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The effects of probiotics on renal function and uremic toxins in patients with chronic kidney disease; a meta-analysis of randomized controlled trials

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ABSTRACT

Context: There is mounting evidence suggesting bidirectional crosstalk between microbiota and host. However, the effects of probiotics on renal function and uremic toxins in chronic kidney disease (CKD) patients are unclear.

Evidence Acquisitions: A literature review was conducted using MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews from inception through November 2017 to identify randomized controlled trials (RCTs) assessing the effects of probiotics on renal function and uremic toxins in CKD patients. Effect estimates from the individual studies were extracted and combined using fixed-effect meta-analysis with inverse variance weights.

Results: Five RCTs with 161 CKD patients were enrolled. Compared to controls, there were no significant differences in serum creatinine and estimated glomerular filtration rate (eGFR) after post-probiotic course (4 weeks to 6 months) with standardized mean differences (SMDs) of 0.01 (95% CI -0.29 to 0.30) and -0.01 (95% CI -0.43 to 0.41), respectively. Compared to the controls, p-cresol levels were significantly reduced after treatment with probiotics with SMD of -0.61 (95% CI -1.04 to -0.19). No significant infectious complications were noted during treatment with probiotics in CKD patients.

Conclusions: Based on the findings of our meta-analysis, there are no significant changes in serum creatinine or eGFR after short-term treatment with probiotics, when compared to controls. However, our meta-analysis suggests potential beneficial effects of probiotics on uremic toxins in CKD patients. Future studies are required to assess its long-term effects on CKD progression and uremic toxins.

Review

Implication for health policy/practice/research/medical education:
The impact of probiotics on renal function and uremic toxins in chronic kidney disease (CKD) patients are unclear. In this systematic review and meta-analysis consisting of five randomized controlled trials (RCTs) with 161 CKD patients, we demonstrate no significant changes in creatinine and eGFR after short-term treatment with probiotics when compared to controls. However, there are potential beneficial effects of probiotics on uremic toxins in CKD patients.

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1. Background

Despite advancements in medicine, chronic kidney disease (CKD) remains a major public health issue (1,2) affecting as many as 10% to 15% of the adult population worldwide (3-8). Studies have demonstrated associations of CKD with increased risks of cardiovascular disease, significant comorbidities, increased health care costs, reduced quality of life, and increased mortality (2, 9). The progressive decline in kidney function in CKD patients can lead to end-stage renal disease (ESRD) resulting

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in further increased morbidity and mortality (10,11). Average annual costs for a dialysis patient (including hospitalizations) range from US $70 000 to $100 000 per patient (2,12).

In recent years, the influence of intestinal microbiota on health and disease has been the focus of increasing interest (13-15). Interactions between hosts and microbes are essential to many physiological aspects including nutrition and immune homeostasis (13). Intestinal dysbiosis, an imbalance between pathogenic and protective microbiota, has been associated with a variety of health conditions including Clostridium difficile (16,17), Crohn's disease (18,19), non-alcoholic steatohepatitis (NASH) (20), and systemic inflammation (21). Studies have also demonstrated the important role of intestinal dysbiosis in renal physiology and pathophysiology (22,23) such as accumulation of uremic toxins, systemic inflammation, and infection, which all may contribute to the development of CKD, its progression, and its complications (22,24-29). Restoration of microbiome diversity by administration of probiotics may provide beneficial effects on kidneys (25,30-33). This has been shown in uremic rats and kidney ischemia reperfusion injury models (34-37). However, the effects of probiotics on renal function and uremic toxins in vivo in CKD patients are still unclear. Therefore, we conducted this systematic review and meta-analysis to assess the effects of probiotics on renal function as well as uremic toxins in CKD patients.

2. Evidence acquisitions

2.1. Literature review and search strategy

C.T. and W.C individually searched published studies and conference abstracts indexed in EMBASE, MEDLINE, and the Cochrane database from inception through November 2017 using the following words: "prebiotics", "synbiotics" or "probiotic" AND "renal" or "chronic kidney disease", or "kidney" (Supplementary file 1). A supplementary search for important studies employing references from the retrieved studies was consequently conducted. Divergent decisions were settled by joint consensus.

