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The Effect of Probiotics/synbiotics Supplementation on Renal and Liver Biomarkers in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized-Controlled Trials

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Abstract

Despite the apparent beneficial effects of probiotics/synbiotics on glucose hemostasis, lipid profile, and inflammatory responses, it is not clear whether these beneficial effects also impact renal and hepatic function in diabetes. Therefore, we sought to assess the effect of probiotics/synbiotics supplementation on renal and liver biomarkers in adults with type 2 diabetes (T2DM) using a systematic review and meta-analysis of randomized controlled trials (RCTs). PubMed, Scopus, Web of Science, and Cochrane Library were systematically searched, up to February 2021. The pooled weighted mean difference (WMD) was estimated using a random-effect model. The methodological quality of studies, as well as certainty of evidence, was assessed using standard scales. Fifteen related trials were identified. Meta-analysis of six trials, involving 426 participants, indicated that probiotics/synbiotics supplementation reduced serum levels of creatinine (WMD= -0.10 mg/dl, 95% CI: -0.20, -0.00; P= 0.01; I^2= 87.7%; P-heterogeneity<0.001), without any significant effect on blood urea nitrogen (BUN), glomerular filtration rate, or microalbuminuria. No significant improvement was found on liver biomarkers following probiotics/synbiotics supplementation. The subgroup analysis showed a significant improvement in BUN when follow-up duration lasted for 12 weeks or more (WMD= -1.215 mg/dl, 95% CI: -1.933, -0.496 ; P= 0.001), and in creatinine levels in patients with renal dysfunction (WMD= -0.209 mg/dl, 95% CI: -0.322, -0.096; P<0.001). Our results are insufficient to advocate the use of probiotics/synbiotics for improving renal or liver function in patients with T2DM. Indeed, due to the low certainty of evidence, these findings need to be affirmed in further high-quality RCTs.

Keywords: Probiotic; Type 2 diabetes; Systematic review; Meta-analysis; Glomerular Filtration Rate; Kidney; Liver; Synbiotics

INTRODUCTION

With the increasing prevalence of obesity, sedentary lifestyles, and urbanization, type 2 diabetes mellitus (T2DM) has become a global health issue, affecting 463 million people in 2019, and is predicted to reach 700 million cases in 2045 [1]. T2DM can lead to a series of additional complications, particularly micro- and macro-vascular damage, and negatively affecting multiple vital organs, including the kidneys, liver, eyes, and cardiovascular system [2].

Studies have reported that 20-40% of patients with diabetes suffer from renal dysfunction, characterized by urine albumin excretion or reduced glomerular filtration rate (GFR), and 40% of them may progress to end stage renal disease (ESRD) [3-6]. The exact cause of diabetic renal impairment is complex, and is proposed to be contributed to hyperglycemia, dyslipidemia, atherosclerotic vascular, obesity, hyperuricemia, and increased systemic and intra-glomerular pressure [7, 8].

Accumulating evidence also indicates that the liver, as an insulin-sensitive tissue and the main regulator of metabolism, is prone to damage by hyperglycemia, leading to further impaired metabolism and inflammatory reactions [9, 10]. Steatosis, elevated liver enzymes, cirrhosis, and carcinoma are among several important liver abnormalities in patients with T2DM [11, 12].

The most well-known strategy to prevent the progression of diabetes-related complications is maintaining glycemic control [13]. In addition to weight control, lifestyle modifications, and medical solutions, there is evidence supporting the effect of gut microbiome in regulating metabolism and energy hemostasis [14, 15]. Recently, studies reported alternations of gut microbiota in patients with diabetes [16-18], and probiotics/synbiotics supplementation was able to exert beneficial effects on lipid profile, glycemic control, blood pressure, and inflammation in these patients [19-25].

The exact mechanism of beneficial effects manifest following probiotic supplementation is not well known. However, its anti-inflammatory properties are very likely contributory. A recent meta-analysis study showed that probiotic therapy significantly decreased C-reactive protein concentration, and increased serum levels of glutathione, malondialdehyde, and total antioxidant capacity in patients with chronic kidney diseases [22]. Moreover, probiotics may improve insulin resistance by increasing liver natural killer T cells, and downregulating tumor necrosis factor α

(TNF-α) and Nuclear factor-κB (NF-κB) activity [26]. Probiotics have also shown angiotensin-converting enzyme (ACE) inhibitor properties, and consequential antihypertensive effects [20, 27].

Although there is evidence regarding the beneficial effects of probiotics/synbiotics on the improvement of metabolic control in patients with diabetes [24, 25, 28-30], so far, no study has systematically examined the effects of probiotics/synbiotics on renal and liver function in these patients. Therefore, we sought to investigate whether probiotic supplementation could improve renal and liver biomarkers, by conducting a systematic and meta-analysis of randomized clinical trials (RCTs).

METHODS

We performed the present meta-analysis in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and [31] adhered the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [32]. This review was registered at in the center of Open Science Framework (OSF) as *https://doi.org/10.17605/OSF.IO/UKXBD.*

Search strategy

We searched for references indexed in PubMed, Scopus, Web of Science, and Cochrane Library, from database inception to 10 February 2021. The terms used in search strategy are provided in **Supplementary Table 1**. We did not impose any keywords in term of interested outcomes and did not apply any restriction for language or publication year. The reference lists of the meta-analyses that examined the effect of probiotic or synbiotic supplementation/fortified foods in T2DM were also searched manually. A specific question was also defined according to the PICOS principle (Participants, Interventions, Control, Outcomes, and Study design) (**Table 1**).

