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Fiber Supplementation Lowers Plasma *p*-Cresol in Chronic Kidney Disease Patients

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Abstract

Objective—To determine the effects of supplemental fiber on plasma *p*-cresol, stool frequency, and quality of life (QoL) in chronic kidney disease (CKD) patients.

Design and Setting—In a 12-week single-blind study, participants were provided with control muffins and supplements (5.5 g sucrose/day) for 2 weeks, muffins containing 10 g/day pea hull fiber and control supplements for 4 weeks, and muffins with 10 g/day pea hull fiber and 15 g/day inulin as a supplement for 6 weeks.

Subjects—Individuals with CKD (n = 13; 6 males, 7 females; aged 65 ± 3 years; estimated glomerular filtration rate <50 mL/minute/1.73^2) completed the study.

Main Outcome Measures—Plasma *p*-cresol was determined by gas chromatography-mass spectrometry, stool frequency by 5-day journals, and QoL by the KDQOL-36™.

Results—Plasma *p*-cresol decreased from 7.25 ± 1.74 mg/L during week 1 to 5.82 ± 1.72 mg/L during week 12 (P < .05), and in participants with high compliance (>70% inulin intake), from 6.71 ± 1.98 mg/L to 4.22 ± 1.16 mg/L (P < .05). Total fiber intake increased from 16.6 ± 1.7 g/day during control to 26.5 ± 2.4 g/day (P < .0001) with the added pea hull and to 34.5 ± 2.2 g/day with pea hull and inulin (P < .0001). Stool frequency increased from 1.4 ± 0.2 stools/day during control to 1.9 ± 0.3 stools/day during both fiber periods (P < .05). No change in overall QoL was observed.

Conclusions—Supplementing the diet of CKD patients with fiber may be a dietary therapy to reduce *p*-cresol and improve stool frequency.

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Introduction

Progressive decline in kidney function leads to an accumulation of uremic molecules, such as *p*-cresol,[1] thought to contribute to uremic symptoms.[2] *p*-Cresol and its sulfated form have been shown to exert renal toxicity *in vitro*,[3–6] while high levels are associated with poor outcomes in hemodialysis patients.[7] In addition, it has been suggested that such molecules are implicated in the progression of chronic kidney disease (CKD)[8] as well as increased insulin resistance.[9,10] As *p*-cresol originates in the large intestine from the microbial breakdown of tyrosine,[11] it has been suggested that protein-rich colon contents, lacking fermentable carbohydrate substrate, may enhance the production of uremic molecules such as *p*-cresol because of increased proteolytic activities.[2] Furthermore, CKD patients consuming a diet very low protein, exhibited reduced serum levels of the uremic toxin, idoxyl sulfate.[12] Increasing the availability of fermentable carbohydrate substrate, primarily fiber, may lead to decreased generation of the uremic molecules.[13] Studies in healthy individuals[14] and hemodialysis (HD) patients[13] suggest a potential benefit of supplementing the diet with fermentable fiber on reducing *p*-cresol generation and concentration.

Supplemental fiber has been shown to lower serum urea nitrogen[15,16] and serum creatinine[17,18] in CKD patients. However, these studies did not investigate the impact fiber has on *p*-cresol or other molecules implicated in uremic symptoms. The aim of this pilot study was to determine the effects of supplemental fiber on plasma *p*-cresol, stool frequency, and quality of life (QoL) in CKD patients.

Methods

Patients with CKD were screened for inclusion criteria of aged >18 years and estimated glomerular filtration rate of ≤50 mL/minute/1.73 m^2. Exclusion criteria included diagnosis of acute kidney injury, glomerulonephritis, current use of immunosuppressant medications, and need for dialysis. This pilot study was approved by the University of Florida's Institutional Review Board 1 (IRB-01) and written informed consent was obtained from all participants.

A 12-week single-blind study was carried out. Participants consumed 1 control muffin/day (incorporated into their usual diet) and 5.5 g/day of sucrose (control supplement) for 2 weeks, muffins containing 10 g of fiber from pea hull (PH) fiber (BEST Pea Fiber; Best Cooking Pulses, Portage la Prairie, Manitoba, Canada) and the sucrose for 4 weeks (PH period), and the muffins containing 10 g of fiber from pea hull fiber and 15 g of inulin (Frutafit® HD; Sensus B.V., Roosendaal, The Netherlands), providing an additional 13.5 g of fiber for 6 weeks (PH + inulin period). The 5.5 g of sucrose was chosen as a control to match the energy content of inulin. Participants were blinded to interventions; however, they may have been able to distinguish between periods based on taste and volume of supplements provided.

