The Role of Dietary Fiber Supplementation in Regulating Uremic Toxins in Patients With Chronic Kidney Disease: A Meta-Analysis of Randomized Controlled Trials

- Hui-Li Yang, BSN
- Ping Feng, MS
- Yi Xu, MS
- Yun-Ying Hou, PhD
- Omorogieva Ojo, PhD
- <u>Xiao-Hua Wang, PhD</u>

Published:March 16, 2021DOI:https://doi.org/10.1053/j.jrn.2020.11.008

Objectives

The results of previously published meta-analyses showed that dietary fiber could reduce the levels of *p*-cresyl sulfate, blood urea nitrogen, and creatinine in patients with chronic kidney disease (CKD). However, these results were based on some trials with pre-post design and randomized controlled trials of low quality. Additionally, it has been suggested that the dosage and duration of fiber supplementation and patients' characteristics potentially influence the effect of dietary fiber in reducing uremic toxins, but it would appear that no research has provided reliable evidence.

Design and Methods

We searched PubMed, Web of Science, and Cochrane Library. Data were pooled by the generic inverse variance method using random effects models and expressed as standardized mean difference (SMD) with 95% confidence interval (CI). Heterogeneity was quantified by *P*. Publication bias was evaluated by Egger's test. **Results**

Ten randomized controlled trials involving 292 patients with CKD were identified. Dietary fiber supplementation can significantly reduce the levels of indoxyl sulfate (SMD = -0.55, 95% CI = -1.04, -0.07, P = .03), *p*-cresyl sulfate (SMD = -0.47, 95% CI = -0.82, -0.13, P < .01), blood urea nitrogen (SMD = -0.31, 95% CI = -0.58, -0.03, P = .03), and uric acid (SMD = -0.60, 95% CI = -1.02, -0.18, P < .01), but not on reducing creatinine (SMD = -0.31, 95% CI = -0.73, 0.11, P = .14). In subgroup analyses, the reduction of indoxyl sulfate was more obvious among patients on dialysis than patients not on dialysis (P for interaction = .03); the reduction of creatinine was more obvious among patients without diabetes than those with diabetes (P for interaction <.01).

Conclusions

This meta-analysis indicates that dietary fiber supplementation can significantly reduce the levels of uremic toxins in patients with CKD, with evidence for a more obvious effect of patients on dialysis and without diabetes. These findings inform recommendations for using dietary fiber to reducing the uremic toxin among CKD patients in clinical practice.

To read this article in full you will need to make a payment

References

1.

- Fujii H.
- Goto S.
- Fukagawa M.

Role of uremic toxins for kidney, cardiovascular, and bone dysfunction.

Toxins (Basel). 2018; **10**: 202

2.

- Yamamoto S.
- Fukagawa M.

Uremic toxicity and bone in CKD.

J Nephrol. 2017; 30: 623-627

3.

- o Vanholder R.
- Schepers E.
- Pletinck A.
- Nagler E.V.
- \circ Glorieux G.

The uremic toxicity of indoxyl sulfate and *p*-cresyl sulfate: a systematic review.

J Am Soc Nephrol. 2014; 25: 1897-1907

4.

- Jourde-Chiche N.
- Burtey S.

Accumulation of protein-bound uremic toxins: the kidney remains the leading culprit in the gut-liver-kidney axis.

Kidney Int. 2020; 97: 1102-1104

- 5.
- Barrios C.
- Beaumont M.
- Pallister T.
- ∘ et al.

Gut-microbiota-metabolite axis in early renal function decline.

PLoS One. 2015; 10: e0134311

6.

- Sirich T.L.
- Funk B.A.
- Plummer N.S.
- Hostetter T.H.
- Meyer T.W.

Prominent accumulation in hemodialysis patients of solutes normally cleared by tubular secretion.

J Am Soc Nephrol. 2014; 25: 615-622

7.

- Itoh Y.
- Ezawa A.
- Kikuchi K.
- Tsuruta Y.
- Niwa T.

Protein-bound uremic toxins in hemodialysis patients measured by liquid chromatography/tandem mass spectrometry and their effects on endothelial ROS production.

Anal Bioanal Chem. 2012; 403: 1841-1850

8.

