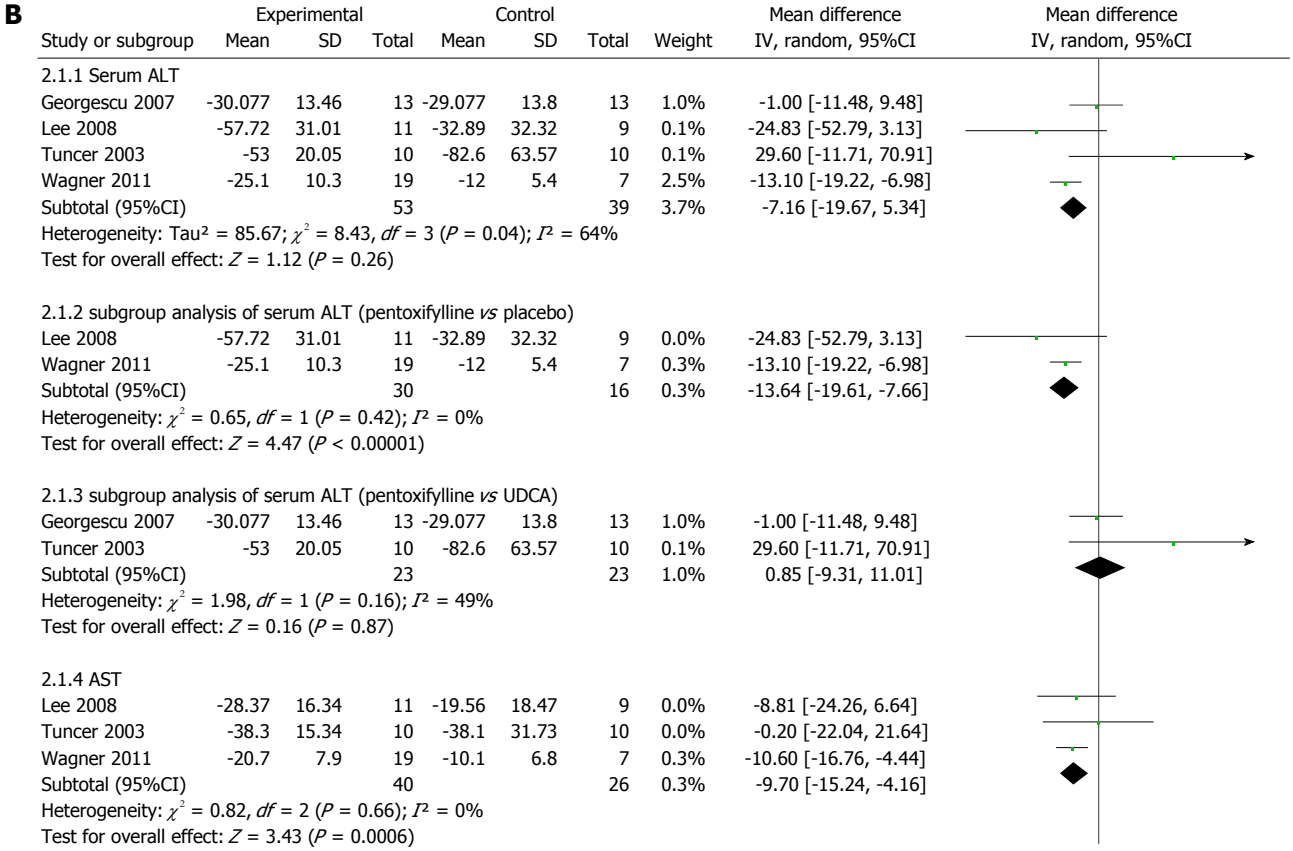
NAFLD is common and occurs in persons of all ages and ethnic groups, and is recognized as a major health issue. NAFLD is closely associated with obesity and insulin resistance, and is now recognized to represent the hepatic manifestation of the metabolic syndrome[28]. At present, there is no registered drug for the treatment of NAFLD. Although lifestyle intervention is often advocated[29,30], it is difficult to maintain. Socha *et al*[31] conducted a meta-