Weight and height were assessed at the first clinic visit during the control period, and weight was reaccessed at study end. Participants completed the self-administered KDQOL-36™ questionnaires, 5-day stool frequency questionnaires, and 3-day food records during each

intervention period. Food records were analyzed for nutrient intake using (Food Processor®, version 10.6.0.0; ESHA Research Inc., Salem, OR). Food compliance was monitored through food records and supplement compliance by returned supplement packets.

Blood samples were collected at laboratories (Quest Diagnostics, Madison, NJ), situated near the participants' homes, twice during each intervention period. Serum urea, serum creatinine, ammonia, cystatin C, and C-reactive protein were analyzed using standard laboratory methods. Additional blood samples were collected at the Food Science and Human Nutrition clinical research facility at study baseline and on the last day of the study to determine plasma *p*-cresol. Total *p*-cresol in plasma was analyzed using a gas chromatography-mass spectrometry (GC-MS) method on plasma samples stored at −80 °C before analysis. After combined acid and heat deproteinization and deconjugation (hydrolysis of conjugates), *p*-cresol was extracted in ethyl acetate and injected into the Thermo Finnigan Trace DSQ Single Quadrupole GC-MS (Thermo Finnigan/Thermo Fisher Scientific, San Jose, CA) instrument. For use as a standard, *p*-cresol was purchased from Acros Organics/Thermo (Fisher Scientific, Morris Plain, NJ). The *p*-cresol-d_7 was obtained from C/D/N Isotopes (Pointe-Claire, Quebec, Canada) and used as internal standard. For the heat-acid intervention of the plasma samples and subsequent *p*-cresol extraction, a previously described method[19] was used, with minor modifications.

All data are presented as mean ± standard error. Analysis of variance was used to compare each mean and overall model significance was determined when $P < .05$. For stool frequency, the KDQOL-36™ subscales, and the individual symptoms list in the *Symptoms/ Problems List* subscale of the KDQOL-36™, paired *t*-tests were calculated. The natural logarithmic transformation was applied to meet the assumptions of normality when comparing the two transformed means of total *p*-cresol.

Results

Figure 1 shows the participant selection flow diagram. Participants ($n = 13$; 6 males, 7 females) were aged 65 ± 3 years (range: 47–80 years) with CKD, 10 with Stage 3, 1 with Stage 4, and 2 with Stage 5 using the National Kidney Foundation criteria.[20] Three patients had diabetes and 12 were hypertensive.

Compliance was 97% for muffins during control period, and 92% during the fiber intervention periods. Compliance was 91% for sucrose supplement during the first 6 weeks of the study. Inulin compliance was 84% (range: 57%–100%) providing an estimated 11.3 ± 0.6 g/day of inulin (range: 7.7–13.5 g/day).

Blood urea nitrogen, ammonia, creatinine, cystatin C, C-reactive protein, and estimated glomerular filtration rate were not significantly different between periods (Table 1). Total plasma *p*-cresol showed a 20% decrease from 7.25 ± 1.74 mg/L to 5.82 ± 1.72 mg/L ($P <$ .05) (Table 1). When excluding less compliant patients (defined as <70% inulin intake), total plasma *p*-cresol decreased with PH + inulin by 37% ($n = 10$), from 6.71 ± 1.98 mg/L to 4.22±1.16 mg/L ($P<.05$). Results of the GC-MS output were adjusted for method of

extraction by adding 10% to the GC-MS output to account for the difference between the 90% efficiency of the extraction method and the absolute total in the blood.[19]

Mean fiber intake increased from 16.6 ± 1.7 g/day (15.6 g, background diet; 1 g, control muffin) to 26.5 ± 2.4 g/day (17.3 g, background diet; 9.2 g, PH muffin) ($P < .0001$) in the PH period and to 34.5 ± 2.2 g/day (14.9 g, background diet; 9.2 g, PH muffin +10.4 g, inulin) during the PH + inulin period ($P <.0001$). Analysis of food records showed no significant changes in energy, fat, protein, or carbohydrate intakes between interventions. Participants reported higher stool frequency during the PH period (1.9 ± 0.3 stools/day) and PH + inulin period (1.9 ± 0.3 stools/day) compared with the control (1.4 ± 0.2) ($P <.05$).