Selection criteria

The titles/abstracts and full text of retrieved references were screened according to the inclusion and exclusion criteria independently by two authors (SS and FM), and any discrepancies were resolved by discussion with a third author (SA). The inclusion criteria of this article were as follows: the RCTs (parallel or crossover) that compared the effects of probiotic/synbiotic supplements or fortified foods (any strains and dosages) with placebo in pre-diabetic or T2DM patients. All included studies needed to report mean and standard deviation of baseline, post, or

change from baseline for at least one of the following liver enzymes or kidney function indicators, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), bilirubin, creatinine, blood urea nitrogen (BUN), uric acid, microalbuminuria, proteinuria, or GFR, or any other renal and liver biomarkers. The exclusion criteria were as follows: (1) trials with less than one-week period, (2) trials without a placebo controlled group, (3) duplicated publications from the same population, (4) trials with insufficient information for calculating the mean or standard deviation (SD) change in the outcome measure(s), (5) trials including pregnant or lactating women, and (6) trials that used probiotic or synbiotic in combination with other treatments and/or the comparator group did not received the same treatment.

Data extraction

The relevant data was extracted by one author and then cross-checked by another (SS, FM), and any discrepancies resolved by discussion with a third author (SA). The following data was extracted: the first author's name, year of publication, study characteristic (study design, follow-up duration, study location, sample size in the intervention and control groups, the species and dosage of probiotic or synbiotic supplementation, and interested outcomes), and participant characteristic (age, sex, health status). The means, along with the respective SDs values, of before and after the intervention or change for AST (U/L), ALT (U/L), GGT (U/L), ALP (U/L), bilirubin (mg/dl), creatinine (mg/dl), BUN (mg/dl), microalbuminuria (albumin/creatinine ratio), GFR (mL/min/1.73m^2), and any other liver or renal related biomarkers also were extracted.

Study quality and Quality of evidence

The quality of the selected articles were evaluated using the Cochrane Collaboration's tool for assessing risk of bias [33]. The quality of evidence assessment was performed with the use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which includes five domains: risk of bias, inconsistency of results, imprecision of results, indirectness of evidence, and publication bias. The quality of evidence of a RCTs was initially considered as high and was downgraded by the following limitations: methodological errors [34], inconsistency [35], imprecision of estimates [36], indirectness [37], or evidence of publication bias

[38]. All quality evaluation and evidence were performed independently by two reviewers (SS and FM), and disagreements were resolved through discussion with a third author (SA).

Statistical analyses

For each outcome, where at least ≥3 RCTs reported sufficient data, the net change in mean and it's 95% CI between the intervention and control groups as the effect size calculate in the meta-analysis. In term of trials that did not provide change values, the mean difference was calculated by minus mean changes the intervention mean minus the control group mean, and standard deviation of the mean change estimated formula suggested by the Cochrane Handbook of Systematic Review [39] where correlation coefficient was imputed [r=0.68 ALP [40], r= 0.42 AST [41-43], r= 0.48 ALT [41], r= 0.73 bilirubin [41, 42], r=0.82 creatinine [44-48], r=0.71 BUN [45-47, 49], r=0.77 microalbuminuria [40, 46], r=0.82 GFR [44, 48]] from included studies reporting both baseline, final values and changes from baseline for each interested outcome. The random-effects model described by Dersimonian and Laird was used to calculate the overall pooled effect [50].

Regarding trials that multiple intervention (probiotic or synbiotic) compared with the single control group, the calculated effect size related to probiotic supplementation were included in main analysis to avoid counting the control group twice in the analysis.

Inconsistencies across trials were assessed with the use of the Cochrane's chi-squared test and the I^2 statistic, where significant heterogeneity was evident as $I^2 \geq 50\%$ [51, 52]. The subgroup analyses were conducted to detect source of heterogeneity if there are adequate trials for each outcome. Sensitivity analysis were conducted to evaluate the impacts of each trial on the meta-analysis results. The presence of publication bias was evaluated by the "Begg's funnel plot" and Egger's test whenever if possible (at least 10 trials included) [53, 54]. Statistical analyses were conducted using STATA version 14 (STATA Corp., College Station, Texas). Two-tailed P values of 0.05 were, *a priori*, considered as statistically significant.

RESULTS

Study selection and characteristics

The study selection process detailed in **Figure 1**. Our initial systematic search identified 4905 potentially relevant studies, after removing duplicates (n= 1348). Following title/abstract review, 98 articles were retained for full-text screening, and then, 83 further articles were excluded due to the wrong population (n=4), wrong intervention (n=16), wrong outcome (n=51), wrong comparison (n=2), insufficient data (n=1), repeated reports (n=6), and without full-text (n=3). The excluded studies as well as the reasons are shown in **Supplementary Table 2**. Finally, 15 trials were eligible for inclusion in the systematic review, and reported following outcomes: ALP (n=4), ALT (n=6), AST (n=6), bilirubin (n=3), BUN (n=5), creatinine (n=6), GFR (n=3), microalbuminuria (n=3), uric acid (n=2), cystatin-C (n=1), albumin (n=1), γ-GT (n=1), and neutrophil gelatinase-associated lipocalin (NGAL) (n=1).