Table 1 Methodological characteristics of the included studies in this meta-analysis

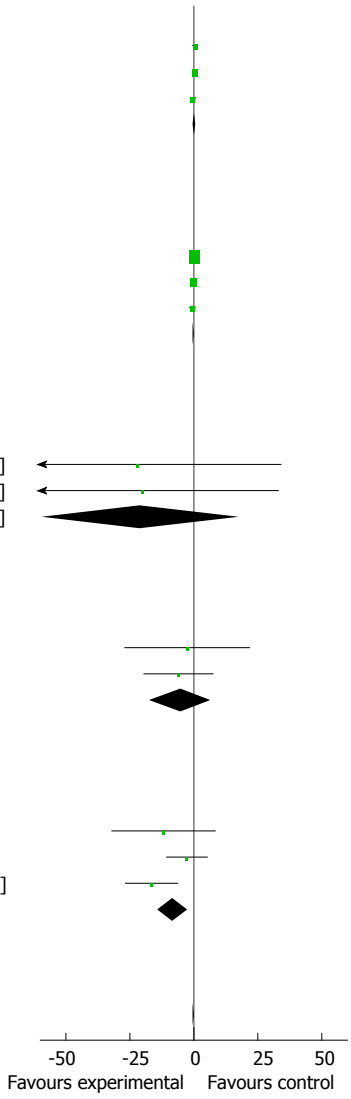
Ref.	Methodological quality	Sample size	Intervention	Control	Duration	Follow-up
Lee *et al*[23]	RCT	20 (11/9)	Pentoxifylline (1200 mg/d) plus low-calorie diet and exercise	Placebo plus low-calorie diet and daily exercise	12 wk	Yes
Tuncer *et al*[24]	Prospective cohort study with concurrent control	20 (10/10)	Pentoxifylline (20 mg/kg per day)	UDCA	24 wk	Yes
Georgescu *et al*[25]	Prospective cohort study with concurrent control	26 (13/13)	Pentoxifylline (800 mg/d)	UDCA	30 wk	Yes
Zein *et al*[26]	RCT	55 (26/29)	Pentoxifylline (1200 mg/d)	Placebo	12 mo	Yes
Van Wagner *et al*[27]	RCT	26 (19/7)	Pentoxifylline (1200 mg/d)	Placebo	12 mo	Yes

RCT: Randomized controlled trial; UDCA: Ursodeoxycholic acid.