- Cosola C.
- Rocchetti M.T.
- Sabatino A.
- Fiaccadori E.
- Di Iorio B.R.
- o Gesualdo L.

Microbiota issue in CKD: how promising are gut-targeted approaches?.

J Nephrol. 2019; 32: 27-37

9.

• Lisowska-Myjak B.

Uremic toxins and their effects on multiple organ systems.

Nephron Clin Pract. 2014; **128**: 303-311

10.

- Mann J.
- Cummings J.H.
- Englyst H.N.
- et al.

FAO/WHO scientific update on carbohydrates in human nutrition: conclusions.

Eur J Clin Nutr. 2007; 61: S132-S137

11.

- Sabatino A.
- Regolisti G.
- Gandolfini I.
- et al.

Diet and enteral nutrition in patients with chronic kidney disease not on dialysis: a review focusing on fat, fiber and protein intake.

J Nephrol. 2017; 30: 743-754

12.

- Sanghavi S.
- Whiting S.
- Uribarri J.

Potassium balance in dialysis patients.

Semin Dial. 2013; 26: 597-603

13.

- Sonnenburg E.D.
- Smits S.A.
- Tikhonov M.
- Higginbottom S.K.
- Wingreen N.S.
- Sonnenburg J.L.

Diet-induced extinctions in the gut microbiota compound over generations.

Nature. 2016; 529: 212-215

14.

• Reimer R.A.

- Soto-Vaca A.
- Nicolucci A.C.
- et al.

Effect of chicory inulin-type fructan-containing snack bars on the human gut microbiota in low dietary fiber consumers in a randomized crossover trial.

Am J Clin Nutr. 2020; 111: 1286-1296

15.

- o Makki K.
- Deehan E.C.
- Walter J.
- Bäckhed F.

The impact of dietary fiber on gut microbiota in host health and disease.

Cell Host Microbe. 2018; 23: 705-715

16.

- Esgalhado M.
- Kemp J.A.
- Azevedo R.
- et al.

Could resistant starch supplementation improve inflammatory and oxidative stress biomarkers and uremic toxins levels in hemodialysis patients? A pilot randomized controlled trial.

Food Funct. 2018; 9: 6508-6516

17.

- Khosroshahi H.T.
- Abedi B.
- Ghojazadeh M.
- Samadi A.
- Jouyban A.

Effects of fermentable high fiber diet supplementation on gut derived and conventional nitrogenous product in patients on maintenance hemodialysis: a randomized controlled trial.

Nutr Metab (Lond). 2019; 16: 18

- Salmean Y.A.
- Segal M.S.
- Palii S.P.
- o Dahl W.J.

Fiber supplementation lowers plasma p-cresol in chronic kidney disease patients.

J Ren Nutr. 2015; 25: 316-320

19.

- Chiavaroli L.
- Mirrahimi A.
- Sievenpiper J.L.
- Jenkins D.J.
- Darling P.B.

Dietary fiber effects in chronic kidney disease: a systematic review and meta-analysis of controlled feeding trials.

Eur J Clin Nutr. 2015; 69: 761-768

20.

- o Wu M.
- Cai X.
- $\circ \quad \text{Lin J.}$
- Zhang X.
- Scott E.M.
- o Li X.

Association between fibre intake and indoxyl sulphate/P-cresyl sulphate in patients with chronic kidney disease: meta-analysis and systematic review of experimental studies.

Clin Nutr. 2019; 38: 2016-2022

21.

- Moher D.
- o Liberati A.
- Tetzlaff J.
- Altman D.G.
- PRISMA Group

Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.

PLoS Med. 2009; 6: e1000097

22.

- Hozo S.P.
- Djulbegovic B.
- Hozo I.

Estimating the mean and variance from the median, range, and the size of a sample.

BMC Med Res Methodol. 2005; 5: 13

23.

- Garofalo C.
- Borrelli S.
- Provenzano M.
- et al.

Dietary salt restriction in chronic kidney disease: a meta-analysis of randomized clinical trials.

Nutrients. 2018; **10**: 732

24.