The studies characteristics are described in **Table 2**. Except for two studies [41, 42], all the included studies were parallel in design. Most of the included studies were carried out in Iran [40-48, 55-57], and the rest of the studies were performed in Ukraine [58], Sweden [59], and Malaysia [60]. Participants were composed of both male and female in all the included studies, and were with T2DM; although, patients with both type 1 and type 2 diabetes were eligible for inclusion in two studies [47, 48], and one study did not provide information about the type of diabetes [45]. Participants in seven studies suffered from nephropathy [40, 44, 45, 47, 57, 59], dialysis [48], and non-alcoholic fatty liver [58]. The mean baseline BMI presented an obesity (>30 kg/m^2) condition in six studies [42, 43, 45, 56, 58, 59], and participants in other studies were in overweight category. Participants in five studies were treated with exogenous insulin [47, 48, 57-59], and oral anti-hyperglycemic drugs were given in rest of the studies.

The duration of intervention ranged from six to 12 weeks. All the included studies administered synbiotics [46] or probiotics [47, 48, 55, 56, 58-60] in solid pharmaceutical formulations (powder or table form), and six studies used soy milk [40, 57], bread [43], honey [45], and an unknown food containing synbiotic [41, 42] as carrier. One study included two doses of probiotic, where the higher dose was considered for analysis [59]. There was also one study that presented data on synbiotic, probiotic, and placebo supplementation, separately, where the probiotic in comparison with placebo was

included in the analysis [43]. Common adverse effects were reported, such as gastric disturbance [59, 60], headache, hypoglycemia, and musculoskeletal symptoms [59].

Risk of bias and quality of evidence

The Cochrane Collaboration's tool was used to assess the methodological quality of studies. Participants, personnel, and outcomes assessor were blind in all the included studies. Of the 15 included randomized studies, two did not describe the randomization, and allocation concealment process [40, 59]. Furthermore, one study was funded partly by a non-academic source, however, the authors declared no conflict of interest, and the company did not interfere with the decision to exploit research results; therefore, we did not downgrade for funding domain [60]. No concern was also found about incomplete data or selective reporting. Altogether, most of the included studies were rated as good quality, and two studies were fair in methodological quality [40, 59] (**Supplementary Table 3**). The quality of evidence showed very low certainty for ALT, ALP, bilirubin, creatinine, GFR, and microalbuminuria, and low certainty for AST and BUN (**Supplementary Table 4**).

Meta-analysis

The effect of probiotics/synbiotics supplementation on liver biomarkers

Pooling data from RCTs revealed probiotics/synbiotics supplementation had no significant effect on ALP [41, 43, 56, 60] (n= 4 studies, 310 participants; WMD= 7.26 U/L, 95% CI: -3.39, 17.91; P= 0.18; I^2= 63.3%; P-heterogeneity=0.04), ALT [41, 43, 56, 58-60] (n= 6 studies, 397 participants; WMD= -0.76 U/L, 95% CI: -4.12, 2.58; P= 0.65; I^2= 57.7%; P-heterogeneity=0.03), AST [41, 43, 56, 58-60] (n= 6 studies, 397 participants; WMD= -0.91 U/L, 95% CI: -3.05, 1.22; P= 0.4; I^2= 28.1; P-heterogeneity=0.22), and bilirubin levels (n= 3 studies, 256 participants; WMD= -0.04 mg/dl, 95% CI: -0.16, 0.08; P= 0.52; I^2= 86.2%; P-heterogeneity= 0.001) (**Figure 2, Supplementary Table 5**). Between-study heterogeneity was moderate to high, although the small number of studies precluded a comprehensive subgroup analysis, the duration of intervention, and liver complications could justify the observed heterogeneity to some extent (**Supplementary Table 6-7**).

The effect of probiotics/synbiotics supplementation on renal biomarkers

Our analysis found probiotics/synbiotics supplementation reduced creatinine levels [44-48, 60] (n= 6 studies, 426 participants; WMD= -0.10 mg/dl, 95% CI: -0.20, -0.00; P= 0.01; I^2= 87.7%; P-heterogeneity<0.001), without any significant effect on GFR [44, 48, 60] (n= 3 studies, 236 participants; WMD= 4.55 mL/min/1.73m^2, 95% CI: -0.94, 10.05; P= 0.1; I^2= 90.7%; P-heterogeneity<0.001), microalbuminuria [40, 46, 59] (n= 3 studies, 139 participants; WMD= -10.36 Alb/Cr (mg/gr), 95% CI: -22.87, 2.16; P= 0.1; I^2= 80.9%; P-heterogeneity= 0.005), or BUN [45-48, 60] (n= 5 studies, 386 participants; WMD= -0.87 mg/dl, 95% CI: -1.91, 0.18; P= 0.1; I^2= 36.1%; P-heterogeneity= 0.18) (**Figure 3, Supplementary Table 5**). Subgroup analysis was performed when the number of studies was sufficient for each outcome, and the results showed a significant reduction in BUN levels when intervention lasted for 12 weeks or more (n= 4 studies, 316 participants; WMD= -1.215 mg/dl, 95% CI: -1.933, -0.496 ; P= 0.001; I^2= 0.0%; P-heterogeneity=0.41), and also showed a significant reduction in creatinine levels in patients with renal complications (n= 4 studies, 220 participants; WMD=-0.209 mg/dl, 95% CI: -0.322, -0.096; P<0.001; I^2= 46.7%; P-heterogeneity= 0.13). Subgroup analysis also identified duration of intervention and renal complication as the potential source of heterogeneity.