2.1.5 TC								
Georgescu 2007	-0.631	1.378	13	-1.146	1.333	13	9.8%	0.51 [-0.53, 1.56]
Lee 2008	0.34	1.1	11	-0.15	0.86	9	14.4%	0.49 [-0.37, 1.35]
Tuncer 2003	0.039	1.25	10	0.385	1.181	10	9.3%	-0.35 [-1.41, 0.72]
Subtotal (95%CI)			34			32	33.5%	0.26 [-0.30, 0.83]
Heterogeneity: χ^2 = 1.75, *df* = 2 (*P* = 0.42); I^2 = 0%								
Test for overall effect: *Z* = 0.92 (*P* = 0.36)								
2.1.6 TG								
Georgescu 2007	-0.046	0.321	13	-0.169	0.92	13	37.8%	0.12 [-0.41, 0.65]
Lee 2008	-0.4	1.13	11	-0.16	0.57	9	18.2%	-0.24 [-1.00, 0.52]
Tuncer 2003	-0.869	0.79	10	-0.325	1.568	10	9.0%	-0.54 [-1.63, 0.54]
Subtotal (95%CI)			34			32	65.0%	-0.07 [-0.47, 0.33]
Heterogeneity: χ^2 = 1.43, *df* = 2 (*P* = 0.49); I^2 = 0%								
Test for overall effect: *Z* = 0.34 (*P* = 0.73)								
2.1.7 AKP								
Georgescu 2007	-79.538	67.64	13	-57.692	77.43	13	0.0%	-21.85 [-77.73, 34.04]
Tuncer 2003	-49	51.88	10	-29	67.99	10	0.0%	-20.00 [-73.01, 33.01]
Subtotal (95%CI)			23			23	0.0%	-20.87 [-59.33, 17.59]
Heterogeneity: χ^2 = 0.00, *df* = 1 (*P* = 0.96); I^2 = 0%								
Test for overall effect: *Z* = 1.06 (*P* = 0.29)								
2.1.8 GGT								
Georgescu 2007	-23.308	35.57	13	-20.693	27.4	13	0.0%	-2.61 [-27.02, 21.79]
Tuncer 2003	-54.8	7.48	10	-48.8	20.53	10	0.1%	-6.00 [-19.54, 7.54]
Subtotal (95%CI)			23			23	0.1%	-5.20 [-17.05, 6.64]
Heterogeneity: χ^2 = 0.06, *df* = 1 (*P* = 0.81); I^2 = 0%								
Test for overall effect: *Z* = 0.86 (*P* = 0.39)								
2.1.9 GLU								
Georgescu 2007	-15.231	23.55	13	-3.385	28.78	13	0.0%	-11.85 [-32.06, 8.37]
Tuncer 2003	-4.4	9.13	10	-1.7	9.1	10	0.2%	-2.70 [-10.69, 5.29]
Wagner 2011	-5.2	4.9	19	11.3	13.5	7	0.1%	-16.50 [-26.74, -6.26]
Subtotal (95%CI)			42			30	0.3%	-8.27 [-14.28, 2.25]
Heterogeneity: χ^2 = 4.47, *df* = 2 (*P* = 0.11); I^2 = 55%								
Test for overall effect: *Z* = 2.69 (*P* = 0.007)								
Total (95%CI)			302			244	100.%	-0.10 [-0.43, 0.23]
Heterogeneity: χ^2 = 75.33, *df* = 23 (*P* < 0.00001); I^2 = 69%								
Test for overall effect: *Z* = 0.60 (*P* = 0.55)								
Test for subgroup differences: χ^2 = 55.75, *df* = 8 (*P* < 0.00001), I^2 = 85.6%								



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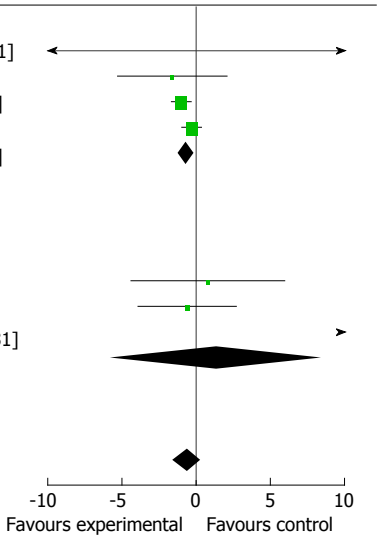
Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, fixed, 95%CI
3.1.1 TNF-α								
Lee 2008	-10.86	15.68	10	-31.35	54.54	8	0.0%	20.49 [-18.53, 59.51]
Tuncer 2003	-3.3	4.89	10	-1.7	3.43	10	1.6%	-1.60 [-5.30, 2.10]
Wagner 2011	-1.179	1.095	19	-0.183	0.644	7	47.6%	-1.00 [-1.68, -0.31]
Zein 2011	-0.1	0.9	23	0.2	1.5	26	47.9%	-0.30 [-0.98, 0.38]
Subtotal (95%CI)			62			51	97.1%	-0.66 [-1.14, -0.18]
Heterogeneity: χ^2 = 3.36, *df* = 3 (*P* = 0.34); I^2 = 11%								
Test for overall effect: *Z* = 2.69 (*P* = 0.007)								
3.1.2 IL-6								
Lee 2008	-7.47	6.81	10	-8.26	4.36	8	3.2%	0.79 [-4.40, 5.98]
Tuncer 2003	-0.5	4.77	10	0.1	2.46	10	7.1%	-0.60 [-3.93, 2.73]
Wagner 2011	-22.1	71	19	-82.9	47.5	7	0.0%	60.80 [13.29, 108.31]
Subtotal (95%CI)			39			25	10.3%	1.35 [-5.75, 8.44]
Heterogeneity: Tau² = 21.99; χ^2 = 6.50, *df* = 2 (*P* = 0.04); I^2 = 69%								
Test for overall effect: *Z* = 0.37 (*P* = 0.71)								
Total (95%CI)			101			76	100.%	-0.64 [-1.57, 0.33]
Heterogeneity: Tau² = 0.44; χ^2 = 10.09, *df* = 6 (*P* = 0.12); I^2 = 41%								
Test for overall effect: *Z* = 1.28 (*P* = 0.20)								