2.2. Selection criteria and outcomes

We included 1) randomized controlled trials (RCTs) published as original studies or conference abstracts that assessed the effects of probiotics on renal function and uremic toxins in non-dialysis CKD patients, 2) studies that included data allowing calculation for mean differences (MDs), standardized mean differences (SMDs), relative risks, or hazard ratios with 95% confidence intervals (CIs), and 3) a reference control group composed of patients without probiotics.

The outcomes of our study consist of changes in serum creatinine and estimated glomerular filtration rate (eGFR), and p-cresol levels after a post-probiotic course. The characteristics and quality of each study are demonstrated in Table 1 (38-42).

2.3. Data abstraction

A classified information collection record was used to obtain the following data: year, study sample, total number, randomized study, double blinding status, placebo control, crossover, washout period, prebiotics, probiotics, and duration of probiotics.

2.4. Statistical analysis

Analysis were completed using the Comprehensive Meta-Analysis 3.3 software (version 3; Biostat Inc, Englewood, NJ, USA). Effect estimates from the individual studies were extracted and combined using fixed-effect meta-analysis with inverse variance weights (43). Given the low likelihood of between-study variances, a fixed-effect model was used. We tested for heterogeneity using the Q-statistic ($P<0.10$ was considered significant) and I^2 test. A value of I^2 of 0%–25% indicates insignificant heterogeneity, 26%–50% low heterogeneity, 51%–75% moderate heterogeneity and 76%–100% high heterogeneity (44). For assessment of publication bias, we performed funnel plots and calculated Egger's regression intercept for studies (45).

3. Results

The search strategy of systematic review produced 491 potentially relevant articles: 427 were omitted because their titles or abstracts explicated that they did not meet inclusion criteria due to the type of article, study design, study population, or outcome of interest (Supplementary file 2). The remaining 64 articles underwent full-length review: 59 were furthered omitted because they were not RCTs (n=17), patient populations included ESRD patients on dialysis (n=7) (46-52) or did not describe outcomes of interest (n=35). Five RCTs (38-42) with 161 CKD patients were included in this systematic review. Of 5 RCTs, 4 RCTs compared probiotics with controls (Table 1), and were included in the meta-analysis. Table 1 and Table 2 show the detailed characteristics, type of probiotics and data of all included RCTs (38-42).

3.1. Effects of probiotics on renal function in CKD patients

Study populations consisted of patients with CKD 3 to 5 (the majority of patients had CKD stage 3 to 4 and <15% had CKD stage 5). The duration of probiotic treatment

Table 1. Main characteristics of the RCTs included in this meta-analysis

Study	Ranganathan et al (38)	Guida et al (39)	Miranda Alatriste et al (40)	Pavan (41)	Rossi et al(42)
Year	2010	2014	2014	2016	2016
Study sample	CKD stage 3-4; SCr > 2.5 mg/dL	CKD stage 3-4	CKD stage 3-4	CKD stage 3-5; not on dialysis	CKD stage 4-5; not on dialysis
Total number	46	30	30	24	31
Randomized study	Yes	Yes	Yes	Yes	Yes
Double blinding	Yes	Yes	Yes	No	Yes
Placebo control	Yes	Yes	No	Yes	Yes
Crossover	Yes	No	No	No	Yes
Washout period	No	N/A	N/A	N/A	4 weeks
Prebiotics	No	Inulin	No	Fructo-oligosaccharides	Insulin, fructo-oligosaccharides, galacto-oligosaccharides
Probiotics	L. acidophilus KB27, B. Longum KB 31, S. Thermophilus KB19 ($90x10^9$ CFU/day, $15x\ 10^9$ CFU/cap, 2 caps x 3 times daily)	Probinul neutron ($5x\ 10^9$ Lactobacillus plantarum, $2x10^9$ Lactobacillus casei subsp rhamnosus, $2x10^9$ Lactobacillus gasseri, $1x10^9$ Bifidobacterium infantis, $1x10^9$ Bifidobacterium longum, $1x10^9$ Lactobacillus acidophilus, $1x10^9$ lactobacillus salivarius, $1x10^9$ lactobacillus sporogenes, $5x10^9$ streptococcus thermophilus) 3 times daily	$8x10^9$ or $16x10^9$ lactobacillus casei shirota daily	$15x10^9$ Streptococcus thermophilus, $15x10^9$ lactobacillus acidophilus, $15x10^9$ bidifobacterium longum; 3 tablets daily	Nine different strains across the Lactobacillus, Bidifobacteria, and streptococcus; $45x10^9$ CFU/cap, 1 cap x 2 times daily
Duration of probiotics	3 months	4 weeks	8 weeks	6 months	6 weeks