Outcomes did not analyze

Uric acid. Two studies evaluated the effect of probiotic supplement and synbiotic food consumption on serum uric acid, and reached to contradictory results. One study found synbiotic food supplementation significantly increased serum uric acid [42], while other study revealed no significant effect following probiotic supplementation [56].

γ-GT. One study suggested significant 12 percent decrease in serumγ-GT following a multi-strain probiotic supplementation in type 2 diabetes patients with non-alcoholic fatty liver disease [58].

Cystatin-C, NGAL. One study showed significant reduction in cystatin-c and marginally significant reduction in NGAL levels in patients with type 2 diabetic nephropathy after consumption of probiotic soy milk compared with control [57].

Sensitivity analysis and publication bias

The leave-one out sensitivity analysis did not identify any study with a significant influence on the pooled effects sizes. An additional sensitivity analysis was conducted excluding the studies that examined synbiotic supplementation, and the results showed significant decreases in creatinine and BUN levels, with a significant reduction in between-study heterogeneity (**Supplementary Table 7**). Publication bias was not examined due to the insufficient study for each outcome.

DISCUSSION

This meta-analysis pooled data from RCTs investigating the effect of probiotics/synbiotics supplementation on kidney and liver parameters in patients with diabetes. Our results revealed probiotics/synbiotics supplementation has no significant effect on ALT, AST, ALP, BUN, bilirubin, GFR, or microalbuminuria. However, it was shown that probiotics/synbiotics may elicit beneficial effects on creatinine levels.

Emerging data indicating gut microbiota modulation by probiotic, prebiotic or synbiotic supplementation can induce favorable effects on lipid profile, glycemic control [61], and antioxidant capacity in patients with diabetes [21]. It has been suggested that inflammation is the major mechanism related to diabetes complications [62, 63]. Indeed, patients with diabetes tend to suffer from chronic inflammation, exacerbated by impaired intestinal function [64]. The gut is known as a potential immune regulation gate [65], and several immune, endocrine, and metabolic pathways accrue between intestinal and other organs [66]. Short chain fatty acids (SCFAs), the main product of gut fermentation, reduce intestinal permeability, bacteria translocation [67], and downregulate the expression of pro-inflammatory cytokines [68]. However, findings from previous meta-analysis are inconsistent [69, 70]. It seems that the anti-inflammatory effects of probiotics are increased when combined with the prebiotics. Moreover, as shown in a meta-analysis, the use of synbiotics may have more beneficial effects in reducing inflammatory factors than probiotics [70], because of the additional substrate for fermentation, and consequential growth stimulation of gut microbiota [71]. However, our results showed a significant reduction in creatinine and BUN levels when analysis restricted to probiotic supplementation. It may be due to the higher dose of probiotic in the studies administered probiotic, exclusively. Moreover, BUN

levels improved in studies administered probiotic/synbiotic for 12 weeks or more. This association disappeared when a sensitivity analysis was conducted for studies with ≥8 weeks follow up duration (**data not shown**). It seems, more than 12 weeks intervention may exert greater beneficial effects of probiotics. However, the number of included studies in our analysis was not enough to draw a definitive conclusion.

In line with a previous systematic review [72], we found probiotic/synbiotic supplementation may improve creatinine levels in patients with renal dysfunction. Although, a meta-analysis by AbdelQadir etal., showed despite a significant improvement in antioxidant indices, there is no association between probiotic supplementation and creatinine, GFR, or BUN levels in patients with diabetic nephropathy [73]. It may be contributed to misclassification of the study by Firouzi etal., [60] which the nephropathy was an exclusion criterion of this study, but it has been included in the analysis.

It is suggested probiotic may improve renal function through increasing anaerobic bacteria such as Lactobacillus and Bifidobacterium leading to decrease PH and urea levels. Moreover, some probiotic species such as Bacteroides can reduce urea by their urease activity [74]. However, our analysis found no significant association for other renal biomarkers. There is accumulating evidence suggesting some new biomarkers for kidney function, such as cystatin-C or NGAL, are more affected in early stages of kidney injuries than BUN, or GFR (71, 72). The Northern Manhattan study also indicated that cystatin-C based GFR may be a better predictor of all-cause mortality in the elderly, in comparison to serum creatinine (73). However, in our study, data were not enough to perform a meta-analysis on these predictor biomarkers.

Concordant with our findings, several previous studies showed contradictory effects of probiotic supplementation on liver enzymes in patients with diabetes [43, 60], or fatty liver diseases [75-77]. As a possible explanation, metformin, which was used by most of our included studied population, is known to improve lipid profile [78], liver function [79], ovarian function [80], beyond glycemic control. It is also evident that metformin reduces micro- and macro-vascular complications, and also alters gut microbiota [81], which may affect our results. Moreover, different probiotic strains were supplemented in included studies, and it is shown that strain variation may produce different effects on the host [82, 83]. However, because of the small number of studies, it was not possible to assess strain-specific effects on interested outcomes. On the other hand, we assessed

liver function using liver enzymes, the factors that change in the later stages of liver damage. It is suggested that standard biomarkers such as ultrasound be used in future studies.