Overall mean scores for KDQOL-36™ questionnaire were not significantly different between periods. There were no changes in the Symptom/Problem List, Effects of Kidney Disease, and Mental Component Summary subscale scores between periods. However, Burden of Kidney Disease subscale mean score improved from 65 ± 8 during control to 77 ± 7 ($P < .05$) and Physical Component Summary subscale increased from 37 ± 3 during control to 41 ± 3 during the PH period ($P < .05$).

Discussion

The role of supplemental fiber in reducing urea and serum creatinine in predialysis CKD patients has been studied, but not the impact on *p*-cresol.[15–17] However in HD patients, providing supplemental fiber has been shown to produce desirable reductions in plasma concentrations of *p*-cresol.[13] Plasma *p*-cresol levels reported in the present study were higher than those of healthy individuals,[19,20] similar to uremic patients,[21] but much lower than seen in hemodialysis patients.[19] Providing pea hull fiber and inulin reduced serum *p*-cresol by 24%, similar to that previously reported with oligofructose and inulin in HD patients,[13] demonstrating a potential benefit to individuals in earlier stages of the disease. Of note, the reduction was greater in patients with the greatest compliance, as determined by inulin intake, suggesting a dose response. Recently, Guida et al. showed a 40% reduction in *p*-cresol with the provision of a symbiotic, containing various probiotic organisms and 6.6 g/day of inulin, to Stage 3 and 4 CKD patients after 15 and 30 days.[22] This reduction is similar to the 37% reduction shown in the present study in those participants with highest compliance. However in the Guida et al. study, participants consumed a lower dose of inulin, suggesting that probiotic organisms provided may also have a role in lowering *p*-cresol. We did not see an effect on urea and creatinine in the present study which may be because of the moderate values observed for most of the participants.

Individuals with kidney disease consume on average 14.6 g of fiber per day, falling below recommendations[23] and the current US adult population intake, currently at 17 g/day.[24] In this study, participants' background fiber intake was 15.6, 17.3, and 14.9 g/day, for the control, PH, and PH + inulin periods, respectively. Providing a food fortified with pea hull, a fiber source very high in insoluble, less fermentable fiber, resulted in increased stool frequency. This finding is in agreement with previous studies of institutionalized elderly[25] and children.[26] This increase was achieved with no reported adverse side effects or impact on energy or macronutrient intake. Participants consumed an average intake 26.7 g/day of

fiber with the added pea hull fiber, meeting fiber recommendations for older women (21 g/day) and men (30 g/day) if a mixed population is considered. Although the participants in this study did not experience constipation, as defined as less than 3 bowel movements a week, this uremic symptom is common, particularly in end-stage kidney disease patients.[27] Insoluble fiber supplementation and its laxation effect may be of significant benefit to those in later stages CKD, particularly those on dialysis.[28] No further increase in stool frequency was observed with inulin supplementation. Although increased stool frequency has been reported with inulin[29] and oligofructose,[30] the expected increase would be small and likely masked by the significant effect of the pea hull fiber.

This study supports the premise that providing a highly fermentable fiber, such as inulin, reduces *p*-cresol generation potentially through the suppression of proteolytic and enhancement of saccharolytic fermentation. Pea hull fiber may have also contributed to the reduction of proteolytic fermentation by decreasing transit time; however, a measure of transit time was not assessed in this study.

Limitations of this pilot study include the small sample size, heterogeneity of participants, and lack of randomization to treatments. Lacking washout periods, and therefore possible carryover effects of interventions, may have impacted the magnitude of effects seen. Given these limitations and the significance of *p*-cresol reduction and potentially many other gut-generated uremic molecules, further study is warranted.

Conclusions

Modulation of colonic fermentation and function may be a therapeutic target to reduce the generation of uremic toxins, without negatively impacting nutritional status. This study supports possible benefits of added and supplemental fiber for individuals with CKD.

Practical Application

Fiber is recommended to optimize gastrointestinal function and prevent constipation. This study provides evidence that foods with added fiber provide this benefit and may provide additional health benefits for individuals with CKD.