Table 2. Data from RCTs included in this meta-analysis

Study	Marker	N of total	Before probiotics	N of probiotics	After probiotics	N of control	Control
Ranganathan et al (38)	Creatinine (mg/dL)	N/A	N/A	46	388.5±229.8	46	414.0±342.3
	Uric acid (mg/dL)	N/A	N/A	46	517.1±99.4	46	504.5±73.9
	BUN (mg/dL)	N/A	N/A	46	23.8±12.0	46	25.9±15.1
Guida et al (39)	p-cresol (mcg/mL)	18	3.1 (1.3-6.5)	18	15 days 2.3 (0.4-3.6); 30 days 0.8 (0.3-3.7)	12	15 days 3.7 (2.0-6.1); 30 days 3.9 (3.2-5.8)
Miranda Alatriste et al (40)	Urea (mL/min)	30	81.7±26.4	30	73.2±19.5	N/A	N/A
	Creatinine (mg/dL)	30	2.48±0.89	30	2.47±1.04	N/A	N/A
	GFR (mL/min/BSA)	30	30.7±11.77	30	31.86±12.34	N/A	N/A
Pavan (41)	Creatinine (mg/dL)	N/A	N/A	12	4.45±0.30	12	4.3±0.31
	GFR (mL/min/BSA)	N/A	N/A	12	14.5±11.7	12	14.9±10.1
	GFR decline (mL/min/BSA)	N/A	N/A	12	-3.4±4.6	12	-11.6±8.6
Rossi et al (42)	Total indoxyl sulfate (µmol/L)	37	18 (12-27)	31	15 (10-26)	31	16 (12-27)
	Total p-cresyl sulfate (µmol/L)	37	110 (71-130)	31	75 (36-101)	31	93 (54-136)
	Free indoxyl sulfate (µmol/L)	37	0.7 (0.4-1.0)	31	0.6 (0.4-0.8)	31	0.5 (0.4-1.0)
	Free p-cresyl sulfate (µmol/L)	37	3.0 (2.0-3.9)	31	2.2 (0.7-2.8)	31	2.4 (1.1-3.4)
	GFR (mL/min/BSA)	N/A	N/A	31	24±8	31	24±8
	Creatinine (mg/dL)	N/A	N/A	31	231±75	31	233±74
	KIM-1 (ng/mL)	N/A	N/A	27	1.1 (0.4-2.7)	27	1.1 (0.4-2.1)
	IL-1B (pg/mL)	N/A	N/A	31	0.8±0.7	31	0.8±0.6
	IL-6 (pg/mL)	N/A	N/A	31	2.2±0.9	31	2.0±0.8
	IL-10 (pg/mL)	N/A	N/A	31	3.6±2.0	31	3.6±2.1
	TNF-alpha (pg/mL)	N/A	N/A	31	2.2±0.8	31	2.0±0.7

was between 4 weeks and 6 months. No significant infectious complications were noted during treatment with probiotics in CKD patients.