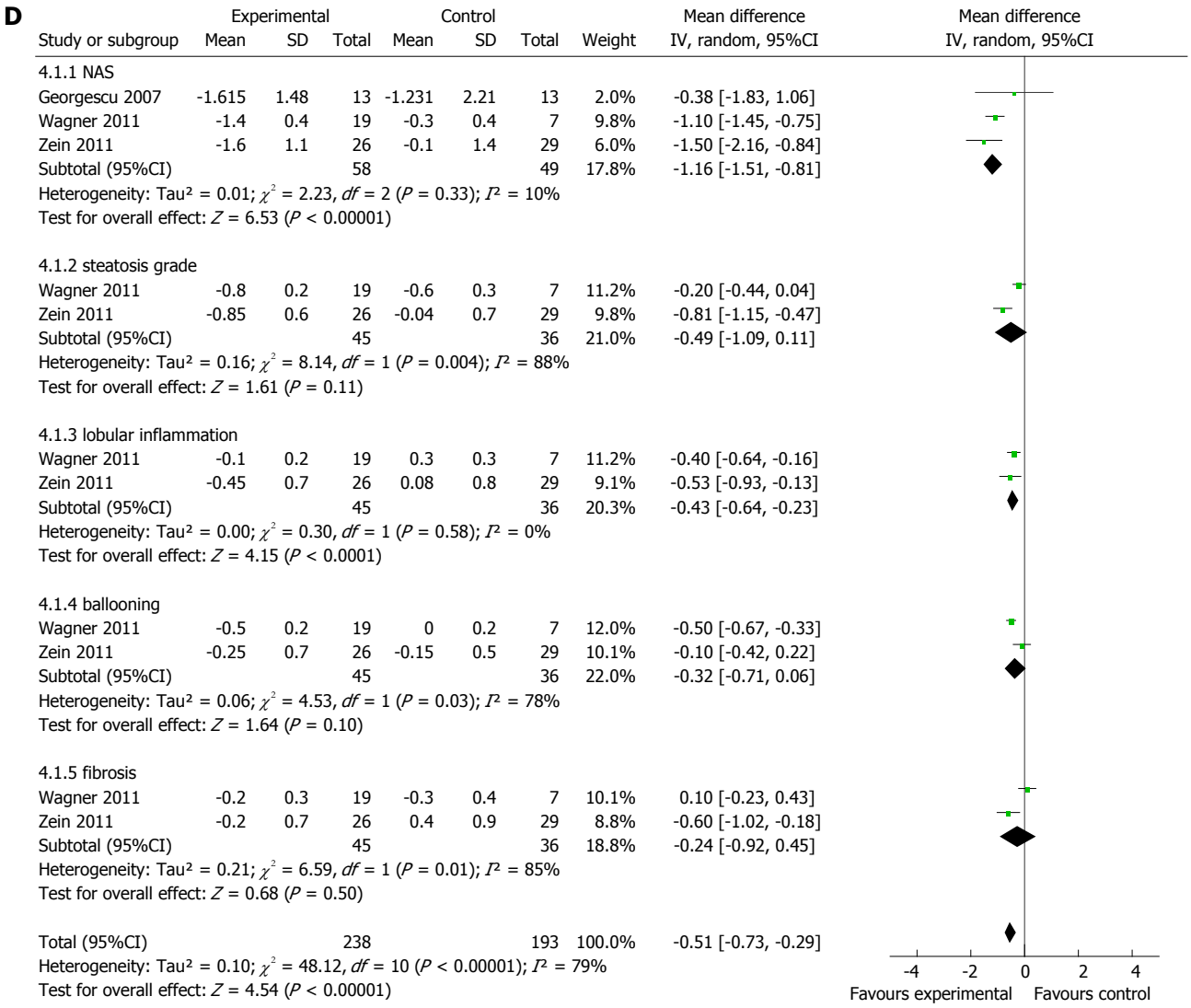


Figure 2 Forest plot of the effects of probiotics in patients with nonalcoholic fatty liver disease. BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate transaminase; UDCA: Ursodeoxycholic acid; TC: Total cholesterol; TG: Triglyceride; AKP: Alkaline phosphatase; GGT: γ-glutamyl transferase; GLU: Glucose; TNF-α: Tumor necrosis factor-α; IL: Interleukin; NAS: NAFLD activity score.

analysis on pharmacological interventions for NAFLD in adults and in children, including pioglitazone, vitamin E, UDCA, probucol, *N*-acetylcysteine, low doses of carnitine, as well as pentoxifylline. However, no firm conclusions on the efficacy of the various treatments for NAFLD have been drawn.

In 2011, a systematic review on pentoxifylline in NASH[32] was performed that found that pentoxifylline reduces AST and ALT levels and may improve liver histological scores in patients with NAFLD/NASH, but it does not appear to affect cytokines and histological improvement. The review only compared the post-treatment indexes, ignoring the differences from baseline. Moreover, the control group contained not only placebo, but also UDCA, which may have influenced the conclusion. Thus, it was necessary to conduct the present meta-analysis.

Oxidative stress and cytokine production play a vital role in the progression of NAFLD[33]. TNF-α is recognized to promote inflammatory, apoptotic and fibrogenic reactions in the development of NAFLD[21], and a large number of studies have shown that TNF-α is associated with the pathogenesis of NAFLD. Furthermore, TNF-α is an important cytokine that regulates insulin resistance in humans[34] by interfering with the insulin signaling transduction pathway[35,36]. Liver biopsy is currently considered the gold standard