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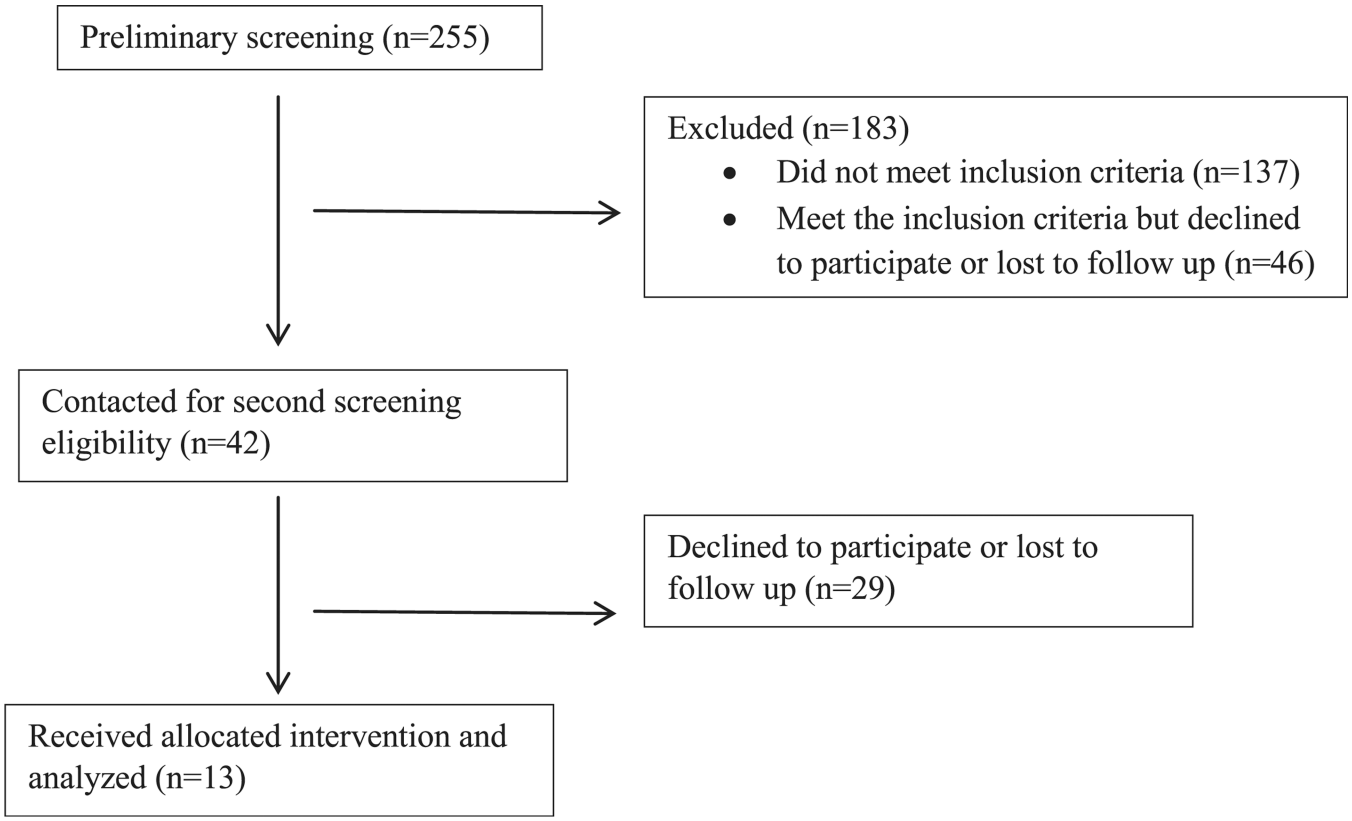

Figure 1.
Participant selection flow diagram.

Table 1

Clinical Markers for Control, Pea Hull, and Pea Hull + Inulin Intervention Periods

Clinical Markers	Control	Pea Hull	Pea Hull + Inulin
p-Cresol (mg/L)	7.25 ± 1.74	ND	5.82 ± 1.72*
BUN (mg/dL)	30 ± 4	30 ± 4	29 ± 4
Ammonia (mmol/L)	43 ± 4	43 ± 3	50 ± 5
Cystatin C (mg/L)	1.61 ± 0.24	1.68 ± 0.26	1.62 ± 0.23
Creatinine (mg/dL)	2.14 ± 0.38	2.17 ± 0.39	2.15 ± 0.40
CRP (mg/dL)	0.33 ± 0.13	0.39 ± 0.12	0.45 ± 0.21
eGFR (mL/min/1.73 m^2)†	37 ± 4	36 ± 4	37 ± 4

BUN, blood urea nitrogen; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ND, not determined.

*$P < .05$

†eGFR was calculated based on the Chronic Kidney Disease Epidemiology Collaboration creatinine equation adjusted for age, sex, and race.[31]