Strengths and limitations

As far as we are aware, this is the first meta-analysis comprehensively investigating the effect of probiotics/synbiotics supplementation on kidney and liver function in patients with type 2 diabetes. However, one previous meta-analysis study investigated the effect of probiotic supplementation on kidney function in patients with diabetic nephropathy, with non-significant results [73]. Pooling data from good quality RCTs permits causal associations to be drawn; however, there are some considerable limitations. First, the number of included studies was small for each outcome, which affects the validity of the results. Second, there was varied setting among studies, which made it difficult to assess the isolate effect of probiotic supplementation on the outcomes; including probiotic species, probiotic carrier, the medication used, and body weight. Third, although macronutrients intake was controlled in most of the included studies, fiber intake, or anti-oxidant nutrients (such as vitamin E, C, D, or omega-3) were not considered in analyses. Fourth, renal and liver biomarkers in most of the included studies were secondary outcomes, therefore, the studies may not have an adequate sample size to detect a significant association. Fifth, none of the included studies used gold standard biomarkers, resulting reduced validity of the results. Sixth, absence of any information on the composition of colon microbiota after the intervention with probiotics/synbiotics makes it difficult to draw conclusions about the effect of the supplement on changing the gut microbiota, which is suggested to be studied in future researches. Seventh, the certainty of evidence was low or very low; as, most of the included participants were from same location (Iran), and the point estimate was smaller than 5% baseline value of interested outcomes, leading to downgrading for inconsistency and imprecision, respectively.

CONCLUSION

In the present systematic review and meta-analysis, we assessed the effects of probiotics/synbiotic treatment on the liver and kidney biomarkers in patients with T2DM. The results of our meta-analysis indicated that probiotics/synbiotic treatment may reduce creatinine levels. However, due to the very low certainty of evidence, more clinical data using gold standard biomarkers are needed, globally, to clarify the role of probiotics, the most beneficial bacteria, and the optimal dosage in T2DM patients.

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Conflict of interest

The authors report no conflict of interest.

Authorship

SA and SS designed the review; FM and SS conducted major database search according to search strategy; FM and SS did data extraction; SS performed analysis; SA wrote the manuscript's draft; and all authors evaluated the final version of the manuscript precisely and approved it.

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Table 1. PICOS criteria for inclusion and exclusion of studies

Parameter	
Participants	Adults (≥18 years) of both sexes and all nationalities, with pre-diabetes or T2DM
Interventions	Probiotic/synbiotic supplements or fortified foods (any strains and dosages)
Control/comparator group	Placebo or non-fortified foods
Outcomes	Any biomarker of renal or liver function, including aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, alkaline phosphatase, bilirubin, creatinine, blood urea nitrogen, uric acid, microalbuminuria, proteinuria, or glomerular filtration rate, etc.
Study design	Randomized controlled trials (parallel or cross-over)

Table 2. The characteristics of trials that investigated the effect of probiotics/synbiotics supplementation on liver and renal biomarkers in adults with type 2 diabetes and were eligible for inclusion in the meta-analysis

Author, year	Participants, sex	Mean age	Mean BMI	Country, Study design	Condition	Type of diabetes	Type of supplement	Probiotic agent	Duration (weeks)	Outcomes	Results
Studies investigated renal biomarkers											
Abbasi, 2017 [40]	40, M&F	56.9 (int) 53.6 (cont)	26.68 (int) 26.58(cont)	Iran, P	Nephropathy	2	Probiotic soy milk	Lactobacillus plantarum A7	8	Microalbuminuria	Significant decrease in microalbuminuria
Abbasi, 2018 [40]	40, M&F	56.9 (int) 53.6 (cont)	26.68 (int) 26.58(cont)	Iran, P	Nephropathy	2	Probiotic soy milk	Lactobacillus plantarum A7	8	Creatinine, GFR	Significant decrease in serum creatinine and significant increase in GFR in probiotic group
Arani, 2018 [45]	60, M&F	62.7 (int) 60.3 (cont)	30.3 (int) 31.1(cont)	Iran, P	Nephropathy	-	Probiotic honey	Bacillus coagulans	12	Creatinine, BUN	No significant change

Asemi, 2013 [56]	54, M & F	50.51 (int) 52.59(cont)	31.61 (int) 30.17 (cont)	Iran, P	-	2	Multispecies Probiotic	Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Bifidobacterium breve, Bifidobacterium longum, Streptococcus thermophilus and fructooligosaccharide	8	Uric acid	No significant change
Asemi, 2014 [42]	62, M & F	53.1 (int) 53.1 (cont)	29.60 (int) 29.90 (cont)	Iran, C	-	2	Synbiotic food	Lactobacillus sporogenes, inulin, isomalt, sorbitol, and stevia	6 (three times a day)	Uric acid	Significant increase in serum uric acid in synbiotic group
Ebrahimi, 2017 [46]	70, M& F	58.71 (int) 58.63(cont)	28.13 (int) 27.30 (cont)	Iran, P	-	2	Synbiotic	Lactobacillus, Bifidobacterium, Streptococus thermophilus, Prebiotics (Fructo	9	Creatinine, Urea, Microalbuminuria, BUN	Significant decrease in microalbuminuria in synbiotic group

