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Review

The effects of prebiotic, probiotic, and synbiotic supplementation on blood parameters of renal function: A systematic review and meta-analysis of clinical trials

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ABSTRACT

Objectives: Recent studies have demonstrated promising results regarding possible improvements in renal function after prebiotic, probiotic, and synbiotic supplementation. The aim of this review was to demonstrate whether such supplementation will improve renal profile indexes including glomerular filtration rate (GFR), creatinine, blood urea nitrogen (BUN), uric acid (UA), and urea.
Method: The meta-analysis included all studies that examined the effect of prebiotic, probiotic, and synbiotic supplements on one or more renal function parameters and had a control group. We searched July 1967 through to March 2016 MEDLINE, Scopus, and Google Scholar databases.
Results: Of 437 studies, 13 were eligible for inclusion in the meta-analysis. GFR levels tended to be reduced; whereas creatinine levels increased in the intervention group compared with the placebo group, both in a non-significant manner. The pooled effect on BUN demonstrated a significant decline compared with the placebo group (MD, –1.72 mmol/L; 95% confidence interval [CI], –2.93 to –0.51; $P = 0.005$). Urea significantly decreased after intervention (–0.46 mmol/L; 95% CI, –0.60 to –0.32; $P < 0.0001$). The UA levels significantly increased in the intervention group compared with the placebo group (12.28 μmol/L; 95% CI, 0.85–23.71; $P = 0.035$).
Conclusion: This study showed a significant increase in UA and a decrease in urea and BUN. The use of prebiotic, probiotic, and synbiotic supplements among those with compromised renal function or those at risk for renal failure should be limited until large-scale, well-designed randomized controlled trials prove the safety and efficacy of these supplements in improving renal function.
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Introduction

Numerous studies have demonstrated that gut microbiome hosts billions of bacteria that interact with many physiological conditions [1]. The range of these conditions varies from gastrointestinal disturbances [2] to glucose homeostasis [3], obesity [4], metabolic endotoxemia [5,6] and bone density [7]. A connection between gut microbiome and kidney function has been suggested in the literature [8,9]. The proof for this claim lies in the fact that the composition of the gut microbiome interacts with levels of urea. It affects uremic retention and solute production, resulting in the generation of uremic toxins with a strong biological effect on progression toward kidney failure [10]. On the other hand, the levels of uremia affect the composition of the gut microbiome through disturbances in the protective epithelial barrier of the intestine and the translocation of the intestinal microbiome in to the body [11].

Considering these facts, a question is raised as to whether manipulation of the gut microbiome with prebiotic, probiotic, or synbiotic supplements will improve kidney function. In recent years, several clinical trials investigated the effect of gut microbiome manipulation on generating uremic toxins among patients on hemodialysis. Results from the studies demonstrated that intervention with probiotics or prebiotics will beneficially reduce toxins that are generated from the kidney [12–14]. A meta-analysis of the randomized controlled trials (RCTs) also proved this positive effect [15].

Although the positive affect of gut microbiome manipulation on renal-generating toxins has been shown previously [12–15], fewer data are available in terms of its effect on renal

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parameters such as urea, creatinine, uric acid (UA), blood urea nitrogen (BUN), and glomerular filtration rate (GFR). Firouzi et al. demonstrated that levels of urea were significantly reduced after probiotic supplementation among individuals with type 2 diabetes, whereas levels of GFR and creatinine remained unchanged [8]. In a randomized crossover study, BUN was significantly reduced among patients with stage III and IV chronic kidney disease (CKD) [16], whereas it did not change among hospitalized, enterally fed elderly patients [17]. In terms of changes in UA level, although probiotic supplementation improved UA levels in patients with stage III and IV CKD [16], it showed no effect on UA among healthy active adults [18], leading to uncertainty about the beneficial effect of probiotics on modulating UA levels.

Overall, data regarding the effects of probiotic, prebiotic, and synbiotic supplementation on renal profiles remains limited and inconclusive. The present systematic review and meta-analysis aimed to discover whether the manipulation of gut microbiome with the aid of prebiotic, probiotic, and synbiotic supplementation will improve renal parameters including urea, creatinine, UA, GFR, and BUN.

Material and methods

Search strategy and study selection criteria

The present meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [19]. A systematic literature search was developed to search the MEDLINE, Scopus, and Google scholar databases for RCTs from July 1967 to March 2016. Additionally, references to identified articles were manually searched to complement the database searching. The following MeSH search terms were used to identify relevant published articles: *prebiotics, probiotics, synbiotics in combination with urinary tract, kidney, UA, urea, creatinine* and *glomerular filtration rate*. No restrictions were made in terms of publication date. We independently performed the literature search, study selection, and data extraction, and disagreements were resolved by consensus.