- Elbourne D.R.
- \circ Altman D.G.
- $_{\circ}$ $\,$ Higgins J.P. $\,$
- Curtin F.
- \circ Worthington H.V.
- Vail A.

Meta-analyses involving cross-over trials: methodological issues.

Int J Epidemiol. 2002; 31: 140-149

25.

- Heyland D.K.
- Novak F.
- $\circ \quad \text{Drover J.W.}$
- ∘ Jain M.
- o Su X.
- Suchner U.

Should immunonutrition become routine in critically ill patients? A systematic review of the evidence.

JAMA. 2001; 286: 944-953

26.

- Higgins J.P.
- Altman D.G.
- Gøtzsche P.C.
- ∘ et al.

The Cochrane Collaboration's tool for assessing risk of bias in randomised trials.

BMJ. 2011; **343**: d5928

- Schünemann H.J.
- Oxman A.D.
- Brozek J.
- et al.

Grading quality of evidence and strength of recommendations for diagnostic tests and strategies.

BMJ. 2008; 336: 1106-1110

28.

- Egger M.
- Smith G.D.

Bias in location and selection of studies.

BMJ. 1998; **316**: 61-66

29.

- o Li L.
- \circ Xiong Q.
- o Zhao J.
- et al.

Inulin-type fructan intervention restricts the increase in gut microbiomegenerated indole in patients with peritoneal dialysis: a randomized crossover study.

Am J Clin Nutr. 2020; 111: 1087-1099

30.

- Laffin M.R.
- Tayebi Khosroshahi H.
- Park H.
- et al.

Amylose resistant starch (HAM-RS2) supplementation increases the proportion of Faecalibacterium bacteria in end-stage renal disease patients: microbial analysis from a randomized placebo-controlled trial.

Hemodial Int. 2019; 23: 343-347

- Poesen R.
- Evenepoel P.
- \circ de Loor H.
- \circ et al.

The influence of prebiotic arabinoxylan oligosaccharides on microbiota derived uremic retention solutes in patients with chronic kidney disease: a randomized controlled trial.

PLoS One. 2016; 11 (Published 2016 Apr 21): e0153893

32.

- Tayebi-Khosroshahi H.
- Habibzadeh A.
- Niknafs B.
- \circ et al.

The effect of lactulose supplementation on fecal microflora of patients with chronic kidney disease; a randomized clinical trial.

J Ren Inj Prev. 2016; 5 (Published 2016 Jul 29): 162-167

33.

- o Meksawan K.
- Chaotrakul C.
- Leeaphorn N.
- Gonlchanvit S.
- Eiam-Ong S.
- Kanjanabuch T.

Effects of fructo-oligosaccharide supplementation on constipation in elderly continuous ambulatory peritoneal dialysis patients.

Perit Dial Int. 2016; 36: 60-66

34.

- Shimada M.
- Nagano N.
- \circ Goto S.
- et al.

Effect of polydextrose intake on constipation in Japanese dialysis patients: a triple-blind, randomized, controlled trial.

J Nutr Sci Vitaminol (Tokyo). 2015; 61: 345-353

35.

- Sirich T.L.
- Plummer N.S.
- Gardner C.D.
- Hostetter T.H.
- Meyer T.W.

Effect of increasing dietary fiber on plasma levels of colon-derived solutes in hemodialysis patients.

Clin J Am Soc Nephrol. 2014; **9**: 1603-1610

36.

- Khan K.
- Jovanovski E.
- Ho H.V.T.
- et al.

The effect of viscous soluble fiber on blood pressure: a systematic review and meta-analysis of randomized controlled trials.

Nutr Metab Cardiovasc Dis. 2018; 28: 3-13

37.

- o Jovanovski E.
- Khayyat R.
- Zurbau A.
- et al.

Should viscous fiber supplementation be considered in diabetes control? Results from a systematic review and meta-analysis of randomized controlled trials.

Diabetes Care. 2019; 42: 755-766

38.

- Thompson S.V.
- Hannon B.A.
- \circ An R.
- Holscher H.D.

Effects of isolated soluble fiber supplementation on body weight, glycemia, and insulinemia in adults with overweight and obesity: a systematic review and meta-analysis of randomized controlled trials.

Am J Clin Nutr. 2017; 106: 1514-1528

39.