								oligosaccharide)			
Firouzi, 2015 [60]	136, M& F	52.9 (int) 54.2 (cont)	29.2 (int) 29.3 (cont)	Malaysia, P	-	2	Multistrain probiotic	Lactobacillus, acidophilus, Lactobacillus casei, Lactobacillus lactis, Bifidobacterium bifidum, Bifidobacterium longum and Bifidobacterium infantis	6 &12	Creatinine, Urea, GFR, BUN	Significant decrease in serum urea in probiotic group
Mafi, 2018 [47]	60, M & F	58.9 (int) 60.9 (cont)	25.3 (int) 26.3 (cont)	Iran, P	Nephropathy	1&2	Multistrain probiotic	Lactobacillus acidophilus strain ZT-L1, Bifidobacterium bifidum strain ZT-B1, Lactobacillus reuteri strain ZT-Lre, and Lactobacillus fermentum strain ZT-L3	12	Creatinine, BUN, Proteinuria	Significant decrease in serum creatinine and BUN in probiotic group
Miraghajani, 2017 [57]	40, M & F	56.9 (int) 53.6 (cont)	26.68 (int) 26.58 (cont)	Iran, P	Nephropathy	2	Probiotic Soy Milk	Lactobacillus plantarumA7	8	Cystatin C, NGAL	Significant decrease in cystatin C in probiotic group

Mobini, 2017 [59]	29, M & F	64 (int) 66 (int) 65 (cont)	32.3 (int) 30.6 (int) 30.7(cont)	Sweden, P	-	2	Probiotic (low &high dose)	Lactobacillus reuteri DSM 17938	12	Microalbuminuria	No significant change
Soleimani, 2017 [48]	60, M & F	54 (int) 59.4 (cont)	25.5 (int) 27.0 (cont)	Iran, P	Dialysis	1&2	Multistrain probiotic	Lactobacillus acidophilus, Lactobacillus casei and Bifidobacterium bifidum	12	Creatinine, BUN, GFR	No significant change
Studies investigated liver biomarkers											
Asemi, 2017 [41]	62, M& F	- -	29.7 (int) 30.1 (cont)	Iran, C	-	2	Synbiotic food	Lactobacillus sporogenes, inulin, isomalt, sorbitol, and stevia	6 (three times a day)	ALP, AST, ALT, Bilirubin	Significant decrease in total bilirubin in synbiotic group
Asemi, 2015 [55]	58, M & F	49.6 (int) 52.1(cont)	31.9 (int) 30.7 (cont)	Iran, P	-	2	Multispecies Probiotic	Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Bifidobacterium	8	ALP, AST, ALT, Bilirubin	Significant decrease in serum ALT in synbiotic group

								breve, Bifidobacterium longum, Streptococcus thermophilus and fructooligosaccharide			
Bahmani, 2015 [43]	54, M& F	51.3 (int) 52.0 (int) 53.4(cont)	30.8 (int) 29.8 (int) 30.5 (cont)	Iran, P	-	2	Synbiotic bread/ Probiotic	Lactobacillus sporogenes and inulin/ Lactobacillus sporogenes	8 (three times a day)	ALP, AST, ALT	No significant change
Firouzi, 2015 [60]	136, M& F	52.9 (int) 54.2 (cont)	29.2 (int) 29.3 (cont)	Malaysia, P	-	2	Multistrain probiotic	Lactobacillus, acidophilus, Lactobacillus casei, Lactobacillus lactis, Bifidobacterium bifidum,Bifidobacterium longum and Bifidobacterium infantis	6 &12	ALP, AST, ALT, Bilirubin, Albumin	No significant change
Kobyliak, 2018 [58]	58, M & F	53.4 (int) 57.2 (cont)	34.82 (int) 34.26 (cont)	Ukraine, P	NAFLD	2	Multistrain probiotic	Lactobacillus, Lactococcus, Bifidobacterium,	8	AST, ALT, γ-GT	Significant decrease in serum AST and γ-GT

								Propionibacterium, Acetobacter			levels in probiotic group
Mobini, 2017 [59]	29, M & F	64 (int) 66 (int) 65 (cont)	32.3 (int) 30.6 (int) 30.7(cont)	Sweden, P	-	2	Probiotic (low & high dose)	Lactobacillus reuteri DSM 17938	12	AST, ALT	No significant change

ALP, Alkaline Phosphatase; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; BUN, Blood urea nitrogen; cont, control group; C, cross-over; F, female; GFR, Glomerular filtration rate; int, intervention group; M, male; NAFLD, non-alcoholic fatty liver disease; NGAL, neutrophil gelatinase-associated lipocalin; P, parallel