Compared to controls, there were no significant differences in serum creatinine and eGFR after post-probiotic course (4 weeks to 6 months) with SMDs of 0.01 (95% CI -0.29 to 0.30, P =0.95, I^2= 0, Figure 1) and -0.01 (95% CI -0.43 to 0.41, P =0.96, I^2= 0, Figure 2), respectively.

The data on the effects of probiotics on progression of CKD were limited. Pavan (41) demonstrated that the decline of eGFR during prebiotic and probiotic administration was significantly lower (-11.6 ± 8.6 vs. -3.4 ± 4.6 mL/min per 1.73 m^2/year, 95% CI -6.45 to -9.86, P< 0.001) when compared to low protein diet alone. Ranganathan et al, also demonstrated a reduction of uric acid levels among patients with CKD stage 3 and 4 treated with probiotics (38,53).

3.2. Effects of probiotics on uremic toxins in CKD patients

Compared to the controls, p-cresol levels were significantly reduced after treatment with probiotics with SMD of -0.61 (95% CI -1.04 to -0.19, P = 0.005, I^2= 77, Figure 3). Due to between-study heterogeneity, a sensitivity analysis was performed using a random-effect model, which demonstrated that probiotics could reduce p-cresol levels. However, the reduction did not approach statistical significance with SMD of -0.79 (95% CI -1.78 to 0.20, P = 0.12, I^2= 77). The data on other uremic toxin were limited. Rossi et al (24) demonstrated a reduction in serum indoxyl sulfate after treatment with *Lactobacillus, Bifidobacteria and Streptococcus* genera with prebiotic. With limited evidence, several studies also showed a small reduction in blood-urea-nitrogen with probiotic treatment (38,40,53).

3.3. Evaluation for publication bias

Funnel plot (Figure 4) and Egger's regression was performed to evaluate for publication bias regarding the effects of probiotics on creatinine. This showed no significant publication bias (P = 0.11). Due to the limited number of studies, however, this test lacked the power to differentiate chance from true asymmetry (54).

4. Discussion

In this systematic review and meta-analysis of 5 RCTs with 161 CKD patients, we demonstrated no significant changes in serum creatinine or eGFR after short-term treatment with probiotics. However, probiotic use potentially reduced uremic toxins in CKD patients.

Some well-known pro-inflammatory uremic toxins including indoxyl sulfate and p-cresol sulfate are mainly produced in the colon (55). In CKD patients, dysbiosis and changes in colonic function (56) can result in further

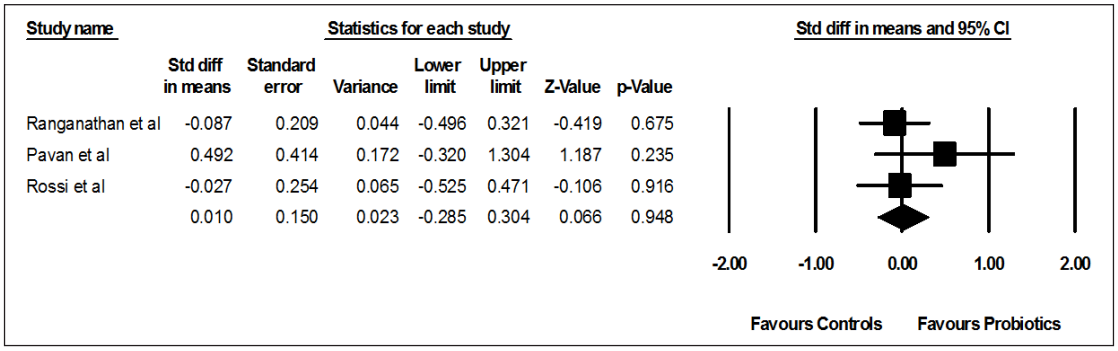

Figure 1. Forest plot evaluating effects of probiotics vs. controls on serum creatinine in CKD patients.