Study inclusion and exclusion criteria

Published articles were included in the meta-analysis if they were in the English language and investigated the effects of prebiotic, probiotic or synbiotic supplements on renal outcomes. These data were extracted from studies that investigated the renal profile as main outcomes, or from other trials where renal data could be obtained from secondary outcomes. Studies that did not have a control group or only investigated renal toxins were excluded. The analysis was restricted to participants with age ≥18 y.

Data extraction

We independently extracted the following data from each article: first author's last name, year of publication, number of participants in the studies, underlying condition of their participants, their age range and mean, sex, the study design, the type of supplement in the intervention and control groups, the dosage of supplements, study duration, and mean and SD of the renal profile tests before and after intervention. Contacts were made with authors of some papers to request additional data. The standardized mean difference and corresponding SEs were calculated by using postintervention data for all eligible reports.

Quality assessment

The quality of the studies was assessed using the Jadad Scale. The scores ranged from 0 to 5, with 5 indicating the best quality of research. The Jadad Scale scores studies based on randomization, blinding, and providing an account of all participants [20].

Statistical analysis

This meta-analysis was conducted on the mean difference and SE for intervention and control groups. To calculate summary mean estimates with their corresponding 95% confidence interval (CI), a random-effects model was used [21]. Cochran's Q test and I^2 were used to examine between study statistical heterogeneity [22]. Subgroup analyses were performed to recognize the possible sources of heterogeneity between studies. A fixed model was run to identify the between-subgroup heterogeneity. Sensitivity analyses were run to examine the extent to which conclusions might rely on a particular study or studies. Visual inspections of funnel plots for asymmetry [23], Egger's regression asymmetry and Begg's adjusted rank correlation test [24] were carried out to evaluate publication bias. Statistical analyses were conducted in Stata, version 11.2 (Stata Corp., College Station, TX, USA). $P < 0.05$ was considered statistically significant.

Results

Literature search

Of 437 screened studies, 25 received full-text reviews. Of these studies, 13 were entered into the meta-analysis (Fig. 1). Cox et al.'s study was included as two reports that evaluated single- and multiple-strains of probiotic supplementation [18]. The full-text of one of the eligible articles was not found despite contacting the corresponding author to obtain as much accurate information as possible; therefore, relevant data were extracted by using its abstract [25]. One study was excluded [16] because it was the pilot of another study, which was used in this meta-analysis [26].

One study was an open-label prospective study [27], one was an open-label RCT [25], three studies were crossover RCTs [26,28,29], and the rest were parallel-group double-blind RCTs [8,17,18,30–34]. The quality of studies was between 1 and 5 using Jadad scaling, with only five having a complete score of 5 [8,28,30,31,34] (Table 1).

Characteristics of studies and participants

Included in these studies, were 721 participants ranging in age from 24 to 84 y, including 326 men and 383 women (the number of each sex was not clear in the Pavan study [25]). In all, 185 participants had CKD, 155 had type 2 diabetes, 162 were hospitalized patients, and 192 were healthy individuals. Duration of intervention ranged from 1 to 24 wk. Three studies used single-strain probiotics for intervention [17,27,33], five used multistrain probiotics [8,26,29,31,32], one used prebiotics [34], three used synbiotics [25,28,30], and one used single and double strains in each arm [18].

Eight studies examined the effects of probiotic supplementation on serum creatinine (N = 464) [8,17,26–28,31,33,34]. Six trials explored changes in GFR (N = 376) [8,25,27,28,30,34] and UA (N = 296) [18,26,29,31,32], three studies evaluated changes in BUN levels (N = 108) [17,26,31] and two studies (three effect sizes) examined changes in urea levels (N = 226) [8,18].

Findings from the meta-analysis

Figure 2 presents the pooled effect of prebiotic, probiotic, and synbiotic supplementation on GFR. A non-significant reduction of GFR after consumption of prebiotics, probiotics, and synbiotics was noted (MD, –2.00 mL/min/1.73 m^2; 95% CI, –5.15 to 1.16; $P = 0.215$). There was significant heterogeneity among studies ($I^2 = 88.9\%$; $P < 0.0001$). Subgroup analyses based on the duration of study, the strain of probiotic supplement, and presence of renal disease could not explain the heterogeneity between studies (Table 2). However, individuals who consumed a single strain of probiotics had significantly lower GFR compared with the control group (MD, –9.32 mL/min/1.73 m^2; 95% CI, –16.92 to –1.73; $P = 0.016$) with no significant heterogeneity ($I^2 = 0.0$; $P = 0.56$) (Table 3). Findings from sensitivity analysis indicated that excluding an individual study would not change the significance of the findings. No evidence of publication bias was observed (for Egger's test, $P = 0.305$).

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