Figure legend

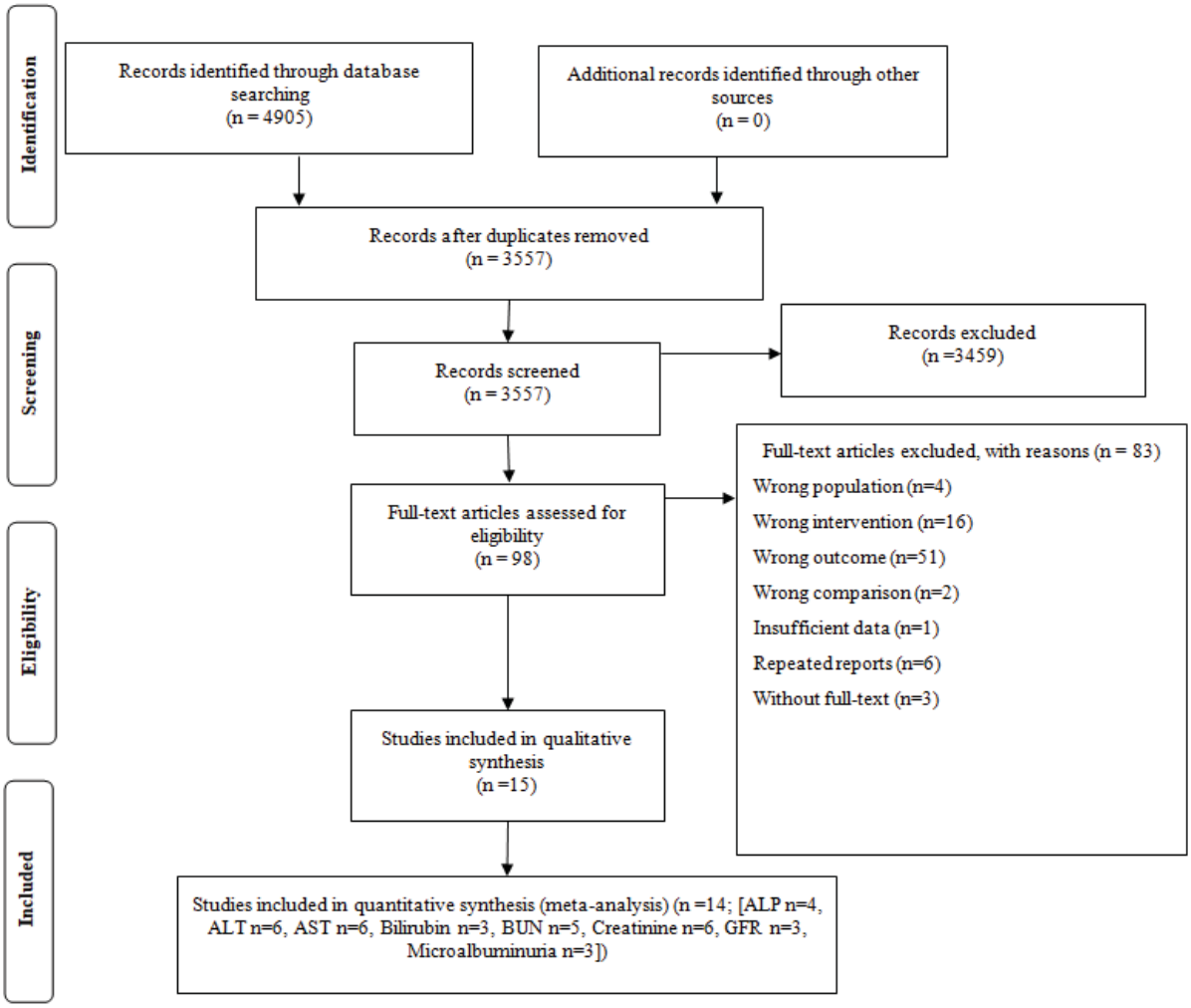

Figure.1 Study selection process

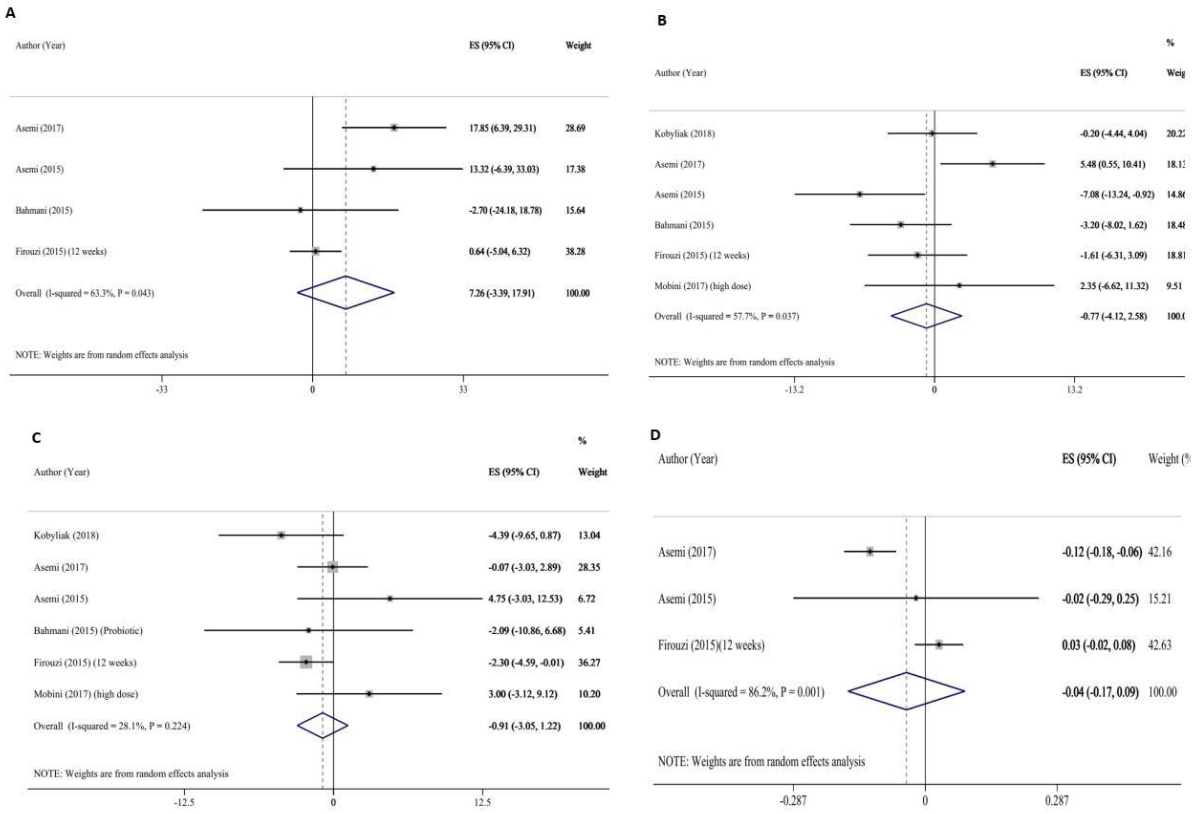

Figure 2. Forest plot of randomized controlled clinical trials illustrating weighted mean difference (WMD) in A; ALP change (U/L), B: ALT change (U/L), C: AST change (U/L), and D: bilirubin change (mg/dl) between the probiotics/synbiotics supplementation and control groups for all eligible studies. Analysis was conducted using random effects model.