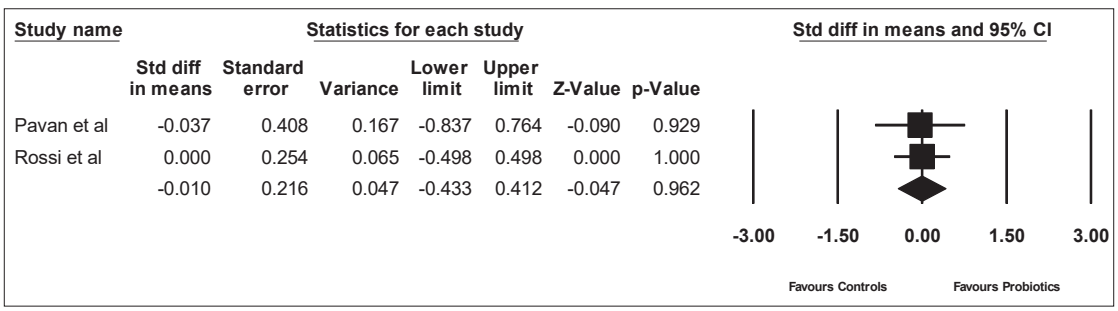

Figure 2. Forest plot of all studies evaluating effects of probiotics vs. controls on eGFR in CKD patients.

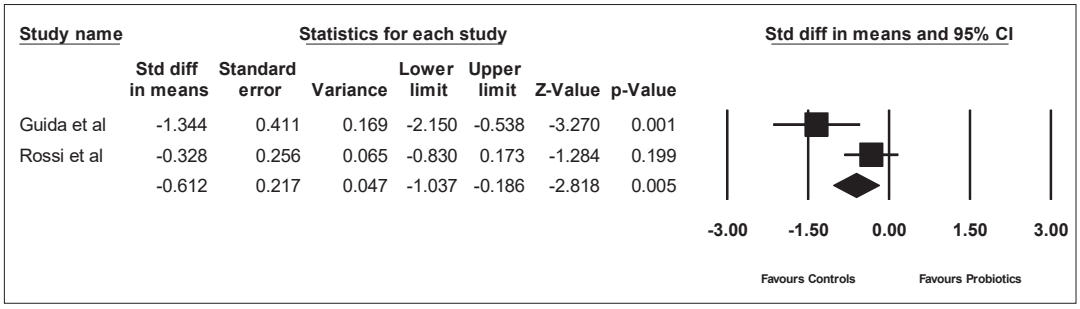

Figure 3. Forest plot of all studies evaluating effects of probiotics vs. controls on p-cresol levels in CKD patients.