for the diagnosis of NAFLD/NASH. Lobular inflammation is one of the histological features of this disease, which is composed of lymphocytes, neutrophils and macrophages. The NAS is the sum of the scores of steatosis (0-3), lobular inflammation (0-3), and ballooning (0-2) and ranges from 0 to 8, with the majority of patients with NASH having a NAS $\geqslant$ 5. The NAS is highly correlated with aminotransferase levels, commonly assumed to be markers of liver disease severity[37]. Our meta-analysis showed that pentoxifylline therapy significantly decreased body weight, lowered serum ALT, AST, glucose and TNF-α, and improved NAS and lobular inflammation on histological examination. Furthermore, pentoxifylline did not influence serum TC, TG, AKP and GGT. Thus, pentoxifylline may represent a novel therapeutic target in NASH by reducing acute inflammatory damage in the liver.

Selection and publication bias should be considered in this study, as two of the studies included were prospective cohort studies with a concurrent control and the other three were RCTs. In these studies, pentoxifylline was administered within the dose range of 800 to 1200 mg/d, and only Lee's study administered pentoxifylline with a low-calorie diet and exercise. The duration of treatment ranged from 12 wk to 12 mo. Given the use of different dosages and durations of treatment, the studies were difficult to reconcile. The diagnosis of NAFLD/NASH was confirmed by percutaneous liver biopsy in all studies, except for some patients who only underwent ultrasonography for diagnosis in Tuncer's research. Although ultrasonography is reasonably accurate, it cannot identify fatty infiltration of the liver below a threshold of 30%. Unfortunately, only three studies had post-treatment histology results.