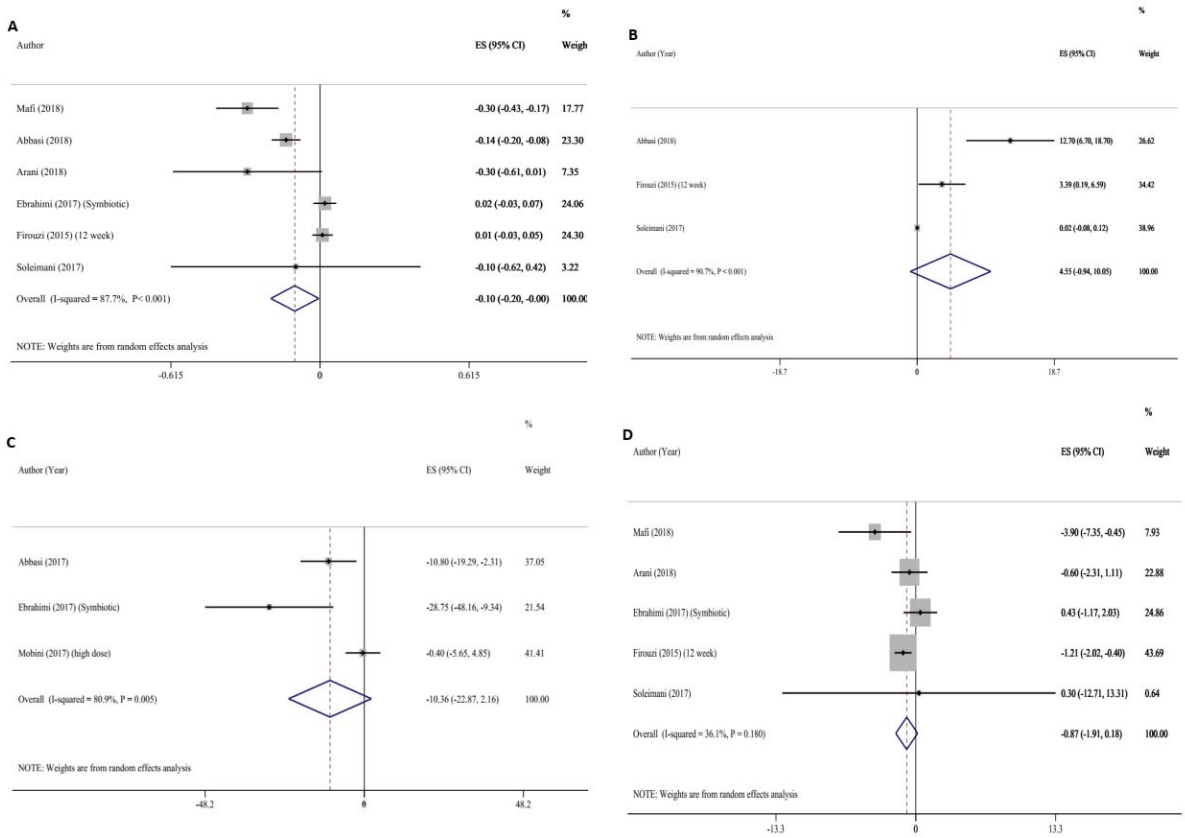

Figure 3. Forest plot of randomized controlled clinical trials illustrating weighted mean difference (WMD) in A; creatinine change (mg/dl), B: GFR change (mL/min/1.73m^2), C: microalbuminuria change (Alb/Cr (mg/gr)), and D: BUN change (mg/dl) between the probiotics/synbiotics supplementation and control groups for all eligible studies. Analysis was conducted using random effects model.