- Mair R.D.
- Sirich T.L.
- Meyer T.W.

Uremic toxin clearance and cardiovascular toxicities.

Toxins (Basel). 2018; **10**: 226

- o Miyamoto Y.
- Watanabe H.
- Noguchi T.

 \circ et al.

Organic anion transporters play an important role in the uptake of *p*-cresyl sulfate, a uremic toxin, in the kidney.

Nephrol Dial Transpl. 2011; 26: 2498-2502

41.

- Deguchi T.
- Ohtsuki S.
- Otagiri M.
- \circ et al.

Major role of organic anion transporter 3 in the transport of indoxyl sulfate in the kidney.

Kidney Int. 2002; 61: 1760-1768

42.

- o Wu W.
- Bush K.T.
- Nigam S.K.

Key role for the organic anion transporters, OAT1 and OAT3, in the in vivo handling of uremic toxins and solutes.

Sci Rep. 2017; 7: 4939

43.

- Lau W.L.
- ∘ Savoj J.
- Nakata M.B.
- Vaziri N.D.

Altered microbiome in chronic kidney disease: systemic effects of gutderived uremic toxins.

Clin Sci (Lond). 2018; **132**: 509-522

44.

- Sabatino A.
- Regolisti G.
- Brusasco I.
- Cabassi A.
- Morabito S.
- Fiaccadori E.

Alterations of intestinal barrier and microbiota in chronic kidney disease.

Nephrol Dial Transpl. 2015; 30: 924-933

45.

- Evenepoel P.
- Meijers B.K.
- Bammens B.R.
- Verbeke K.

Uremic toxins originating from colonic microbial metabolism.

Kidney Int Suppl. 2009; 76: S12-S19

46.

- Koh A.
- De Vadder F.
- Kovatcheva-Datchary P.
- Bäckhed F.

From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites.

Cell. 2016; 165: 1332-1345

47.

- Brändle E.
- Sieberth H.G.
- Hautmann R.E.

Effect of chronic dietary protein intake on the renal function in healthy subjects.

Eur J Clin Nutr. 1996; 50: 734-740

48.

- Waikar S.S.
- Bonventre J.V.

Can we rely on blood urea nitrogen as a biomarker to determine when to initiate dialysis?.

Clin J Am Soc Nephrol. 2006; 1: 903-904

49.

- Firouzi S.
- Haghighatdoost F.

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

Nutrition. 2018; **51-52**: 104-113

50.

• Treviño-Becerra A.

Uric acid: the unknown uremic toxin.

Contrib Nephrol. 2018; 192: 25-33

51.

- Sun Y.
- Sun J.
- Zhang P.
- Zhong F.
- Cai J.
- Ma A.

Association of dietary fiber intake with hyperuricemia in U.S. adults.

Food Funct. 2019; 10: 4932-4940

52.

- Koguchi T.
- Nakajima H.
- $_{\circ}$ $\,$ Wada M. $\,$
- et al.

Dietary fiber suppresses elevations of uric acid and allantoin in serum and urine induced by dietary RNA and increases its excretion to feces in rats.

J Nutr Sci Vitaminol (Tokyo). 2002; 48: 184-193

53.

- Camerotto C.
- Cupisti A.
- \circ D'Alessandro C.
- $\circ \quad \text{Muzio F.}$
- o Gallieni M.

Dietary fiber and gut microbiota in renal diets.

Nutrients. 2019; 11: 2149

54.

- Dworatzek P.D.
- Arcudi K.
- Gougeon R.
- Husein N.
- Sievenpiper J.L.
- \circ Williams S.L.

Nutrition therapy.

Can J Diabetes. 2013; 37: 45-55

55.

- o Mann J.I.
- De Leeuw I.
- $\circ \quad \text{Hermansen K.}$
- et al.

Evidence-based nutritional approaches to the treatment and prevention of diabetes mellitus.

Nutr Metab Cardiovasc Dis. 2004; 14: 373-394

Article info

Publication history

Published online: March 16, 2021 Footnotes

Conflicts of Interest: The authors declare no conflicts of interests.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Identification

DOI: https://doi.org/10.1053/j.jrn.2020.11.008