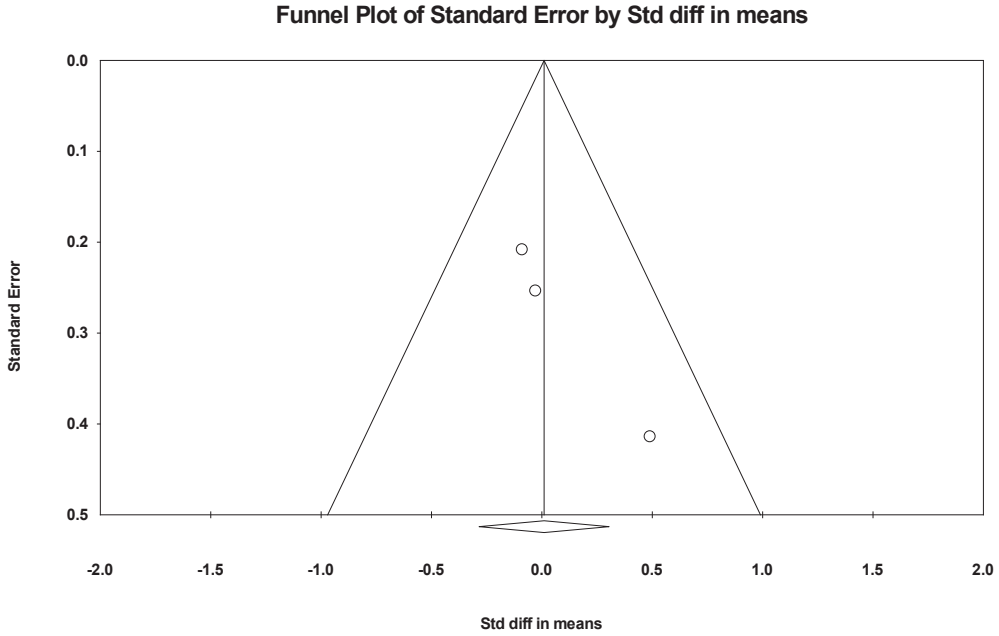

Figure 4. Funnel plot evaluating publication bias regarding the effects of probiotics on creatinine.

accumulation of uremic toxins (22,24-26,28). Human and animal models suggest that a shift in microbiome consisting of an increase in bacteria that produce urease, uricase, p-cresol- and indole-forming enzymes and a decrease in bacteria that possess short-chain fatty acid forming enzymes can lead to the findings of higher uremic toxins (56,57). Thus, restoration of microbiome by probiotics may provide beneficial effects in CKD patients by reducing uremic toxin production in the gut (25,30-33). Our meta-analysis would support this hypothesis with the finding of a potential reduction in uremic toxins in CKD patients treated with probiotics.

Bacterial toxic products such as p-cresol, indoxyl sulfate, and trimethylamine N-oxide can affect podocytes and renal tubules (58-60). Thus, probiotics may help improve renal function by the direct reduction of uremic toxins (22,53). Furthermore, several studies have shown that probiotics may potentially reduce inflammation and oxidative stress in CKD patients (61-63). Additionally, manipulation of gastrointestinal flora can affect urinary oxalate excretion and decrease urinary supersaturation levels (64); this may decrease nephrolithiasis formation rates and help manage oxalate nephropathy. Treatment with probiotics, however, did not significantly reduce serum creatinine or eGFR after 4 weeks to 6 months treatment when compared to controls in our study. Despite the nonsignificant probiotic effects on creatinine or eGFR in our meta-analysis, Pavan (41) had demonstrated that prebiotic and probiotic administration reduced the downward trend of eGFR in CKD patients when compared to controls. As there are numerous potential contributors and causes of CKD, it is still possible that probiotics may provide benefit in specific CKD subgroups and that a larger sample size is needed in those populations to detect a statistical significance.

Several limitations of our meta-analysis are noteworthy. First, there was statistical heterogeneity between the

studies that evaluated the impacts of probiotics on p-cresol levels. Consequently, using a random-effect model, the effects of probiotics on p-cresol levels did not achieve statistical significance. Further studies consisting of larger RCTs are needed. Second, the colon has been identified as the primary source (greater than 30%) of plasma uremic toxins/compounds in addition to p-cresol sulfate (55). Although it is possible that probiotics may provide benefits on other uremic solutes, these data are still limited (42). Third, the rate of creatinine or eGFR decline in CKD patients will vary significantly based on each individual patient's underlying CKD etiologies and management. Consequently, the treatment duration and follow-up period may have been too short to detect a significant change in the creatinine or eGFR in a relatively small number of patients. A larger sample size with longer treatment and follow-up due to the heterogeneity of CKD patients would be beneficial.

5. Conclusions

In conclusion, this systematic review and meta-analysis shows no significant differences in serum creatinine or eGFR, after short-term treatment (4 weeks to 6 months) with probiotics. However, probiotics may reduce uremic toxins in CKD patients. Future studies are needed to evaluate the long-term effects of probiotics on CKD progression and uremic toxins.

Authors' contributions

CT and WC performed data acquisition, and statistical analysis. CT and MM were involved in manuscript creation. WC and MM supervised the project. All authors approved the manuscript.

Conflicts of interest

The authors deny any conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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Supplementary Materials

Supplementary file 1. Search Strategy.
Supplementary file 2. Outline of search methodology.

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