In our meta-analysis, two studies used UDCA as the control treatment. UDCA is a naturally occurring bile acid with multiple hepatoprotective activities. It was first demonstrated to improve ALT, AST, AKP and GGT in an open-label pilot study compared with clofibrate[38]. However, the results were found to be controversial in later research[39-41]. UDCA is now recommended to improve liver biochemical tests in patients with a wide range of chronic liver and hepatobiliary diseases. In the present meta-analysis of TC, TG, AKP and GGT, there was no significant difference between the pentoxifylline and UDCA groups. Therefore, the effect of pentoxifylline on improving abnormal liver function may be similar to UDCA.

There were other limitations in this review. Pentoxifylline was administered with a low-calorie diet and exercise in one study[23], and the researchers ignored the effects of the dietary restriction and exercise/physical activities as they were not described. The sample sizes in some trials, as well as the number of trials for some comparisons, were small.

COMMENTS

Background

The prevalence of nonalcoholic fatty liver disease (NAFLD) is increasing worldwide. The metabolic steps and underlying mechanisms of disease progression remain complex and poorly understood. Diet and lifestyle changes are primary therapies in the management of NAFLD patients. Human and animal studies have shown that pentoxifylline, which is a nonspecific phosphodiesterase inhibitor, results in a variety of physiological changes and affects multiple steps in the cytokine/chemokine pathway, and may be important in treating NAFLD. Thus, it was necessary to conduct a meta-analysis to assess the effects of pentoxifylline on physiological indicators, liver function and histological changes in NAFLD patients.

Research frontiers

Pentoxifylline is a methylxanthine derivative with potent hemorrheologic properties and is commonly used in the treatment of intermittent claudication in western countries. However, recent human and animal studies have indicated that pentoxifylline may have an influence on a variety of physiological changes at the cellular level, cyclic AMP and tumor necrosis factor (TNF)-α gene transcription, affecting multiple steps in the cytokine/chemokine pathway, which are all related to the mechanism of NAFLD. Whether treatment with pentoxifylline is effective in patients with NAFLD has therefore become a research hotspot.

Innovations and breakthroughs

In 2009, a meta-analysis was conducted on pharmacological interventions for NAFLD in adults and children. However, no firm conclusions could be drawn. In 2011, a systematic review on pentoxifylline in nonalcoholic steatohepatitis (NASH) was performed, but it did not appear to affect cytokines or histology. The control group contained placebo and ursodeoxycholic acid and had no subgroup analysis, which may have influenced the conclusions. Thus, a meta-analysis was necessary.

Applications

Use of pentoxifylline can reduce body weight, serum alanine aminotransferase, aspartate transaminase, glucose and TNF-α. With regard to histological changes, pentoxifylline only reduced the NAFLD activity score and improved lobular inflammation. Thus, pentoxifylline may represent a new method for treating or preventing NAFLD.

Terminology

NAFLD is characterized by large vacuoles of triglyceride that accumulate in liver cells *via* the process of steatosis in non-alcohol users. NAFLD can progress into NASH, liver fibrosis, cirrhosis, and more rarely, liver carcinoma. Pentoxifylline is a nonspecific phosphodiesterase inhibitor and can cause a variety of physiological changes at the cellular level, affect the levels of cyclic AMP and decrease *TNF-α* gene transcription, which are all important mechanisms in the progression of NAFLD.

Peer review

This meta-analysis is interesting and it extends the present knowledge on pentoxifylline and NAFLD. However, the authors need to improve some aspects of the manuscript. The most important section of the manuscript, the results section, is too confusing and difficult to read. The figures are confusing. The authors could reduce the number of figures and include two or three figures with all the variables. Also, there needs to be significant editing on the grammar and spelling.

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